Laser treatment of congenital melanocytic naevi: a systematic review

Eggen, C.A.M.; Lommerts, J.E.; Zuuren, E.J. van; Limpens, J.; Pasmans, S.G.M.A.; Wolkerstorfer, A.

Abstract

Background

Rosacea is a common chronic facial skin condition, characterised by flushing, redness, pimples and dilated blood vessels. The eyes are often involved and thickening of the skin (phymas), especially of the nose, can occur in some people. A range of treatment options are available, but it is unclear which are most effective.

Objectives

To assess the efficacy and safety of treatments for rosacea.

Search methods

We updated our searches to March 2018, of: CENTRAL in *The Cochrane Library*, MEDLINE, EMBASE, LILACS, and Science Citation Index. We searched five trials registers and checked reference lists for further relevant studies.

Selection criteria

Randomised controlled trials in people with moderate to severe rosacea.

Data collection and analysis

Study selection, data extraction, risk of bias assessment and analyses were carried out independently by two authors.

Main results

We included 152 studies, comprising 20,944 participants with a mean age of 48.6 years, including more women than men. Sample sizes of 30-100 and study duration of two to three months were most common.

A wide range of comparisons (93) were evaluated. Topical interventions: brimonidine, oxymetazoline, metronidazole, azelaic acid, ivermectin, or other topical treatments. Systemic interventions: oral antibiotics, combinations with topical treatments or other systemic treatments, i.e. isotretinoin. Several studies evaluated laser or light-based treatment.

The majority of studies (84/152) were assessed as 'unclear risk of bias', 52 'high risk' and 16 'low risk'. Thirty-four studies provided no usable or retrievable data (e.g. none of our outcomes were addressed, or limited data in abstracts).

Of our primary outcomes 21 studies assessed 'change in quality of life', 75 assessed participant-assessed changes in rosacea severity and 98 assessed adverse events, although often limited data were provided. In most comparisons there were no statistically significant differences in number of adverse events: most being mild and transient. Physicians' assessments including investigators' global assessments, lesion counts and erythema were evaluated in three-quarters of the studies, but time needed for improvement and duration of remission were incompletely or not reported.

The certainty of evidence was rated moderate to high for most outcomes, but for some outcomes low to very low.

For reducing background erythema, topical brimonidine was more effective than vehicle in two studies. At three hours, participants' assessments reported a risk ratio (RR) of 2.11 (95% confidence interval (CI) 1.60 to 2.78). Physicians' assessments

confirmed these data (both high certainty evidence). Topical oxymetazoline also reduced erythema more than vehicle in two studies. Participants assessments at three hours showed a RR of 1.65 (95% CI 1.23 to 2.21), which was confirmed by the physicians' assessments (both moderate certainty evidence). Pulsed dye laser (PDL) was more effective than yttrium-aluminium-garnet (Nd:YAG) laser in reducing erythema and telangiectasia based on one study (low certainty evidence), and long PDL appeared to be as effective as intense pulsed light therapy (moderate certainty evidence).

For papules and pustules, pooled data from physicians' assessments in three trials demonstrated that metronidazole was more effective than placebo (RR 1.98, 95% CI 1.29 to 3.02)(moderate certainty evidence). Six trials showed that, according to the participants, azelaic acid was more effective than vehicle (RR 1.40, 95% CI 1.28 to 1.53)(high certainty evidence). The results from three studies were contradictory on which of these two treatments was most effective. Based on two studies, topical ivermectin increased the number of participants indicating that rosacea had no effect on their quality of life when compared with vehicle (RR 1.55, 95% CI 1.34 to 1.79)(high certainty evidence). Participants' assessments showed a RR of 1.84 (95% CI 1.62 to 2.09)(high certainty evidence), supported by physicians' assessments (moderate certainty evidence). Topical ivermectin appeared to be slightly more effective than topical metronidazole (based on one study) for improving quality of life, participants' and physicians' assessed outcomes (moderate to high certainty evidence). Topical clindamycin combined with tretinoin was not considered to be effective compared to placebo (moderate certainty evidence). The same was true for clindamycin versus vehicle (low to moderate certainty evidence). Topical minocycline foam was more effective than vehicle according to physicians based on one study (RR 2.33, 95% CI 1.35 to 4.00) with a large reduction in lesion count. However, the improvement in quality of life was small (moderate certainty of evidence for these outcomes).

Oral treatments for papules and pustules showed low certainty evidence that tetracycline was effective. In three trials according to physicians doxycycline appeared to be significantly more effective than placebo (RR 1.69, 95% CI 1.26 to 2.28) (high certainty evidence). There was little to no difference in physicians' assessments between 100 mg and 40 mg doxycycline, but there were fewer adverse events with the lower dose (RR 0.25, 95% CI 0.11 to 0.54) (low certainty evidence). Based on one study, minocycline 100 mg may result in little to no difference in participant-assessed improvement (good or excellent) compared to doxycycline 40 mg (RR 1.10, 95% CI 0.72 to 1.72)(low certainty evidence), nor in reduction of lesion counts (mean difference (MD) -1.00, 95% CI -7.96 to 5.96)(moderate certainty evidence). But physicians' assessments favoured minocycline 100 mg (3.43, 95% CI 1.67 to 7.04)(moderate certainty evidence). There was very low certainty evidence from one study that azithromycin was as effective as doxycycline 100 mg. Low dose minocycline (45 mg) was as effective as minocycline combined with topical azelaic acid (low certainty evidence). Based on one study low dose isotretinoin 0.25 mg/kg improves quality of life when compared to placebo (moderate certainty evidence) and resulted in a large improvement of participants' satisfaction (low certainty evidence). This was confirmed by physicians' assessments (RR 4.89, 95% CI 2.28 to 10.49) and number of participants with ≥ 90% reduction in lesion count (RR 5.51, 95% CI 2.37 to 12.83)(both high certainty evidence). Low dose isotretinoin 0.3 mg/kg was considered by both participants (RR 1.23, 95% CI 1.05 to 1.43) and physicians

(RR 1.18, 95% CI 1.03 to 1.36) to be slightly more effective than doxycycline 50-100 mg (moderate certainty evidence).

For ocular rosacea topical ciclosporin ophthalmic emulsion demonstrated effectiveness and improved quality of life (low certainty evidence). Topical ciclosporin may improve quality of life slightly when compared with oral doxycycline 200 mg for the first month and 100 mg for the following two months. This was supported by disease severity assessments of both participants and physicians (low certainty evidence for all outcomes). Omega 3 fatty acids likely improve symptoms of dry eyes and also improve tear gland function (moderate certainty evidence).

Authors' conclusions

For background erythema there was high certainty evidence to support the effectiveness of topical brimonidine and moderate certainty for oxymetazoline. There was low to moderate certainty evidence for laser and intense pulsed light therapy.

For papules and pustules, there was high certainty evidence for effectiveness of topical azelaic acid and topical ivermectin, and moderate to high certainty evidence for doxycycline and isotretinoin. Moderate certainty evidence was available for topical metronidazole and topical minocycline. There was low certainty evidence for tetracycline and low dose minocycline.

For ocular rosacea, there was moderate certainty evidence that oral omega 3 fatty acids was effective and low certainty evidence for ciclosporin ophthalmic emulsion and oral doxycycline.

Time needed until improvement and response duration should be addressed more completely, with more rigorous reporting of adverse events. Further studies on combinations of treatment and on ocular rosacea are warranted.

Plain language summary

Treatments for rosacea

Review question

Which treatments are effective for rosacea?

Background

Rosacea is a common skin condition causing flushing, redness, red pimples and pustules on the face, and should not be confused with acne. Dilated small blood vessels may appear near the surface of the skin (spider veins; telangiectasia). Rosacea can also cause inflammation of the eyes or eyelids, or both (ocular rosacea). Some people can develop a thickening of the skin, especially of the nose (rhinophyma). Although the cause of rosacea still remains unclear, a wide variety of treatments are available for this persistent (chronic), recurring and often distressing disease. These include medications applied directly to the skin (topical), oral medications and light-based therapies. We wanted to discover how people with rosacea assessed their treatments: if the treatments changed their quality of life, if they saw changes in their condition and if there were side effects. From the doctors, we wanted to discover whether treatments changed the severity of rosacea, as well as how long it took before symptoms reduced and reappeared.

Study characteristics

We reviewed 152 studies (up to March 2018) which included 20,944 people with moderate to severe rosacea. Most were between 40 and 50 years old, with more than twice as many women as men. Most studies lasted between eight to 12 weeks, with the longest lasting 40 weeks. The majority of people in these studies suffered from pimples and pustules, or persistent redness, or had a combination of these two features.

Of the 152 studies, 102 reported that they received funding, mainly by pharmaceutical companies, and 61 reported competing interests of the investigators. We were confident that this mostly did not affect the results, but we had concerns about 20 studies.

Key results

Most of the treatments appeared to be effective in treating rosacea. Almost half of the studies reported how people assessed their treatments. Only 21 assessed changes in quality of life. Almost all studies reported side effects, although this information was often limited. Studies mostly evaluated changes in the number of pimples and pustules, and redness. Only nine studies were about ocular rosacea.

Topical treatments

Two treatments specifically for reducing redness, brimonidine and oxymetazoline, were shown to work from three up to 12 hours after being applied. Both treatments did not show more side effects than the same product without the medication in it. Very few experienced redness, flushing, itching or skin irritation.

Three separate treatments, metronidazole, azelaic acid and ivermectin, were effective and safe in reducing pimples and pustules. Improvements tended to appear after three to six weeks, and ivermectin was slightly more effective than metronidazole. With metronidazole and ivermectin, very few people experienced mild itching, skin irritation or dry skin. For some, azelaic acid caused mild burning, stinging or irritation. More research is needed to determine which of these three is best.

Topical minocycline foam showed a large reduction in pimples and pustules, according to the doctors, and patients reported a small improvement of quality of life. Topical clindamycin was not effective for treating rosacea, and neither was it effective when it was combined with tretinoin.

Oral treatments

Antibiotics such as tetracycline, a low dose of doxycycline (40 mg) or a low dose of minocycline (45 mg) reduced the number of pimples and pustules. Low dose doxycycline was likely as effective as 100 mg, but with much fewer side effects like diarrhoea and nausea. Azithromycin may be as effective as 100 mg doxycycline, but only one study addressed this treatment. Oral minocycline 100 mg showed as much effectiveness as doxycycline 40 mg, according to the findings of both patients and doctors, but the doctors favoured minocycline.

Low dose isotretinoin (0.25 mg/kg) improved quality of life, increased patients' satisfaction, and according to doctors decreased pimples and pustules by 90%. Another low dose of isotretinoin (0.3 mg/kg) appeared to be slightly more effective than 50-100 mg doxycycline for treating pimples and pustules. However, when using isotretinoin extra precautions need to be taken regarding contraception in women of childbearing age as it is known to cause malformations in the foetus.

Light-based therapies

Laser therapy and intense pulsed light therapy were both effective for the treatment of dilated blood vessels, but the studies examining these treatments only reported limited data.

Rosacea of the eyes or eyelids, or both (ocular rosacea)

Ciclosporin 0.05% ophthalmic emulsion increased quality of life of people and according to doctors improved the amount and quality of tears, compared to artificial teardrops. When compared to oral doxycycline, topical ciclosporin seemed slightly more effective in improving quality of life and decreasing symptoms, according to both patients and doctors. Based on one study, omega 3 fatty acids likely improve dry eyes and tear gland function.

Certainty of the evidence

We rated the certainty of the evidence for the outcomes from very low to high. There was high certainty evidence for the effectiveness of brimonidine, azelaic acid, topical ivermectin, and moderate to high certainty evidence for doxycycline and isotretinoin. The lower certainty evidence for other treatments was caused mostly by having not enough people participating in the studies and that participants knew (or might have known) which treatments they were receiving.

Background

We have listed unfamiliar terms in the glossary of terms in Table 1.

Description of the condition

Definition and clinical features

Rosacea is a chronic inflammatory dermatosis affecting the cheeks, nose, eyes, chin and forehead. It is characterised by recurrent episodes of flushing of transient erythema (redness), persistent erythema, papules (pimples), pustules, and telangiectasia (permanent distended blood capillary vessels with a reticulated pattern) (Elewski 2011; Korting 2009; Marks 2007; van Zuuren 2017). Previously, the National Rosacea Society Expert Committee (NRSEC) in 2002 proposed standardised criteria for diagnosis and classification of rosacea (Wilkin 2002). They posited that any one of the following primary features in a centrofacial distribution would be sufficient for diagnosis: flushing, non-transient erythema, papules/pustules or telangiectasia. Secondary features included burning/stinging, erythematous plaques, dry appearance, oedema, peripheral location, phymatous changes and ocular manifestations. Furthermore, they grouped a combination of these features into four subtypes and one variant, respectively erythematotelangiectatic rosacea, papulopustular rosacea, phymatous rosacea, ocular rosacea and granulomatous rosacea (the variant) (Wilkin 2002).

However, shortcomings in these diagnostic criteria and subtyping have become apparent (Tan 2016). This includes the lack of specificity of some primary features (flushing, papules/pustules, telangiectasia), the exclusion of phyma as a primary feature, and the conflation of multiple features into subtypes (Tan 2016). For example, the erythematotelangiectatic subtype comprises flushing and persistent central facial erythema with, or without telangiectasia while the papulopustular subtype comprises persistent central facial erythema with transient, central facial papules and/or pustules. Thus, both have persistent central facial erythema as a

common feature. This has led to confusion in research on prevalence whereby some studies consider them as separate categories while others aggregate all with central facial erythema as erythematotelangiectatic, a subgroup of which is papulopustular. Further, it does not account for patients presenting with a solitary diagnostic criterion but none of the others defining a subtype. For example, how would one classify a patient with telangiectasia alone – previously considered as an independent diagnostic criterion – but without flushing and persistent central facial erythema? In addition, severity determination of subtypes is hindered by the presence of multiple features each of which may vary in individual severity and responsivity to intervention. However, these individual features were not typically evaluated separately. Furthermore, in clinical practice, subtyping may inadequately capture the signs and symptoms of individual patients as some features can extend across subtypes.

Consequently, revised diagnostic criteria have been proposed and recommendations made to abandon subtyping. Both an international Rosacea Consensus panel and updated NRSEC guidance recommend use of harmonized diagnostic criteria and a phenotype-led approach (Gallo 2018; Tan 2016). The following are independently considered diagnostic of rosacea: fixed centrofacial erythema that may periodically intensify, or phymatous changes. In their absence, diagnosis can also be established by two or more major features: papules and pustules, flushing, telangiectasia, ocular manifestations (lid margin telangiectasia, interpalpebral conjunctival injection, spade shaped infiltrates in the cornea, scleritis and sclerokeratitis) (Gallo 2018). While secondary features may occur - burning or stinging, oedema, dry appearance – these are not diagnostic, alone or in combination. This redirection in diagnosis and elimination of subtypes should provide greater accuracy in diagnosis, establish clearly defined targets for research, facilitate development of severity measures and improve patient-centred care (Gallo 2018).

Symptoms

Rosacea primarily affects the face and may be accompanied by the physical discomfort of flushing, stinging and burning sensations and ocular irritation. The disease can cause embarrassment, anxiety, low self-esteem and lack of confidence, and may even lead to depression, social anxiety disorder or body dysmorphic disorder (Abram 2009; Dirschka 2015; Egeberg 2016; Elewski 2011; Halioua 2017; Landow 2005). Up to three quarters of the patients with rosacea have ocular symptoms, such as foreign-body sensation, dryness, burning, itching, redness, photophobia, tearing, and blurred vision (Lazaridou 2011; Oltz 2011; Vieira 2013). Ocular involvement may occur at any time concurrently or independent of cutaneous features (Oltz 2011). Ocular rosacea may result in a spectrum of presentation from mild ocular symptoms such as foreign body sensation to severe manifestations including corneal ulcers and loss of vision (Ghanem 2003; Lazaridou 2011; Oltz 2011; Vieira 2013; Wladis 2017).

Several studies have demonstrated that objective clinical parameters of skin disease are often poorly correlated with quality of life, and that physicians tend to underestimate the impact of skin disease (Chren 1996; Nicholson 2007). Rosacea has a significant adverse impact on quality of life (Aksoy 2010; Cresce 2014; Moustafa 2014; Oussedik 2018; van der Linden 2014). Only one validated disease-specific quality of life instrument (RosaQoL) has been developed, and RosaQoL scores have been used in several studies as one of the outcome parameters

(Baldwin 2010; Bamford 2012; Fleischer 2005; Kini 2010; Nicholson 2007). However, this scale does not include phymatous changes and no minimal clinically important difference has been established.

In daily clinical practice as well as in studies on rosacea, independent assessment of rosacea severity of each phenotype will be helpful for evaluation of treatment efficacy (Gallo 2018; Tan 2016; Tan 2017). However, few severity scales are validated and/or tested for reliability: the Clinician's Erythema Assessment (CEA) and the Patient's Self-Assessment (PSA) (Tan 2014; Tan 2015). Scale development should be based on phenotypes and should not only focus on clinician reported outcomes but also on patient reported outcomes (PRO). Much work remains to be done to improve the quality of reporting of patient reported outcomes (PRO) in studies on rosacea (van Zuuren 2013).

Epidemiology and causes

The prevalence of rosacea varies from less than 1% to more than 20%, indicating a range which is most likely attributable to differences in the populations studied and methodologies used (Tan 2013b). According to a recent review of literature, global prevalence of rosacea was estimated to be 5.46% (95% CI 4.91 to 6.04) of the general population, with higher estimates of self-reported rosacea and lower estimates of reported physician-diagnosed rosacea (Gether 2018). Recent data suggest that rosacea affects men and women equally (Culp 2009; Gether 2018; Powell 2005). Rosacea usually presents in the third or fourth decade of life and is reportedly more common in fair-skinned people of Celtic and northern European heritage (Culp 2009; Korting 2009; van Zuuren 2017). Phymatous phenotype of rosacea affects men much more often than women (Powell 2005; Tan 2013; Wilkin 2004). Prevalence studies of rosacea in darker skin phototypes are sparse and centrofacial erythema as a diagnostic criterion in dark phototypes may confound case-finding (Tan 2017).

While there have been advances in clarifying the pathophysiology of rosacea, causation remains unclear. Several hypotheses have been proposed. Both genetic and mostly environmental stimuli and triggers, for example heat, sunlight, stress, certain food and Demodex mites stimulate an augmented innate immune response and neurovascular dysregulation by selective receptor activation, which may correlate with different phenotypic outcomes of rosacea (Del Rosso 2012; Elewski 2011; Holmes 2017; Reinholz 2016; Steinhoff 2011; Steinhoff 2013). In rosacea affected skin, elevated abnormal cathelicidin (an antimicrobial peptide) and elevated serine protease (kallikrein-5) induce increased LL-37, which results in inflammation, neurovascular effects and vascular changes (Del Rosso 2012; Holmes 2017; Yamasaki 2007; Yamasaki 2011). More recently mechanisms of rosacea pathophysiology have been categorised into (a) increased Toll-like receptors on keratinocytes, (b) augmented innate immunity, (c) neurovascular dysregulation, (d) neurogenic inflammation mediated by specific transient receptor potential (TRP) channels, (e) vascular changes, (f) reactive oxygen species (ROS), (g) stratum corneum permeability barrier dysfunction, (h) ultraviolet (UV) radiation and (i) microbes, e.g. Demodex, *Bacillus oleronius* (Chang 2015; Chang 2017; Del Rosso 2012; Del Rosso 2013a; Holmes 2017; Moran 2017 Steinhoff 2011; Tisma 2009; Two 2015). The current hypothesis is that rosacea is an inflammatory disorder that may develop in individuals with rosacea-prone skin, initiated by several triggers (Aldrich 2015; Chang 2015; Steinhoff 2011). Possible triggers that have been

investigated are gastrointestinal (digestive) tract diseases, infestation with *Helicobacter pylori*, *Demodex folliculorum*, *Bacillus oleronius*, epidermal barrier defect, and childhood stye (Bamford 2006; Chang 2017; Elewski 2009; Forton 2007; Forton 2012; Lacey 2007; Moran 2017; Yang 2018).

Description of the intervention

As with most chronic skin diseases, rosacea requires long-term treatment. Currently available therapies are numerous, and their use frequently based on anecdotal evidence (Elewski 2011; Layton 2013; Powell 2005). Management strategies for people with rosacea should include phenotype-based treatments, in accordance with current classification of rosacea (instead of the previous subtype-classification) (Gallo 2018; Schaller 2017). Because rosacea can have an adverse impact on quality of life, these strategies should also be directed towards achieving improvements in general well-being by targeting those aspects that are most bothersome to the patient (Bikowski 2004; Elewski 2011; Schaller 2017). In certain individuals successful management of rosacea is possible through avoidance of some of the triggers, in particular those which cause flushing, that is certain foods and beverages, sunlight and some types of cosmetics (Elewski 2011; Schaller 2017; van Zuuren 2017).

Topical interventions

The only topical treatments approved for rosacea by the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) are azelaic acid, metronidazole, ivermectin, brimonidine and oxymetazoline. (Del Rosso 2013c; Fowler 2012a; Fowler 2013a; Kircik 2018; Kuang 2018; Layton 2013; Stein 2014a; Stein-Gold 2018). If a small number of papules or pustules are present, a topical rather than systemic intervention is considered first-line (Del Rosso 2013b; Elewski 2011; Schaller 2017; van Zuuren 2017). Azelaic acid, metronidazole and ivermectin are recommended (Culp 2009; Del Rosso 2013b; Elewski 2011; Korting 2009; Schaller 2017; van Zuuren 2017). Alternative, off-label treatments are permethrin 5% cream, tretinoin cream, 10% sulphacetamide with sulphur (5%) and benzoyl peroxide alone or in combination with erythromycin or clindamycin (Culp 2009; Del Rosso 2013b; Elewski 2011; Korting 2009; Schaller 2017; van Zuuren 2017). Brimonidine tartrate gel 5%, a topical selective α_2-adrenergic receptor agonist with vasoconstrictive activity and oxymetazoline hydrochloride 1% cream, an α_1-adrenergic agonist and a partial α_2-adrenergic agonist, are both considered to be effective for the treatment of persistent facial erythema of rosacea (Baumann 2018; Del Rosso 2013c; Fowler 2012a; Fowler 2013a; Kircik 2018; Kuang 2018).

Eyelid hygiene, warm compresses and artificial tears are recommended for ocular rosacea (Schaller 2017; Stone 2004; Oltz 2011; Vieira 2013; van Zuuren 2017; Wladis 2017). Topical ciclosporin eyedrops, metronidazole gel and fusidic acid gel are also reportedly successful (Arman 2015; Barnhorst 1996; Seal 1995; Schechter 2009; Vieira 2013).

Systemic interventions

If papules and/or pustules are more extensive, oral antibiotics are usually recommended (Alikhan 2010; Bakar 2009; Culp 2009; Elewski 2011; Reinholz 2013; Schaller 2017; van Zuuren 2017).

Modified-released doxycycline 40 mg once daily (subantimicrobial dosage), is the only FDA and EMA approved systemic treatment for inflammatory lesions. (Del

Rosso 2007a; Del Rosso 2007b; Del Rosso 2008; Schaller 2017; van Zuuren 2017). This dosage is associated with fewer side effects and reduces the risk of bacterial resistance in comparison with 100 mg doxycycline (Del Rosso 2008).

Oral tetracycline, widely used for rosacea since the 1950s, is efficacious in reducing inflammatory lesions, but associated with more side effects than doxycycline (Alikhan 2010; Korting 2009; Schaller 2016). Another member of the tetracycline group, minocycline is also frequently prescribed for inflammatory lesions associated with rosacea, but few studies support its efficacy (Jackson 2013; van der Linden 2017). Albeit rare, serious adverse reactions including hyperpigmentation of the skin and other tissues, drug-induced systemic lupus erythematosus and auto-immune hepatitis, may occur due to minocycline (Garner 2012; Lebrun-Vignes 2012; Smith 2005; van Zuuren 2017).

Treatment with azithromycin, erythromycin and clarithromycin may be considered an alternative therapy for those patients, who for any reason are unable or unwilling to take doxycycline. Their efficacy is supported primarily by observational studies (Powell 2005; Reinholz 2013; Schaller 2016; van Zuuren 2017).

As the rosacea improves, systemic treatment can be discontinued and improvement maintained by topical treatment alone (Asai 2016; Bhatia 2012; Elewski 2011;Reinholz 2013; Schaller 2017; van Zuuren 2017). In the more severe or persistent inflammatory lesions, for refractory rosacea, for clinically inflamed phyma, and in case oral antibiotics are insufficiently effective, low-dose (0.25-0.30 mg/kg/day) oral 13-cis-retinoic acid (isotretinoin) therapy may be appropriate (Elewski 2011; Gollnick 2010; Sbidian 2016; Schaller 2016; Two 2015b; van Zuuren 2017). Isotretinoin has potential adverse events ranging from dryness of skin and mucosa to teratogenicity. Accordingly, it should be prescribed and monitored by experienced clinicians with use of Pregnancy Prevention Programs where appropriate (Korting 2009; Nickle 2014; Schaller 2016; van Zuuren 2017).

For ocular rosacea, oral antibiotics, including tetracyclines, are well known treatment options (Oltz 2011; Schaller 2016; van Zuuren 2017; Wladis 2017).

Other interventions

The vascular manifestations of rosacea appear to respond to light-based therapies such as pulsed dye laser or intense pulsed light (Culp 2009; Hofmann 2016; Kawana 2007; Korting 2009; Tanghetti 2014).

Clinically non-inflamed phyma may require surgical intervention, but laser therapy has also been used (Powell 2005; Taghizadeh 2008; Tanghetti 2014; van Zuuren 2017).

How the intervention might work

Although an incomplete understanding of the pathophysiology of rosacea continues to hamper therapeutic efforts (Baldwin 2006; Elewski 2011), metronidazole, azelaic acid and ivermectin are generally considered as first-line topical medications. It is also now widely recognised that the therapeutic efficacy of metronidazole can be attributed to its anti-inflammatory and antioxidant effects (Bhatia 2012; Elewski 2011; Feldman 2014; Naranayan 2007; Two 2015b). Azelaic acid decreases kallikrein 5 and cathelicidin expression (Coda 2013; Two 2015b). Ivermectin has demonstrated activity against Demodex in addition to possible inflammatory properties (Deeks 2015; Layton 2013; Schaller 2017b; Stein 2014a). Brimonidine and oxymetazoline

target the α-adrenergic receptors in the smooth muscle sheath located around the vessel wall of the superficial blood vessels of the skin resulting in vasoconstrictive activity which can provide a reduction of facial erythema after application (Del Rosso 2013c; Kircik 2018; Kuang 2018).

Tetracyclines have anti-inflammatory effects, through down-regulation of production of inflammatory cytokines, inhibition of matrix-metalloproteinases (MMP), inhibition of leukocyte chemotaxis and through anti-oxidant activity (Alikhan 2010; Baldwin 2006; Del Rosso 2007a; Perret 2014; Sapadin 2006). Furthermore, doxycycline has been shown to inhibit neutrophil activity and several pro-inflammatory reactions including those associated with phospholipase A2, endogenous nitric oxide and interleukin-6 (Baldwin 2006; Bikowski 2003; Korting 2009; Perret 2014; Sloan 2008). Using sub-antimicrobial doses of doxycycline (40 mg modified release), instead of the 100 mg dose, can be important in minimising the development of microbial resistance (Bikowski 2003; Korting 2009; Sloan 2008).

Isotretinoin has anti-inflammatory properties, which are attributable to the inhibition of Toll-like receptor 2 signalling. Furthermore, it diminishes sebaceous gland size and number, and may reduce development of rhinophyma (Baldwin 2006; Dispenza 2012; Erdogan 1998; Gollnick 2010; Schaller 2016; Uslu 2012).

Laser therapy can reduce both erythema and telangiectasia (Butterwick 2006; Garden 2017; Hofmann 2016; Shim 2013;Tanghetti 2014). The pulsed dye laser (PDL) with the 595 nm wavelength targets haemoglobin and delivers all of the administered energy in a wavelength that is actively taken absorbed by the haemoglobin in blood vessels causing vessel destruction (Bernstein 2008; Bernstein 2018; Butterwick 2006; Kim 2011; Kim 2017; Shim 2013). The 532 nm frequency-doubled, potassium-titanyl-phosphate (KTP) and the neodymium-doped, yttrium-aluminium-garnet (Nd:YAG) laser also deliver laser wavelengths readily absorbed by haemoglobin (Bernstein 2008; Butterwick 2006; Karsai 2008). Intense pulsed light with a wavelength between 550 nm and 670 nm is readily absorbed by both melanin and oxyhaemoglobin, and has also been used in the treatment of telangiectasia and background erythema (Butterwick 2006; Hofmann 2016; Kawana 2007; Nymann 2010).

Why it is important to do this review

Although rosacea is a common and distressing disorder, there is continuing debate over which therapy, or which combination of therapies, is most likely to offer benefits to patients. This systematic review was conducted to examine the different management options and to try and determine the most effective strategy in the treatment of rosacea. Furthermore, this review is important to align evidence based treatment options with the new phenotype approach.

Objectives

To assess the efficacy and safety of treatments for rosacea.

Methods

Criteria for considering studies for this review

Types of studies

Randomised controlled trials (RCTs).

Types of participants

People ≥ 18 years with moderate to severe rosacea (diagnosed clinically).

Types of interventions

Any type of intervention used, either alone or in combination, to treat rosacea versus placebo, no treatment or active treatment. We also considered the effects of avoidance of some foodstuffs, for example spicy food, as well as the use of certain cosmetics and sunscreens.

Types of outcome measures

Primary outcomes

1. Change in health-related quality of life (HRQOL) at end of study
2. Participant-assessed changes in rosacea severity at end of study
3. Proportion of participants who reported an adverse event throughout the study period

Secondary outcomes

1. Physician-assessed changes in rosacea severity. These included the following:

- physician's global assessment of rosacea severity at end of study;
- assessment of erythema or telangiectasia, or both, at end of study;
- reduction in lesion counts (treatment success defined as greater than 50% reduction in lesion counts);
- time needed until improvement;
- duration of remission.

We produced 'Summary of findings' tables of the following outcomes listed according to priority:

1. change in HRQOL;
2. participant-reported improvement of rosacea;
3. proportion of participants who reported an adverse event;
4. physician's global assessment of improvement of rosacea;
5. assessment of erythema or telangiectasia, or both;
6. reduction in lesion counts;
7. time needed until improvement;
8. duration of remission.

Search methods for identification of studies

We aimed to identify all relevant RCTs regardless of language or publication status (published, unpublished, in press or in progress).

Electronic searches

For this update, we revised the search strategies for all our databases (see the section on Differences between protocol and review for details). We searched the following databases up to 6 March 2018:

- Cochrane Central Register of Controlled Trials (CENTRAL) (2014, Issue 6) in *The Cochrane Library* using the strategy in Appendix 1;
- MEDLINE via Ovid (from 1946) using the strategy in Appendix 2;
- EMBASE via Ovid (from 1974) using the strategy in Appendix 3;
- LILACS (Latin American and Caribbean Health Science Information database) (from 1982) using the strategy in Appendix 4;
- Science Citation Index (from 1988) (see Appendix 5); and
- BIOSIS (previously searched from 1970 to March 2002) (see Appendix 6).

Trials registers

We (EvZ and MvdL) searched the following trials registers on 13 March 2018 with the search terms 'rosacea' and 'rhinophyma':

- metaRegister of Controlled Trials (www.controlled-trials.com);
- US National Institutes of Health Ongoing Trials Register (www.clinicaltrials.gov);
- Australian and New Zealand Clinical Trials Registry (www.anzctr.org.au);
- World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch);
- the Ongoing Skin Trials Register (www.nottingham.ac.uk/ongoingskintrials).

Searching other resources

References from published studies

The reference lists of all identified RCTs and key review articles were checked for further references to relevant trials (EvZ and ZF).

Unpublished literature

Attempts were made (EvZ and ZF) to locate unpublished and ongoing trials through correspondence with authors and pharmaceutical companies (see Table 2 and Table 3).

Translation

We did not apply any language restrictions and several studies published in the French, Spanish, Italian, Norwegian and Danish languages were translated by one author (EvZ). One article in the Chinese language was translated by Ching-Chi Chi and one by Xiamomeng Liu and Na Luo (see Acknowledgements).

Data collection and analysis

We followed the previously published protocol (van Zuuren 2000) for this review. Changes made since the original protocolare disclosed in 'Differences between protocol and review'. Some parts of the methods section of this review use text that was originally published in Cochrane reviews co-authored by EVZ, ZF and BC (predominantly El-Gohary 2014 and van Zuuren 2012).

Selection of studies

Two review authors (EvZ and ZF) independently assessed the abstracts of studies identified from the searches. We obtained full-text copies of all relevant and potentially relevant studies, those appearing to meet the inclusion criteria, and those for which there were insufficient data in the title and abstract to make a clear decision. The two authors then independently assessed the full-text papers and

resolved any disagreement on the eligibility of included studies through discussion and consensus, or through a third party (MvdL). All irrelevant studies were excluded and their details and reasons for exclusion were noted in the 'Characteristics of excluded studies' table in RevMan (Revman 2014).

Data extraction and management

Details of eligible trials were extracted and summarised using structured data extraction forms (EvZ, ZF). Disagreements were resolved by discussion. Study details were entered into the 'Characteristics of included studies' table in RevMan (Revman 2014) by two authors (EvZ, ZF). The review authors only included data if there was an independently reached consensus, and any disagreements were resolved by discussion between the authors.

The following details were extracted:

1. trial methods, method of allocation, masking of participants and outcomes assessors, and date and setting of study;
2. participants, sample size, age, sex, inclusion and exclusion criteria, if there was ocular involvement, exclusion of participants after randomisation, and proportion of losses at follow up;
3. intervention and comparison, length of study, type and dosage;
4. outcomes, primary and secondary outcomes reported in the study;
5. sources of funding and support if reported.

Assessment of risk of bias in included studies

Two review authors (EvZ and ZF) independently assessed risk of bias using the Cochrane Collaboration tool for assessing risk of bias as described in Chapter 8, section 8.5 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

The following domains were rated for each of the included studies as 'low risk of bias', 'high risk of bias', and 'unclear risk of bias' if the risk of bias was uncertain or unknown:

(a) the allocation sequence was adequately generated ('sequence generation');
(b) the allocation was adequately concealed ('allocation concealment');
(c) knowledge of the allocated interventions was adequately prevented during the study ('blinding');
(d) incomplete outcome data were adequately addressed;
(e) reports of the study were free of suggestion of selective outcome reporting; and
(f) the study was apparently free of other sources of bias that could put it at high risk of bias. This would include adequate study duration, i.e. a minimum of four weeks, and that previous oral and topical rosacea therapy was discontinued for a minimum of four weeks prior to the initial assessment. If the investigators declared any support or funding of the study by the pharmaceutical industry this was noted and assessed to determine if it represented a potential risk of bias in the conduct or reporting of the study (Bero 2013).

These assessments were reported in the 'Risk of bias' table for each individual study. See 'Characteristics of included studies'.

We also categorised and reported the overall risk of bias of each of the included studies according to the following:

- low risk of bias (plausible bias unlikely to seriously alter the results) if all criteria were met;
- unclear risk of bias (plausible bias that raises some doubt about the results) if one or more criteria were assessed as unclear; or
- high risk of bias (plausible bias that seriously weakens confidence in the results) if one or more criteria were not met.

Measures of treatment effect

Two treatment comparisons

We presented continuous outcomes, where possible, on the original scale as reported in each individual study with a mean change from baseline with its associated standard deviation in parentheses. Risk ratios (RR) were calculated for dichotomous outcomes and if statistically significant were presented with either: the number needed to treat for one additional beneficial outcome (NNTB); or number needed to treat for one additional harmful outcome (NNTH).

Any outcome data which reported physician-assessments of the time needed until improvement were presented as a descriptive narrative of the general trend within the groups at the first time point where an improvement was seen. In future updates, and if studies report adequate time-to-event outcomes data, we will follow the recommendations for analysing this type of outcome as described in Chapter 9, section 9.2.6 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

All outcome data were reported with their associated 95% confidence interval (CI).

Skewed data

Outcome data reported for asymmetrical distributions as counts, for example papules or pustules, were often skewed and frequently inappropriately analysed. We did not enter these types of outcome data into a meta-analysis but reported them separately for individual comparisons, where this was possible (section 9.4.5.3) (Higgins 2011).

Unit of analysis issues

Cross-over studies

Unit of analysis issues can arise in studies where participants have been randomised to multiple treatments in multiple periods, or where there has been an inadequate wash-out period. In general, for cross-over studies we only used data from the first treatment period, unless otherwise stated.

Within-patient studies

In studies that reported paired data but where these were not adjusted for the within-participant variability, a McNemar's test was applied and presented with the corresponding P value. If only the crude RR or raw data were presented and we were not able to adjust for the within-participant variability, the RR was reported without a P value or 95% CI. In future updates, paired data from studies with no suspicion of contamination across intervention sites will be analysed separately

using the generic inverse-variance method in RevMan after accounting for the within-participant variability (see Chapter 16, section 16.4.4: Methods of analysis for cross-over trials) (Higgins 2011). If this is not possible but adequate data are available, the McNemar's test will be applied. For future updates and in those instances where data from within-participant studies may be pooled together with data from between-participant studies, the RR from the between-participant studies will be calculated and combined in a meta-analysis using the generic inverse-variance method.

More than two treatment comparisons

Multi-arm trials were included in the review if at least one arm constituted a relevant intervention for rosacea, and separate data extraction was carried out for each pair-wise comparison. These studies were included as pair-wise comparisons. For future updates, to prevent double-counts of participants if treatment arms from multi-arm studies are to be pooled more than once, these will be partitioned according to the number of comparisons carried out and the analysis will follow the recommendations in Chapter 16, section 16.5.4 in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011).

Dealing with missing data

If data were missing from trials which were less than 10 years old, reasonable attempts were made to contact the investigators or sponsors of these studies (see Table 2; Table 3). We re-analysed data according to the intention-to-treat (ITT) principle whenever possible. For dichotomous outcomes, if authors had conducted a per-protocol analysis we carried out an ITT analysis with imputation setting the missing data to their baseline values, after checking the degree of imbalance in the dropouts between the arms to determine the potential impact of bias (section 16.2.2 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011)). For continuous outcomes a per-protocol analysis was carried out in place of an ITT analysis.

Assessment of heterogeneity

Clinical heterogeneity was assessed by examining the characteristics of the studies, the similarity between the types of participants, the interventions, the comparisons and the outcomes as were specified in the criteria for included studies. Although there is inevitably a degree of heterogeneity between the studies included in a review, if this could be explained by clinical reasoning and a coherent argument could be made for combining the studies, these were entered into a meta-analysis.

The clinical diversity between many of the studies in this review as well as the limited number of studies that could be combined for each intervention only allowed us to make assessments of heterogeneity between the studies in just two of the comparisons. We assessed heterogeneity based on thresholds for the interpretation of I^2 where < 40% might not be important, 30% to 60% represents moderate and 50% to 90% substantial heterogeneity (Higgins 2011). If the I^2 statistic was more than 60% (Higgins 2011) and could not be explained by clinical reasoning we did not enter these data into a meta-analysis.

Assessment of reporting biases

The low number of studies evaluating similar interventions and comparisons did not permit an assessment of publication bias.

Data synthesis

Two review authors (EvZ, ZF) analysed the data in RevMan (Revman 2014) and reported them as specified in Chapter 9 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We used a random-effects model to combine the results of individual studies in this review. If applicable in future updates, synthesis of data and reporting of analyses from multiple studies evaluating similar interventions will take into consideration individual studies categorised with a summary high or variable risk of bias. If a sufficient number of such studies are identified, we will present analyses stratified according to overall risk or alternatively restrict the analyses to studies at low risk of bias and this will be reported accordingly.

The GRADE approach was applied to interpret the results for the main comparisons, and GRADEproGDT was used to create 'Summary of findings' tables (GRADEpro GDT 2015). Outcome-specific information concerning the certainty of evidence from studies per comparison was addressed and the magnitude of effect of the interventions was examined and presented.

Subgroup analysis and investigation of heterogeneity

In view of the paucity of included studies covering any one specific intervention, we did not carry out any subgroup analyses. In future updates, we plan to carry out subgroup analyses if we identify at least moderate to substantial heterogeneity (as defined above) and if we are able to include at least 10 studies. The subgroups we will consider include: differences in treatment effect by differing baseline risk, and possible differences in effect caused by the range of modes of administration of the interventions used, that is topical, systemic and different dosing regimens.

Sensitivity analysis

We did not conduct any sensitivity analyses in this review. If a sufficient number of studies (n = 10) investigating similar interventions had been included, we planned to conduct sensitivity analyses to assess the robustness of our review results.

Results

Description of studies

See 'Characteristics of included studies' and 'Characteristics of excluded studies'.

Results of the search

The updated searches for this review identified an additional 219 citations of potentially eligible studies. Searching the trial registers identified 38 ongoing studies giving a total of 257 references. There were 14 duplicates, and a further 160 references were excluded from further evaluation after examination of the titles and abstracts. The remaining 83 studies were further assessed for eligibility. Of these, 46 studies (reported in 44 references as two references reported on two studies) were included. Sixteen studies appeared to be duplicate publications and are listed under the primary references, 18 studies are awaiting further assessment (see 'Characteristics of studies awaiting classification'), and 19 are ongoing trials (see 'Characteristics of ongoing studies' section) (in total 53 studies, see Figure 1). Total number of studies in Characteristics of studies awaiting classification is 40 (22 of

former update are in this list) and 24 studies in Characteristics of ongoing studies (of which five of former update).

Included studies

This review has 152 included studies out of which 106 studies were already in the former update, so there are 46 newly included studies (see Table 4). A total of 20,944 participants were studied (see 'Characteristics of included studies'). Thirty-five of the studies were carried out before the year 2000, the remainder (117) were conducted after 2000.

It was agreed between the review authors that two studies, NCT01426269 and Thiboutot 2008 should be included but that these were considered as maintenance studies. In NCT01426269, 130 participants took part in the second phase of the study and were randomised to doxycycline 40 mg or placebo after having obtained an Investigator's Global Assessment (IGA) of clear or near clear during the open-label first phase of treatment with doxycycline 40 mg combined with metronidazole gel, both once daily. In Thiboutot 2008, the investigators enrolled 172 participants in the pilot phase of the study out of which only 136 continued into the second phase (maintenance phase), but these constituted the participants who had already achieved an improvement of > 75% reduction in inflammatory lesions.

Also Stein Gold 2014c and Stein Gold 2014d were included, although these were two identical safety studies to evaluate long-term safety of ivermectin 1% cream in comparison to azelaic acid 15% gel. In these studies (extensions of Stein 2014a and Stein 2014b respectively, also identical) the participants in the ivermectin 1% cream group had used ivermectin 1% cream for 12 weeks, before the extension part, were treated over the next 12 weeks with ivermectin 1% cream (Study 1), whilst the participants in the azelaic gel 15% acid group had used the vehicle for the 12 weeks before the extension part. Therefore, there is a clear baseline imbalance between intervention groups for these extension studies.

Characteristics of the participants

The majority of studies focused on inflammatory lesions in patients with rosacea and a minority mainly on erythema and telangiectasia. The participants were generally between 40 and 50 years of age, with a mean of 48.6 years; there were more women (12575) than men (5313) and the gender was unreported for 3056 participants. The number of participants in the individual studies varied widely from 6 to 1299 and sample sizes of between 30 and 100 participants were the most common and 52 studies had more than 100 participants.

Characteristics of the interventions

The trials were grouped into 12 categories of interventions: topical brimonidine only; topical oxymetazoline only; topical metronidazole only; topical azelaic acid only; topical ivermectin only; topical metronidazole, azelaic acid and/or other topical treatments; oral antibiotics; oral antibiotics combined with topical treatments; oral antibiotics compared with topical antibiotics; other systemic treatments; laser and light-based therapies; and other treatments or combined treatments.

In 23 of the studies the individuals served as their own controls (within-participant), where active treatment and placebo assigned to either the left or right side of the face (Alam 2013; Barnhorst 1996; Bleicher 1987; Buendia-Bordera 2013; Carmichael 1993; EUCTR2011-002057-65-DE; EUCTR2011-002058-30-DE; EUCTR2013-

005083-26-DE; Fabi 2011; Han 2014; Karsai 2008; Kim 2017; Maddin 1999; Mostafa 2009; NCT03035955; Neuhaus 2009; Nymann 2010; Park 2016; Raoufinejad 2016; Tirnaksiz 2012; Waibel 2016; Yoo 2011; Zhong 2015).

The duration of treatment ranged between one and 40 weeks with a mean of 10.6 weeks. Only nine studies addressed interventions for ocular rosacea (Arman 2015; Barnhorst 1996; Bhargava 2016; Heitz 2014; NCT00560703; Salem 2013; Schechter 2009; Sharquie 2006; Wittpenn 2005).

Heterogeneity in study design, skewed data, missing standard deviations, and a mix of different comparators and dosing regimens did not, in general, permit pooling of the data or allow the authors to make accurate and direct comparisons of a substantial number of the interventions.

Characteristics of the outcomes

Only 22 out of the 152 included studies (Arman 2015; Bamford 2012; Braithwaite 2015; Bribeche 2015; Chang 2012; Draelos 2013a; Draelos 2015; EUCTR2006-001999-20-HU; Heitz 2014; Jaque 2012; Luger 2015; Mrowietz 2018; NCT00560703; NCT01426269; NCT02147691; Sbidian 2016; Schechter 2009; Stein 2014a; Stein 2014b; Taieb 2015; van der Linden 2017; Weissenbacher 2007) reported assessments of change in 'quality of life' as a result of the interventions. However, this number has risen by 19 since 2010, which would appear to illustrate the steadily increasing recognition of quality of life as a key outcome by investigators in rosacea studies. Nearly half (75) of the remaining studies evaluated participant-assessed changes in rosacea severity. The patient-reported outcomes (PROs) which were reported in the 75 studies included not only assessments of changes in severity but also, in almost a quarter of the cases, patient satisfaction associated with these changes.

We evaluated these PROs against the checklist for describing and assessing patient-reported outcomes in clinical trials (see Table 5), which is described in Chapter 17.6 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We found that hardly any of them matched the recommended criteria. In the vast majority of studies the self-assessments were made by way of questionnaires and instruments which evaluated the resolution of symptoms either jointly or separately with patient satisfaction related to the treatment. While most of these instruments were based on Likert-type scales, a very small number of the studies utilised visual analogue scales (VAS) in their assessments (Braithwaite 2015; Faghihi 2015;Jaque 2012; NCT02147691; Neuhaus 2009; Nymann 2010; Park 2016; Weissenbacher 2007).

There was wide diversity in the format of the questionnaires; many appeared to be unvalidated, used a range of scaling which offered a choice of from three to seven points on a Likert scale covering similar outcomes across the different questionnaires, and in several of them the physician and participant assessments were combined and expressed as composite scores. In the majority of the questionnaires it was not clear how the ratings correlated with the scaling of the items nor how reliable the interval-level measurements were between the individual items (see also van Zuuren 2013). Additionally, in a number of the patient satisfaction questionnaires the answer-categories appeared to have been phrased in such a way that only positive responses were possible, which would most likely lead

to biased assessments (Bjerke 1999; Breneman 1998; Lebwohl 1995; Maddin 1999; Sauder 1997).

The quality of life assessment tools which were utilised in 22 of the studies had been validated and were internationally recognised. Five studies used more than one instrument (Draelos 2015; EUCTR2006-001999-20-HU; Stein 2014a; Stein 2014b; Taieb 2015). The disease-specific RosaQoL was used in 11 studies (Bamford 2012; Chang 2012; Draelos 2013a; Draelos 2015; Luger 2015; Mrowietz 2018; NCT01426269; Stein 2014a; Stein 2014b; Taieb 2015; van der Linden 2017). Another disease-specific instrument, the Ocular Surface Disease Index (OSDI), was used in Arman 2015, Schechter 2009 and NCT00560703. The dermatology-specific instrument Dermatology Life Quality Index (DLQI) was used in 10 studies (Braithwaite 2015; Bribeche 2015; Draelos 2015; EUCTR2006-001999-20-HU; Jaque 2012; NCT02147691; Stein 2014a; Stein 2014b; Taieb 2015; Weissenbacher 2007). Only in the study of Sbidian 2016 the Skindex was used (Chren 1996) and two studies used a generic instrument, the EQ-5D (Draelos 2015; EUCTR2006-001999-20-HU). In all of these studies the investigators provided citations to reports indicating that the tools had been previously validated, as was specified in the PRO checklist (Table 5).

Adverse events were addressed in more than half (98) of the included studies, although often limited data were provided.

Physician-assessed rosacea severity was addressed in 117 studies. Most of the studies (109) assessed erythema or telangiectasia, or both. There were clearly more studies over the last 10 years focusing on erythema, which was assessed utilising mostly four to five-point Likert scales. The Clinician's Erythema Assessment with a grading scale from 0 (clear skin, no signs of erythema) to 4 (severe erythema, fiery redness) was used in 29 of the studies (Baumann 2018; Bribeche 2015; Del Rosso 2007a; Del Rosso 2007b; Del Rosso 2008; Di Nardo 2016; EUCTR2009-013111-35-DE; EUCTR2011-002057-65-DE; EUCTR2012-001044-22-SE; Fowler 2007; Fowler 2012a; Fowler 2012b; Fowler 2013a; Fowler 2013b; Jackson 2013; Kendall 2014; Kircik 2018; Krishna 2015; Leyden 2011; Layton 2015; Mrowietz 2018; NCT01426269; NCT01579084; NCT01735201; NCT02147691; Stein-Gold 2017; Two 2014; van der Linden 2017; Wolf 2006). The inter-rater and intra-rater reliability of this scale have recently been evaluated, and were demonstrated to be reliable when used by trained investigators (Tan 2014). In 86 studies clinician-assessed numbers of papules or pustules were used as an outcome in preference to a more patient-relevant measure such as participant assessment of appearance.

Funding

In 102 of the 152 included studies the investigators reported they had received funding, mostly from pharmaceutical companies, and declarations of competing interest were provided by the investigators in 61 of the 152 studies. In 20 instances we were not reassured that the funding support, or employment, of any of the investigators by the pharmaceutical company would not represent a potential source of bias. However, in most cases when studies were double or even triple-blinded and there was no evidence of selective reporting we did not consider funding an additional source of bias.

Excluded studies

Sixty-two studies were excluded in former versions of this review. Of these thirty-nine out of the total number of studies were excluded only after evaluation of their full-text copies and this was largely on the basis that they were non-randomised trials. Eleven studies were designated controlled clinical trials after contact with the investigators or following examination of the full-text of the reports, and the remaining 12 studies were excluded for other reasons (see 'Characteristics of excluded studies').

Risk of bias in included studies

Only 16 of the studies (Bleicher 1987; Chang 2012; Del Rosso 2007a; Del Rosso 2007b; Fowler 2012a; Fowler 2012b; Fowler 2013a; Fowler 2013b; Gollnick 2010; Jaque 2012; Kuang 2018; Layton 2015; Luger 2015; Mrowietz 2018; Stein 2014a; Stein 2014b) met all of the criteria across all of the domains in the Cochrane Collaboration's tool for assessing the risk of bias, and therefore these studies were considered to be at 'low risk of bias' (plausible bias unlikely to seriously alter the results). More than half of the studies (84) were categorised as 'unclear risk of bias' (plausible bias that raised some doubt about the results) because one or more criteria were assessed as unclear, and the remaining 52 studies were assessed as 'high risk of bias' (plausible bias that seriously weakened confidence in the results) because one or more of the criteria were not met. Further details of these assessments are available in the 'Risk of bias' table corresponding to each study in the 'Characteristics of included studies', and are also presented in the 'Risk of Bias' graph in Figure 2 and the 'Risk of Bias' summary in Figure 3.

Some of these assessments were to a certain extent based on the inadequate reporting of the criteria that are a prerequisite in the evaluation of methodological rigour in terms of trial design and conduct. Concealment of the allocation sequence and blinding are key domains in the assessment of risk of bias and most of the studies in this review provided insufficient detail to enable accurate judgements to be made. Protocol deviations, losses to follow-up with incomplete data, and subsequent per-protocol analyses, were other important sources of potential bias in a number of the included studies (see 'Risk of bias' table in 'Characteristics of included studies').

Allocation (selection bias)

The methods used to generate the allocation sequence and how the sequence was concealed, such that participants and investigators enrolling participants could not foresee the upcoming assignment, are the most important and sensitive indicators that bias has been minimised in a clinical trial (Schulz 1995).

Sequence generation

In 87 out of the 152 trials in this review the method of sequence generation was not described at all, or was at best unclear. One study (Espagne 1993) did not provide any reassurance that the allocation sequence was adequately generated and there was lack of evidence that any form of central randomisation and therefore we judged this domain as high risk of bias. In the remaining studies (64) the method used to generate the allocation sequence was described in sufficient detail; therefore this domain was judged as low risk of bias for these studies.

Allocation concealment

Concealment of the allocation sequence was reported adequately in only 45 of the trials and involved either a form of central allocation, was pharmacy-controlled or

was through the use of serially numbered opaque envelopes (see 'Risk of bias' tables in 'Characteristics of included studies'). The majority of studies received a judgement of unclear risk of bias for this domain and the investigators in three studies (Akhyani 2008; Bribeche 2015; Kim 2011) informed us that the providers of care had access to the computer-generated list, which we judged as high risk of bias.

Blinding (performance bias and detection bias)

Effective blinding was achieved in 61 of the 152 studies by the use of unmarked or identically appearing tubes, capsules or tablets. Some of the interventions were coded left or right for the within-patient studies. Blinding of outcome assessment was reported clearly in only 60 of the 152 included studies.

Incomplete outcome data (attrition bias)

In slightly more than half of the studies (88/152) incomplete outcome data appeared to have been adequately addressed and any missing outcome data were reasonably well-balanced across intervention groups with similar reasons for missing data across the groups. However, in 15 of the 106 studies the reporting of missing outcome data was largely inadequate. Attrition was one of the main causes of incomplete outcome data. The reasons for attrition varied and these were often dependent on the assignment of the participant to one or other particular group; thus, for example, more dropouts tended to occur in groups receiving the active intervention secondary to any side effects, as opposed to dropouts due to lack of efficacy in the corresponding placebo group. In 49 studies we judged this domain as at unclear risk of bias. When there were more than 20% of dropouts and no ITT analysis was applied, or when dropouts in one arm exceeded 20%, we judged this domain as at high risk of bias.

Selective reporting (reporting bias)

The reporting quality in most of the older studies was consistent with the editorial style and standards existing at the time of publication. Although the protocols for a great part of the included studies were not available, based on the information in the methods section of the reports 108 out of the 152 studies appeared to have reported all pre-specified outcomes and were therefore judged to be free of selective reporting. In the remaining studies, rarely was more than one outcome inadequately addressed, but in some instances these outcomes were reported only as a graph plot without any clearly discernible data. For 29 studies this domain was therefore judged as at unclear risk of bias. In those instances where one or more pre-specified primary or secondary outcomes were not addressed, or if the data analysis appeared to be flawed after it was re-analysed, we judged this domain as at a high risk of bias (15 studies).

Other potential sources of bias

Ninety-three of the studies appeared to be free of other forms of bias, whereas in 50 studies this domain was judged to be unclear. This judgement was based in part on an assessment of the extent to which funding by the sponsors may have had an impact on the results of a study. When there was no evidence of selection bias, nor performance or detection bias as double-blinding was ensured, we did not consider sponsoring or financial compensation a threat for other bias. However, if we were uncertain about selection bias and if the method of blinding was not described in

sufficient detail, we concluded that there was insufficient information to permit a clear judgement. Further reasons for possible other bias were: if groups were treated unequally or, in some of the older studies, if there was an inadequate wash-out period before the start of the study. Nine of the included studies were largely not free of other forms of bias. In most of these studies there was baseline imbalance between the groups, but in one study participants switched to the other treatment arm if they failed to respond to the allocated treatment, and one study was designed as a superiority trial but reported as a non-inferiority trial.

Effects of interventions

Thirty-four studies provided no usable or retrievable data and did not contribute further to the results of this review (see Table 6). The main reasons why data could not be used were: none of our outcomes were addressed, no separate data were reported for participants with rosacea, very limited or unusable data were reported (e.g. in abstracts to conference proceedings), or it was unclear how many participants were randomised to each treatment arm.

A substantial number of the studies included in this review were categorised as 'unclear' or 'high' risk of bias (see Figure 2 and Figure 3) and therefore caution is advised in the interpretation of their results and in the extrapolation of the effects of the interventions.

We have addressed our pre-specified outcomes under the following intervention headings.

- Topical interventions: studies with only topical brimonidine (comparisons 1 to 4).
- Topical interventions: studies with only topical oxymetazoline (comparison 5)
- Topical interventions: studies with only topical metronidazole (comparisons 6 to 10).
- Topical interventions: studies with only topical azelaic acid (comparisons 11 to 13).
- Topical interventions: studies with only topical ivermectin (comparison 14 to 15).
- Topical interventions: studies with topical metronidazole, azelaic acid, and/or other topical treatments (comparisons 16 to 55).
- Systemic interventions: studies with oral antibiotics (comparisons 56 to 64).
- Systemic interventions: studies with oral antibiotics combined with topical treatments (comparisons 65 to 71).
- Systemic interventions: studies with oral antibiotics compared with topical treatments (comparison 72 to 73).
- Studies with other systemic treatments (comparisons 74 to 83).
- Other interventions: studies with laser/light-based treatment (comparisons 84 to 88).
- Other treatments or combined treatments (89 to 93)

Topical interventions: studies with only topical brimonidine

(1) Various concentrations of topical brimonidine gel once daily versus vehicle once daily after a single application

In a single study assessed at low risk of bias, various concentrations of brimonidine gel (0.07%, 0.18% and 0.5%) were compared versus vehicle to determine which concentration was most effective for reducing erythema in rosacea after a single

application (Fowler 2012a). Brimonidine 0.5% tartrate equals brimonidine 0.33% topical gel.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

This outcome was evaluated with Patient's Self Assessment (PSA) scores ranging from 0 to 4 (clear to severe). A cumulative grade 1 improvement was experienced over 12 hours by 25/28 (89.3%) participants in the 0.07% group, 27/31 (87.1%) in the 0.18% group, 28/31 (90.3%) in the 0.5% group, and in 18/32 (56.3%) in the vehicle group. The highest concentration (0.5%) of brimonidine was more effective than vehicle in reducing erythema based on participants' assessments (RR 1.61, 95% CI 1.16 to 2.23; P = 0.004; NNTB = 3, 95% CI 3 to 8).

A cumulative grade 2 improvement over 12 hours was observed in 12/28 (42.9%) participants in the 0.07% group, 14/31 (45.9%) in the 0.18% group, 19/31 (61.3%) in the 0.5% group, and 7/32 in the vehicle group. The 0.5% brimonidine gel was more effective than vehicle (RR 2.80, 95% CI 1.37 to 5.71; P = 0.005; NNTB = 3, 95% CI 2 to 6).

Proportion of participants who reported an adverse event throughout the study period

Most of the adverse events were transient and mild in intensity, consisting of skin irritation, erythema, skin burning and dry skin. In the 0.07% group 5/28 participants reported an adverse event, 4/31 in the 0.18% group, 6/31 in the 0.5% group, and 6/32 in the vehicle group. Comparing the highest brimonidine concentration with vehicle there was no statistically significant difference in participants experiencing an adverse event between the two groups (RR 1.03, 95% 0.37 to 2.86).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Physicians used the Clinician's Erythema Assessment (CEA) scale (0 to 4, clear to severe) to assess this outcome. Cumulative 1 grade improvement over 12 hours was reached in 24/28 (85.7%) participants treated with 0.07%, in 28/31 (90.3%) treated with 0.18%, in 30/31 (96.7%) treated with 0.5%, and in 21/32 (65.6%) treated with vehicle. The physician-assessed changes in the comparison of the highest concentration (0.5%) with vehicle showed that brimonidine 0.5% was more effective (RR 1.47, 95% CI 1.14 to 1.91; P = 0.003; NNTB = 4, 95% CI 3 to 8).

A cumulative 2 grade improvement was seen in 14/28 (50%) of the participants in the 0.07% gel group, in 24/31 (77.4%) with 0.18%, in 24/31 (77.4%) with 0.5% gel, and in 9/32 (28.1%) with vehicle gel. Brimonidine 0.5% demonstrated greater efficacy than vehicle (RR 2.75, 95% CI 1.53 to 4.94; P = 0.0007; NNTB = 3, 95% CI 2 to 4). These physician-assessed changes were concordant with the assessments made by the participants.

Erythema was also assessed with a Chroma Meter, and the investigators reported that the values for brimonidine 0.5% were lower (investigators report P < 0.001) and that the onset of effect was within 30 minutes, reaching a maximum effect with a duration of between four to six hours, followed by a reappearance of the redness after eight hours.

- Lesion counts

No data were provided but investigators reported that "no aggravations in the severity of inflammatory lesions were observed".

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(2) Various concentrations of topical brimonidine gel versus vehicle, with different dosing regimens over four weeks

A dose-ranging study assessed as at low risk of bias to evaluate optimal concentration and dose regimen of brimonidine tartrate (BT) (0.18% once a day (QD), 0.18% twice a day (BID), 0.5% QD versus vehicle (QD and BID) (Fowler 2012b). We have only reported end-of-study data, that is at day 29.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

A 2 grade improvement on the Patient's Self Assessment (PSA) scale (0 to 4, clear to severe) was assessed every three hours up to 12 hours for participants treated with brimonidine 0.18% once daily, 0.18% twice daily, 0.5% once daily and vehicle once or twice daily. Of note, the participants in the vehicle twice daily group scored themselves better on the PSA scale than in the vehicle once daily group.

PSA 2 grade improvement	BT 0.18% QD	BT 0.18% BID	BT 0.5% QD	Vehicle QD	Vehicle BID
3 hours after application	17/54	20/54	25/53	7/55	11/53
6 hours after application	13/54	15/54	26/53	8/55	11/53
9 hours after application	9/54	19/54	22/53	5/55	13/53
12 hours after application	9/54	16/54	20/53	5/55	10/53

At three hours after application, brimonidine 0.5% was shown to be more effective than once daily vehicle (RR 3.71, 95% CI 1.75 to 7.83; P = 0.0006; NNTB = 4, 95% CI 2 to 6) and also when compared to vehicle twice daily (RR 2.27, 95% CI 1.25 to 4.13; P = 0.007; NNTB = 4, 95% CI 3 to 10). Brimonidine 0.5% was more effective than vehicle once or twice daily at every time point, even at 12 hours, compared to vehicle twice daily (RR 2.00, 95% 1.04 to 3.86; P = 0.04; NNTB = 6, 95% CI 3 to 50).

Proportion of participants who reported an adverse event throughout the study period

Adverse events were mild and transient with fewer participants reporting adverse events in the vehicle twice daily group. There were no meaningful changes in intraocular pressure, blood pressure or heart rate in any of the treatments. In the 0.18% once daily group 22/54 participants reported an adverse event, in the 0.18% twice daily group 25/54, in the 0.5% once daily group 24/53, in the vehicle once daily group 25/55, and in the vehicle twice daily group 17/53. There was no statistically significant difference in the proportion of participants that experienced an adverse event in the 0.5% brimonidine group versus vehicle twice daily group (RR 1.41, 95% CI 0.86 to 2.31).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome was assessed with the CEA scale (0 to 4, clear to severe), and a 2 grade improvement at the different time points was compared.

CEA 2 grade improvement	BT 0.18% QD	BT 0.18% BID	BT 0.5% QD	Vehicle QD	Vehicle BID
3 hours after application	21/54	22/54	27/53	12/55	9/53
6 hours after application	21/54	18/54	23/53	12/55	12/53
9 hours after application	20/54	23/54	26/53	12/55	15/53
12 hours after application	17/54	18/54	20/53	15/55	16/53

Three hours after application, the number of participants in the brimonidine 0.5% group achieving a 2 grade improvement on the CEA scale was statistically significant higher than in vehicle twice daily (RR 3.00, 95% CI 1.56 to 5.75; P = 0.0009; NNTB = 3, 95% CI 2 to 6). Participants in the brimonidine 0.5% group showed greater improvement than vehicle twice daily at all time points with the exception of 12 hours after application where it was not statistically significant (RR 1.25, 95% CI 0.73 to 2.14).

- Lesion counts

No data were provided but investigators reported that "no aggravations in the severity of inflammatory lesions were observed".

- Time needed until improvement

Not assessed.

- Duration of remission

In the four week follow-up no important exacerbation in facial erythema was observed in any of the groups. Isolated cases with worsening in PSA or CEA were seen but were not associated to a specific treatment group.

(3) Topical brimonidine 0.5% tartrate once daily versus vehicle once daily over four weeks

Two studies with similar study design assessed as at low risk of bias addressed this comparison (Fowler 2013a; Fowler 2013b) (see Summary of findings table 1). A third study (EUCTR2012-001044-22-SE) at unclear risk of bias has never been published and provided very limited data and the outcome data of participants and physicians were pooled and could therefore not be combined with the data of the two other studies. Brimonidine 0.5% tartrate equals brimonidine 0.33% topical gel.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Assessments with the PSA scale (0 to 4, clear to severe) were performed at day 1, 15 and 29, but we have chosen to report only day 29 data.

PSA 1 grade improvement **Fowler 2013a**	**BT 0.5%**	**Vehicle**	**PSA 2 grade improvement** **Fowler 2013a**	**BT 0.5%**	**Vehicle**
30 minutes after application	92/129	65/131	30 minutes after application	39/129	19/131
3 hours after application	99/129	61/131	3 hours after application	61/129	28/131
6 hours after application	96/129	63/131	6 hours after application	54/129	23/131
9 hours after application	93/129	59/131	9 hours after application	50/129	26/131
12 hours after application	85/129	59/131	12 hours after application	48/129	25/131
PSA 1 grade improvement **Fowler 2013b**	**BT 0.5%**	**Vehicle**	**PSA 2 grade improvement** **Fowler 2013b**	**BT 0.5%**	**Vehicle**

30 minutes after application	93/148	73/145	30 minutes after application	36/148	25/145
3 hours after application	112/148	77/145	3 hours after application	53/148	26/145
6 hours after application	106/148	72/145	6 hours after application	56/148	26/145
9 hours after application	106/148	71/145	9 hours after application	52/148	25/145
12 hours after application	94/148	78/145	12 hours after application	48/148	26/145

After 30 minutes a 1 grade improvement on the PSA scale (pooled data of Fowler 2013a; Fowler 2013b) was seen in 185/277participants (66.7%) in the brimonidine group compared to 138/276 with vehicle (50%)(RR 1.34, 95% CI 1.16 to 1.55; P < 0.0001; I^2 = 0%; NNTB = 6, 95% CI 4 to 11)(Analysis 1.1). A 2 grade improvement was observed in 75/277 participants (27%) in the brimonidine group and in 44/276 with vehicle (15.9%)(RR 1.70, 95% CI 1.16 to 2.48; P = 0.007; I^2 = 23%; NNTB = 9, 95% CI 6 to 23)(Analysis 1.2)

We have chosen to not report RR at every time point and have only reported the data three hours after application as it is fairly clear that the effect of brimonidine diminishes progressively over the 12 hour period. Three hours after application a 1 grade improvement on the PSA scale was reported in 211/277 treated with brimonidine and in 138/276 with vehicle (RR 1.52, 95% CI 1.32 to 1.75; P < 0.00001; I^2 = 9%; NNTB = 4, 95% CI 3 to 5)(Analysis 1.3). Brimonidine was more effective than vehicle at each time point in both studies except at 12 hours in Fowler 2013b.

A statistically significant 2 grade improvement in PSA was noticed in the brimonidine group three hours after application (RR 2.11, 95% CI 1.60 to 2.78; P < 0.00001; I^2 = 0%; NNTB = 5, 95% CI 3 to 7)(Analysis 1.4). At each time point in both studies brimonidine was significantly more effective than vehicle.

EUCTR2012-001044-22-SE used a composite score in which patients and physicians assessments were combined (composite success is defined as a 1 grade improvement in both PSA and CEA). At 30 min 27/57 (47.3%) in the brimonidine group reached composite success versus 7/55 (12.7%) with vehicle (RR 3.72, 95% CI 1.77 to 7.83; P = 0.0005; NNTB = 3, 95% CI 2 to 5). After three hours 48/57 (84.2%) in the brimonidine group had a composite success versus 32/55 (58.1%) with vehicle (RR 1.45, 95% CI 1.13 to 1.86; P = 0.004; NNTB = 4, 95% CI 2 to 10).

Proportion of participants who reported an adverse event throughout the study period

In the brimonidine group (Fowler 2013a; Fowler 2013b) adverse events were reported in 88/277 participants compared to 68/276 in the vehicle group (RR 1.29, 95% CI 0.98 to 1.69; I^2 = 0%)(Analysis 1.5). In both studies (Fowler 2013a; Fowler 2013b) adverse events were mild and transient. Most frequently reported were worsening of erythema, flushing, pruritus and skin irritation. The number of participants experiencing an adverse event in the brimonidine group (17/57) of study EUCTR2012-001044-22-SE was much higher than in the vehicle group (3/55) (RR 5.47, 95% CI 1.70 to 17.62; P = 0.004; NNTH = 4, 95% 3 to 9). Combining these

data with the data of the other two studies would cause too much heterogeneity (I^2 = 68%) and therefore these are not pooled.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

No data were reported for both studies (Fowler 2013a; Fowler 2013b) other than "no aggravations in the severity of telangiectasia, IGA or inflammatory lesion counts were observed during either the treatment or follow-up phase of either study".

- Assessment of erythema or telangiectasia, or both, at end of study

As with the participants' assessments we chose to report the end of study (day 29) data.

CEA grade 1 improvement **Fowler 2013a**	**BT 0.5%**	**Vehicle**	**CEA grade 2 improvement** **Fowler 2013a**	**BT 0.5%**	**Vehicle**
30 minutes after application	87/129	57/131	30 minutes after application	31/129	11/131
3 hours after application	105/129	64/131	3 hours after application	61/129	22/131
6 hours after application	107/129	70/131	6 hours after application	54/129	23/131
9 hours after application	98/129	58/131	9 hours after application	46/129	22/131
12 hours after application	94/129	63/131	12 hours after application	36/129	15/131

CEA grade 1 improvement **Fowler 2013b**	**BT 0.5%**	**Vehicle**	**CEA grade 2 improvement** **Fowler 2013b**	**BT 0.5%**	**Vehicle**
30 minutes after application	96/148	70/145	30 minutes after application	36/148	25/145
3 hours after application	119/148	78/145	3 hours after application	60/148	33/145
6 hours after application	111/148	85/145	6 hours after application	55/148	28/145
9 hours after application	112/148	81/145	9 hours after application	44/148	29/145
12 hours after application	95/148	72/145	12 hours after application	48/148	33/145

Physicians' assessments at 30 minutes after application recorded a grade 1 improvement in the CEA scale (0 to 4,clear to severe) in 183/277 (66.1%) participants in the brimonidine group versus 127/276 (46.0%) in the vehicle group, which was statistically significant in favour of brimonidine, and in concordance with

the assessments made by the participants (RR 1.43, 95% CI 1.23 to 1.67; P < 0.00001; I^2 = 0%; NNTB = 5, 95% CI 4 to 8)(Analysis 1.6). A grade 2 improvement 30 minutes after application was seen in 31/129 (24%) participants treated with brimonidine versus 11/131 (8.3%) treated with vehicle (RR 2.86, 95% CI 1.50 to 5.45; P = 0.001; NNTB = 6, 95% CI 4 to 15). This was not confirmed in Fowler 2013b (RR 1.41, 95% CI 0.89 to 2.23). Data were not pooled as there was unexplainable heterogeneity (I^2 = 68%).

At three hours after application a grade 1 improvement in CEA was seen in 224/277 (80.9%) in the brimonidine group versus 142/276 (51.4%) in the vehicle group (RR 1.57, 95% CI 1.38 to 1.78; P < 0.00001; I^2 = 0%; NNTB = 4, 95% CI 3 to 6). At all time points in both studies brimonidine was more effective than vehicle in reaching a grade 1 improvement on the CEA scale.

At three hours after application, a grade 2 improvement in CEA was observed in 121/277 (43.7%) in the brimonidine group versus 55/276 (19.9%) in the vehicle group (RR 2.21, 95% CI 1.41 to 3.46; P = 0.0005; I^2 = 62%; NNTB = 4, 95% CI 3 to 6)(Analysis 1.8), which was statistically significant in favour of brimonidine. In both studies there was a statistically significant difference favouring brimonidine at all time points except at 30 minutes, 9 and 12 hours in Fowler 2013b,

- Lesion counts

See above, no aggravations.

- Time needed until improvement

Improvement was seen within 30 minutes.

- Duration of remission

There was no rebound or worsening of erythema after treatment cessation in comparison to baseline assessments.

(4) Brimonidine 0.33% once daily versus vehicle once daily over eight days

One study assessed as at low risk of bias examined the effect of brimonidine 0.33% gel versus vehicle on erythema and considered mainly patient-reported outcomes (Layton 2015).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Patient-reported outcomes were assessed using the following instruments: a 'facial redness questionnaire' that addressed satisfaction, embarrassment and self-consciousness; a 'subject satisfaction questionnaire' which addressed satisfaction with overall treatment, improvement of facial redness and time it took to work; and a 'Subject Diary' (treatment compliance and redness control). PSA was also

addressed, but no exact data were provided and it was reported that the mean scores were statistically significantly lower in the brimonidine group.

The results of the facial redness questionnaire at baseline showed that a small number of participants, 2/48 in the brimonidine group and 0/44 in the vehicle group, were satisfied to very satisfied with their appearance. At day 8 (end of study) 18/48 (36.9%) in the brimonidine group were satisfied or very satisfied compared to 9/44 (21.5%) in the vehicle group (RR 1.83, 95% CI 0.92 to 3.65; P = 0.08, however the investigators reported P < 0.05). Participant assessments included perceptions of embarrassment, such that at baseline 44/48 (91.7%) in the brimonidine group felt embarrassed and in the vehicle group 42/44 (95.5%). At day 8 the figures were 34/48 (71.7%) compared to 40/44 (90.4%) respectively (RR 0.78, 95% CI 0.64 to 0.96; P = 0.02; NNTB = 5, 95% CI 3 to 20). Feeling self conscious was also evaluated by the participants, and at baseline 40/48 (83.3%) in the brimonidine group felt self conscious and 41/44 (93.1%) in the vehicle group. At day 8 35/48 (73.4%) in the brimonidine group and 39/44 (88%) in the vehicle group felt self conscious (RR 0.82, 95% CI 0.67 to 1.01; P = 0.06).

The results of the Subject Satisfaction Questionnaire (SSQ) (feedback on treatment regimen) revealed that 25/48 (52.2%) in the brimonidine group were either satisfied or very satisfied with the overall treatment compared to 14/44 (30.9%) in the vehicle group (RR 1.64, 95% CI 0.98 to 2.73; P = 0.06). Improvement in facial redness was scored satisfied or very satisfied in 21/48 (43.5%) in the active treatment group versus 8/44 (19%) in the vehicle group (RR 2.41, 95% CI 1.19 to 4.87; P = 0.01; NNTB = 4, 95% CI 3 to 15). The time taken to reach an effect was assessed by the participants and 22/48 (45.6%) in the brimonidine group were satisfied to very satisfied compared to 9/44 (21.4%) in the vehicle group (RR 2.24, 95% CI 1.16 to 4.33; P = 0.02; NNTB = 4, 95% CI 3 to 15).

The participant diaries revealed that 39/48 (81.1%) of the participants in the brimonidine group were able to control their facial redness that day compared to 18/44 (40.6%) participants in the control group (RR 1.99, 95% CI 1.36 to 2.90; P = 0.0004; NNTB = 3, 95% CI 2 to 5).

On day 1 a PSA grade 1 improvement with brimonidine was seen in 38/48 (79.2%) compared to 18/44 (41.9%) on vehicle (RR 1.94, 95% CI 1.32 to 2.84; P = 0.0007; NNTB = 3, 95% CI 2 to 5). On day 2 the numbers were 42/48 (87.2%) versus 18/44 (41.9%)(RR 2.14, 95% CI 1.48 to 3.10; P = 0.0001; NNTB = 2, 95% CI 2 to 3). On day 8 37/48 (76.1%) in the brimonidine group versus 21/44 (47.6%) in the vehicle group reported a PSA grade 1 improvement (RR 1.62, 95% CI 1.14 to 2.28; P = 0.007; NNTB = 3, 95% CI 2 to 10).

Proportion of participants who reported an adverse event throughout the study period

The adverse events that were reported were mild and transient worsening of erythema or worsening of rosacea, more of which were reported in the brimonidine group, with 14/48 participants in the brimonidine group reporting an adverse event versus 7/44 in the vehicle group (RR 1.83, 95% CI 0.82 to 4.12).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

  On both day 1 and 2 a CEA grade 1 improvement was seen in 38/48 (79.2%) participants on brimonidine compared to 17/44 (38.6) using vehicle (RR 2.05, 95% CI 1.37 to 3.06; P = 0.0004; NNTB = 2, 95% CI 2 to 5). On day 8 the numbers were 34/48 (70.8%) versus 16/44 (36.4%)(RR 1.95, 95% CI 1.27 to 3.00; P = 0.002; NNTB = 3, 95% CI 2 to 7).

- Lesion counts

  Not assessed.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

Topical interventions: studies with only topical oxymetazoline

(5) Topical oxymetazoline 1% cream once daily versus vehicle once daily over four weeks

Two studies with similar study design assessed at unclear risk of bias addressed this comparison (Baumann 2018; Kircik 2018). See Summary of findings table 2.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Participants assessed improvement on the Subjective Self-Assessment scale (5 point Likert scale; 0 = no signs of unwanted redness, 4 = severe redness).

SSA grade 2 improvement **Baumann 2018**	**Oxymetazoline 1%**	**Vehicle**	**SSA grade 2 improvement** **Kircik 2018**	**Oxymetazoline 1%**	**Vehicle**
3 hours after application	54/224	35/221	3 hours after application	45/222	24/218
6 hours after application	56/224	32/221	6 hours after application	52/222	28/218
9 hours after application	49/224	35/221	9 hours after application	52/222	26/218
12 hours after application	53/224	35/221	12 hours after application	56/222	25/218

As with the brimonidine comparison, we have chosen to not report RR at every time point, and have only reported the data three hours after application. Three hours after application a grade 2 improvement on the SSA scale was reported in 99/446 (22%) treated with oxymetazoline and in 59/439 (13.4%) treated with vehicle (RR 1.65, 95% CI 1.23 to 2.21; P = 0.0009; I^2 = 0%; NNTB = 11, 95% CI 7 to 27)(Analysis 2.1). Oxymetazoline was more effective than vehicle at each time point in both studies except at nine hours in Baumann 2018 where it was not statistically significant.

Proportion of participants who reported an adverse event throughout the study period

Data were presented in both studies as number of adverse events and not as proportion of participants experiencing an adverse event. In the oxymetazoline group 94 adverse events were reported in 446 participants versus 70 in 439 participants in the vehicle group (RR 1.32, 95% CI 0.97 to 1.78; I^2 = 13%)(Analysis 2.2). Application site dermatitis, pruritus, and erythema, worsening of inflammatory lesions and headache were the most reported adverse events and were considered mild or moderate in severity. During the 29 days follow-up period six patients in the oxymetazoline group experienced worsening erythema (rebound) versus two in the vehicle group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

As with the participants' assessments we chose to report the end of study (day 29) data. Physicians used the Clinician's Erythema Assessment (CEA) scale (0 to 4, clear to severe erythema) to assess this outcome.

CEA grade 2 improvement **Baumann 2018**	Oxymetazoline 1%	Vehicle	CEA grade 2 improvement **Kircik 2018**	Oxymetazoline 1%	Vehicle
3 hours after application	99/224	54/221	3 hours after application	87/222	50/218
6 hours after application	80/224	51/221	6 hours after application	81/222	41/218
9 hours after application	84/224	54/221	9 hours after application	75/222	42/218
12 hours after application	65/224	47/221	12 hours after application	57/222	38/218

At three hours after application a grade 2 improvement in CEA was seen in 186/446 (41.7%) in the oxymetazoline group versus 104/439 (23.7%) in the vehicle group (RR 1.76, 95% CI 1.44 to 2.15; P < 0.00001; I^2 = 0%; NNTB = 6, 95% CI 4 to 8)(Analysis 2.3). At all time points in both studies oxymetazoline was more effective

than vehicle in reaching a grade 2 improvement on the CEA scale except at 12 hours in the study of Baumann 2018 where it was not statistically significant.

- Lesion counts

  Not assessed

- Time needed until improvement

  Not assessed.

- Duration of remission

  Duration of remission is not assessed. However, during the 29 days follow-up period six patients in the oxymetazoline group experienced worsening erythema (rebound) versus two in the vehicle group.

Topical interventions: studies with only topical metronidazole

(6) Topical metronidazole versus placebo

Nine trials at low to high risk of bias provided data for this comparison (Barnhorst 1996; Beutner 2005; Bitar 1990; Bjerke 1989; Bleicher 1987; Breneman 1998; Dahl 1998; Koçak 2002; Nielsen 1983a), see also Summary of findings table 3. Both interventions were applied once or twice daily across the studies

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Only three studies reported relevant data and although these could not be pooled for this outcome they provided some evidence that metronidazole was more effective than placebo.

In Bjerke 1989 43 out of 50 participants in the metronidazole group considered themselves improved compared with 24 out of 47 in the placebo group (RR 1.68, 95% CI 1.25 to 2.28; P = 0.0007; NNTB = 3, 95% CI 2 to 6); and similarly in Nielsen 1983a 25 out of 41 (metronidazole group) versus 8 out of 40 (placebo) (RR 3.05, 95% CI 1.57 to 5.94; P = 0.001; NNTB = 3, 95% CI 2 to 5). The data of these two studies could not be pooled (too much heterogeneity I^2 = 65%). A within-participant design was used in Bleicher 1987, which did not report the analysis adjusted appropriately for this design, therefore pooling of data with the other two studies was not possible. In this study the majority (28/37) of participants reported a greater improvement on the metronidazole treated side than on the placebo side (4/37), RR of 7.

Proportion of participants who reported an adverse event throughout the study period

Six of the studies (Beutner 2005; Bitar 1990; Bjerke 1989; Breneman 1998; Koçak 2002; Nielsen 1983a) provided adequate data for this outcome. In the three-armed study of Beutner 2005 the proportion of participants reporting adverse events in the two active treatment arms were similar (32% to 33%) and, therefore, following

statistical advice these totals were combined and entered into the analysis. The number of participants in the metronidazole group compared to the placebo group who experienced adverse events (RR 1.19, 95% CI 0.94 to 1.51; I^2 = 0%) was not significantly different across the six studies and in most instances these adverse events were mild and consisted of pruritus, skin irritation and dry skin. See Analysis 3.1.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The pooled data from three studies (Bjerke 1989; Breneman 1998; Nielsen 1983a) for this outcome pointed to an improvement in rosacea severity in the active intervention group, which was largely in agreement with the participant-assessed outcomes for this comparison. Topical metronidazole was more effective than placebo (RR 1.98, 95% CI 1.29 to 3.02; P = 0.002; NNTB = 4, 95% CI 3 to 10). Heterogeneity between the studies was assessed with I^2 = 44%. See Analysis 3.2.

Although a different rating scale (1 to 7, worst = 7) was used in Bitar 1990, the results were not dissimilar to those in the other three studies. In this study the mean rating in severity in the metronidazole group (n = 50) was 2.80 (SD 1.41) and 3.30 (SD 1.41) in the placebo group (n = 50) with a mean difference (MD) of -0.50 (95% CI -1.05 to 0.05; P = 0.08).
In the split-face study (Bleicher 1987) 29/37 participants were assessed as improved on the metronidazole treated side compared with 1/37 on the placebo side (RR = 29).

Only one study assessed ocular rosacea (Barnhorst 1996) but the data as reported were unusable and not amenable to re-analysis. See Analysis 3.3.

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema was assessed in seven studies (Bitar 1990; Bjerke 1989; Bleicher 1987; Breneman 1998; Dahl 1998; Koçak 2002; Nielsen 1983a). However, in all of these studies this outcome was inadequately reported that is standard deviations were missing or data were given without baseline values except for the three-armed study of Koçak 2002. In this study the mean change from baseline in erythema score (0 to 3) was -1.45 (SD 2.00) in the metronidazole group compared to -0.05 (SD 1.39) in the placebo group with a MD of -1.40 (95% CI -2.47 to -0.33; P = 0.01). Bjerke 1989; Bleicher 1987; Breneman 1998; Dahl 1998 and Nielsen 1983a also showed a greater reduction of erythema with metronidazole treatment (see Analysis 3.3).

- Lesion counts

In eight of the studies these outcomes were reported as continuous data but without the corresponding SDs and the data were skewed, that is not normally distributed. Although the data analysis in these studies was potentially flawed, it did nevertheless provide some supporting evidence of a positive treatment effect of metronidazole over placebo (see Analysis 3.3).

- Time needed until improvement

This was not a pre-specified outcome for any of the studies but based on interim data from five of the studies (Bitar 1990; Bjerke 1989; Bleicher 1987; Breneman 1998; Nielsen 1983a) a noticeable improvement was seen at around four weeks.

- Duration of remission

Only one trial (Dahl 1998) addressed this outcome and demonstrated that continued treatment with metronidazole gel alone could maintain remission (initiated by tetracycline and topical metronidazole) of moderate to severe rosacea.

(7) Metronidazole and sunscreen sun protection factor (SPF) 15 twice daily versus vehicle twice daily

Only one study at high risk of bias with a 26% dropout rate and skewed data provided data for this comparison (Tan 2002).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Although the data for this outcome were presented as graph plots and were largely indiscernible, the investigators reported that there was a more noticeable improvement in rosacea severity in the metronidazole combined with sunscreen SPF 15 group than in the vehicle group (P = 0.0002).

Proportion of participants who reported an adverse event throughout the study period

A small number of participants reported adverse events and these were similar in both groups: 1/61 in the metronidazole group and 3/59 in the vehicle (RR 0.32, 95% CI 0.03 to 3.01). There was no statistically significant difference in local tolerance of the intervention between the two groups.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In the metronidazole group 17/61 had clearing or marked improvement compared to 2/59 in the vehicle group (RR 8.22, 95% CI 1.99 to 34.04; P = 0.004; NNTB = 5, 95% CI 3 to 9).

- Assessment of erythema or telangiectasia, or both, at end of study

The mean reduction in erythema at the end of the study, measured on a 4-point scale (4 = severe) was 0.89 (SD 0.6) in the treatment group and 0.58 (SD 0.13) in the vehicle group (P = 0.001), however these data were skewed. Telangiectasia (on a 4-point scale) were reduced by 0.3 (SD 0.53) in the metronidazole + sunscreen SPF 15 group compared to 0.07 (SD 0.47) in the vehicle group (P = 0.03).

- Lesion counts

There was a reduction in the mean number of lesions, 13.6 (SD 17.25) in the active intervention group compared with vehicle, 4.6 (SD 12.28) (MD -9.00, 95% CI -15.23 to -2.77). However the data were incomplete and skewed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(8) Metronidazole 0.75% cream once daily versus metronidazole 1% cream once daily

Only one study assessed as at high risk of bias compared these interventions and provided relevant outcome data (Dahl 2001).

Primary outcomes

Change in HRQOL at end of study

Not assessed

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Adverse events were mild and comparable in both groups, 14/36 compared to 15/36 (RR 0.93, 95% CI 0.53 to 1.64).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

There was no statistically significant difference in assessments between the two groups at the end of the study. Twenty of the 36 participants using the 0.75% metronidazole cream were clear or nearly clear at the end of the study compared with 13 out of 36 in the 1% cream group (RR 1.54, 95% CI 0.91 to 2.60).

- Assessment of erythema or telangiectasia, or both, at end of study

The percentage change in the total erythema severity score from baseline to endpoint was comparable (range 25% to 30%) with a difference that was not statistically significant between the two groups.

- Lesion counts

The overall reductions in lesion counts were similar in both groups at the end of the study (62% versus 60%).

- Time needed until improvement

After six weeks both groups showed a reduction in inflammatory lesion counts of around 50%.

- Duration of remission

Not assessed.

(9) Metronidazole 0.75% cream twice daily versus 0.75% gel twice daily

The investigators in a single study assessed as at a high risk of bias compared these two interventions and were unable to provide any additional data over and above what had been reported in the poster (Dreno 1998).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

No serious adverse events were reported, with no details about the number of participants reporting side effects.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Although this was a pre-specified outcome it was not addressed (see 'Risk of Bias' under Characteristics of included studies for this study).

- Assessment of erythema or telangiectasia, or both, at end of study

The investigators reported "both erythema and telangiectasia scores were not significantly different at evaluation time".

- Lesion count

The reduction in lesion count was similar in both the cream and gel groups (61.3% in the cream group versus 63.5% in the gel group).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(10) Metronidazole 0.75% in microemulsion twice daily versus metronidazole 0.75% in commercial gel twice daily

One within-participant study assessed as at unclear risk of bias, evaluated this comparison (Tirnaksiz 2012).

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

There were no side effects on either treated side of the face.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

The mean change from baseline in erythema (0 to 3, with 3 being worse) was -1.75 (SD 0.49) for the microemulsion group compared to -0.91 (SD 0.60) in the commercial gel group with a MD of -0.84, however no 95% CI or P value could be calculated as we were not able to adjust for within-participant variability. Telangiectasia were also scored on a scale from 0 to 3 and the mean change from baseline was -1.28 (SD 0.37) for the microemulsion group versus -0.41 (SD 0.65) in the commercial gel group, with a MD of -0.87; like in the assessment of erythema no 95% CI nor P value could be calculated.

- Lesion counts

The mean change from baseline in lesion counts was -2.18 (SD 2.02) in the microemulsion group compared to -1.18 (SD 1.24) in the commercial gel group, with a MD of -1.0, but we were not able to adjust for within-participant variability and therefore no 95% CI and P value could be calculated.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Topical interventions: studies with only topical azelaic acid

(11) Azelaic acid twice daily versus twice daily vehicle

This comparison was based on seven trials assessed as at unclear risk of bias (Bjerke 1999; Carmichael 1993; Draelos 2013a; Draelos 2015; NCT00617903; Thiboutot 2003a; Thiboutot 2003b), see also Summary of findings table 4.

Primary outcomes

Change in HRQOL at end of study

This outcome was addressed in Draelos 2013a and Draelos 2015. Only limited data were provided in Draelos 2013a where investigators reported "there were no statistically significant differences between the two groups in end-of-treatment or end-of-study erythema, telangiectasia, or QOL scores". E-mail correspondence with the trialists yielded no additional details. In Draelos 2015 three different instruments were used to measure this outcome (data in subsequent paper (Tyring 2016) which is listed under the primary reference Draelos 2015). The Dermatology Quality of Life Index (DLQI) was used as well as the Rosacea Quality of Life Index (RosaQOL) and the EuroQOL (5-dimension 5-level questionnaire (EQ-5D-5L)). At baseline the DLQI was 5.4 in both groups and decreased by 2.6 in the azelaic group compared to 2.1 with vehicle. The authors reported "P = 0.018", but a difference of 0.5 on the DLQI is not clinically important (Basra 2008; Basra 2015). Improvements were also seen in the RosaQOL, but less in the EuroQOL. The authors reported regarding RosaQoL"(6.8 vs 6.4; P =.67), while EQ-5D-5L scores changed minimally from baseline (0.006 vs 0.007; P =.50)."

Participant-assessed changes in rosacea severity at end of study

Six studies reported this outcome. Pooled data from these indicated improvement in rosacea severity with rates of participant-assessed complete remission or marked improvement, as 60% to 80% in the azelaic acid group as compared with 45% to 55% with vehicle (RR 1.40, 95% CI 1.28 to 1.53; P < 0.00001; NNTB = 6, 95% CI 5 to 8). Heterogeneity between the studies was assessed with I^2 = 0%. See Analysis 4.1.

Proportion of participants who reported an adverse event throughout the study period

There was no statistically significant difference in the number of adverse events reported by participants in four pooled studies (Bjerke 1999; Draelos 2013a; Draelos 2015; NCT00617903); 200/799 with azelaic acid compared to 143/760 with vehicle (RR 1.29, 95% CI 0.92 to 1.81; I^2 = 46%)(see Analysis 4.2). In the Carmichael 1993 study, 24/33 participants reported adverse events on the side treated with azelaic acid and 19/33 on the side treated with vehicle. The adverse events were transient and of mild to moderate intensity, with burning, stinging or irritation most commonly.

Adverse events data in Thiboutot 2003a and Thiboutot 2003b were combined and inadequately reported with minimal data available for adverse events in the vehicle group. Adverse events related to azelaic acid were reported for 18% in Thiboutot 2003a and 8.4% in Thiboutot 2003b. Burning, stinging and itching were more frequent in the azelaic acid treated group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Data from six studies showed that azelaic acid was more effective than vehicle with minimal to no lesions for 556/1068 in the azelaic acid group compared with 398/1012 in the vehicle group (RR 1.30, 95% CI 1.19 to 1.43; P < 0.00001; I^2 = 5%; NNTB = 8, 95% CI 6 to 12). See Analysis 4.3.

In the single within-patient study (Carmichael 1993), 16/33 of the participants showed an improvement, based on a Likert scale rating, on the azelaic acid treated side compared with 1/33 on the vehicle treated side. There was no visible

improvement in the remaining 16 (P < 0.001, McNemar's test). There was an overall improvement with complete remission or marked improvement in 30/33 sides treated with azelaic acid compared to 11/33 of the sides treated with vehicle; crude RR of 2.72. The report did not provide SDs for any of the outcomes data and it was not possible to calculate the RR, therefore the data were not pooled with the other studies evaluating this comparison.

- Assessment of erythema or telangiectasia, or both, at end of study

  There was moderate to no effect in improvement of erythema and telangiectasia in six of the studies (see Analysis 4.4). Only the study of Draelos 2015 showed that 258/420 (61.5%) of the participants in the azelaic acid foam group had an improvement of the erythema compared with 204/398 (51.3%) in the vehicle foam group (RR 1.20, 95% CI 1.06 to 1.35; P = 0.004; NNTB = 10, 95% CI 6 to 29).

- Lesion counts

  The mean difference was -3.00 inflammatory lesions (95% CI -4.13 to -1.86; P < 0.0001; I^2 = 9%) in favour of azelaic acid but a difference of three inflammatory lesions does not seem important. See Analysis 4.5. No SDs were reported for these outcomes in Bjerke 1999; Thiboutot 2003a and Thiboutot 2003b, and in Carmichael 1993 the data were skewed. See Analysis 4.4.

- Time needed until improvement

  This was not a pre-specified outcome in any of the studies but all studies showed clear improvement after three to six weeks.

- Duration of remission

  Not assessed.

(12) Azelaic acid 15% gel once daily versus azelaic acid 15% gel twice daily

A single study at high risk of bias compared the safety and effectiveness of azelaic acid 15% gel applied once daily versus twice daily (Thiboutot 2008). No statistically significant differences were reported in any of the efficacy endpoints between the two regimens.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

At end of study 29/45 participants on the once daily regimen considered themselves improved, which they rated as marked to excellent, compared to 27/47 on the twice daily regimen (RR 1.12, 95% CI 0.81 to 1.56).

Proportion of participants who reported an adverse event throughout the study period

Number of participants experiencing adverse events was comparable 18/45 in the once daily group versus 17/47 with twice daily (RR 1.11, 95% CI 0.66 to 1.86), with pain, pruritus and burning sensations being the most frequently reported.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

There was no statistically significant difference between the two treatment regimens: 20/45 participants with single daily application improved versus 22/47 with twice daily (RR 0.95, 95% CI 0.61 to 1.48). Treatment success, defined as clear or minimal lesions, was achieved in 13/45 in the once daily group versus 15/47 with twice daily group (RR 0.91, 95% CI 0.49 to 1.68).

- Assessment of erythema or telangiectasia, or both, at end of study

No exact data were provided but the investigators stated that "treatment with AzA 15% gel led to a decrease in the intensity of erythema over the course of the study with no statistically significant difference between the QD group and BID group", where QD is treatment once daily and BID twice daily. Six participants in both groups showed an improvement in telangiectasia (RR 1.04, 95% CI 0.36 to 3.00).

- Lesion counts

Mean change from baseline in the once daily group in lesion counts was -11.60 (SD 4.98) compared to -13.80 (SD 4.65) for the twice daily group (MD 2.20, 95% CI 0.23 to 4.17; P = 0.03). This difference was statistically significant but not clinically important.

- Time needed until improvement

Improvement was seen from week four in both groups.

- Duration of remission

Not assessed.

(13) Azelaic acid 15% gel twice daily as maintenance therapy versus vehicle twice daily

Thiboutot 2009 was a two-phase study in which participants, demonstrating a level of treatment effectiveness at week 12, were randomised to receive either azelaic acid gel or its vehicle twice daily as maintenance therapy. We have only included data from the maintenance phase (second phase) of this study. The study was assessed at high risk of bias due to selective reporting.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

This was a predefined outcome but was not addressed and we therefore judged the domain for selective reporting as at a high risk of bias (see 'Risk of Bias' under Characteristics of included studies for this study).

Proportion of participants who reported an adverse event throughout the study period

Adverse events were reported in 22/67 using azelaic acid and in 20/69 in the vehicle-only group (RR 1.13, 95% CI 0.68 to 1.87).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Success determined by an IGA of clear, minimal or mild was reported for 39/67 in the azelaic acid group and for 31/69 in the vehicle-only group (RR 1.30, 95% CI 0.93 to 1.80). The differences was no statistically significant.

- Assessment of erythema or telangiectasia, or both, at end of study

No exact data were provided, but the investigators stated that no change in erythema or in telangiectasia was observed in either group.

- Lesion counts

The increase in mean inflammatory lesion count in the maintenance phase was 5.5 with azelaic acid and 7.5 (data estimated from figure) with vehicle. Investigators stated that P = 0.03. However, this difference of two lesions between groups was not considered to be clinically important.

- Time needed until improvement

Not applicable.

- Duration of remission

Relapse rates were 17/67 in the azelaic acid group compared to 24/69 with vehicle (RR 0.73, 95% CI 0.43 to 1.23) with no statistically significant difference between the two groups.

Topical interventions: studies with only topical ivermectin

(14) Various concentrations of topical ivermectin cream versus vehicle, with different dosing regimens over 12 weeks

One dose-finding study (EUCTR2006-001999-20-HU) assessed as unclear risk of bias evaluated the efficacy and safety of three concentrations (1%, 0.3% and 0.1%) of ivermectin once or twice daily versus vehicle and versus metronidazole (latter will be discussed in comparison 20)

Primary outcomes

Change in HRQOL at end of study

Only a generic comment was made by the investigators "The patient’s quality of life demonstrated a dose related increase of overall quality of life per DLQI".

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

The number of participants reporting an adverse event was highest in the twice daily 1% ivermectin group. In the 0.1% once daily ivermectin group 21/51 reported an adverse event (41.1%), in the 0.3% once daily ivermectin group 23/47 (48.9%), in the 1% once daily ivermectin group 21/52 (40.3%), in the 1% twice daily group 28/48 (58.3%) and in the vehicle group 26/50 (52%). Side effects reported were irritative dermatitis, watery eyes, burning of eyes, facial burning and pruritus.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

After 12 weeks investigators evaluated improvement with an Investigator Global Assessment score 1, which was a composite score of erythema and inflammatory lesions. Treatment success was defined clear or almost clear on a 5 point Likert scale. In the 0.1% once daily group 32/51 (62.7%) were considered to have reached treatment success compared with 30/47 (63.8%) with 0.3% once daily, 34/52 (65.4%) with 1% once daily, 34/48 (70.8%) with 1% twice daily and 21/50 (42%) with vehicle.

- Assessment of erythema or telangiectasia, or both, at end of study

No exact data are provided but the investigators reported "the difference in decrease in erythema scores between any of the CD5024 (*ivermectin*) doses and the vehicle was not statistically significant; mean score changes ranged from -0.7 (vehicle) to -1.0 (CD5024 1% BID). The telangiectasia severity score remained almost unchanged in all treatment groups"

- Lesion counts

Percent change in lesions count at week 12 showed a dose-response relationship with reduction of 65.5% (SD 31.5) in the 0.1% once daily group, 67.5% (SD 36.8) in the 0.3% once daily group, 70.0% (SD 38.1) in the 1% once daily group, 69.2% (SD 34.3) in the 1% twice daily group and 46.5% (SD 59.4) in the vehicle group.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(15) Topical ivermectin 1% once daily versus vehicle once daily

Two studies at low risk of bias addressed this comparison (Stein 2014a; Stein 2014b), as well as one study at unclear risk of bias which has not yet been published (EUCTR2010-018319-13-DE). See also Summary of findings table 5.

Primary outcomes

Change in HRQOL at end of study

This outcome was evaluated in Stein 2014a and Stein 2014b. More participants in the ivermectin group experienced improvements in HRQOL at the end of the study than in the control groups. Based on DLQI scores at end of studies, 467/910 participants in the ivermectin group compared to 153/461 in the vehicle group were in the category where the disease had "no effect on their overall quality of life" (RR 1.55, 95% CI 1.34 to 1.79; P < 0.00001; I^2 = 0%; NNTB = 6, 95% CI 4 to 8). See Analysis 5.1.

Scores in the DLQI range from 0 to 30: a DLQI score of 0 to 1 is considered to have almost no impact on HRQOL, whereas 2 to 5 is considered to have a small effect, 6 to 10 a moderate effect, 11 to 20 a very large effect and 21 to 30 an extremely large effect on HRQOL. Therefore a reduction in score can be seen as an improvement in HRQOL. The MD in mean change from baseline in DLQI (per-protocol data were provided) was -1.15 (95% CI -1.44 to -0.85; P < 0.00001; I^2 = 0%) in favour of ivermectin. See Analysis 5.2. Although the minimal important difference (MID) for the DLQI is yet to be established for the different skin diseases there is general acceptance that this ranges between 2.5 and 5, and therefore the impact of both treatments provided a small improvement in HRQOL but the difference, although statistically significant, was not clinically important (Basra 2008; Basra 2015).

In re-analysing the data for this outcome we used the identical N per protocol populations for the groups as for the DLQI outcome. The disease-specific RosaQoL (range 1 to 5) assessments in Stein 2014a showed reductions of 0.64 (SD 0.7) for ivermectin and 0.35 (SD 0.5) for vehicle (MD -0.29, 95% CI -0.38 to -0.20; P < 0.00001). In Stein 2014b the reductions were 0.60 (SD 0.6) for ivermectin versus a reduction of 0.35 (SD 0.5) for vehicle (MD -0.25, 95% CI -0.34 to -0.16; P < 0.00001). Although the differences were statistically significant, the clinical importance was unclear as the MID for RosaQoL still needs to be established.

Participant-assessed changes in rosacea severity at end of study

Data for this outcome were reported in an ITT analysis (last observation carried forward (LOCF)). Participants' assessments at the end of the study (Stein 2014a; Stein 2014b) showed that there was a good to excellent improvement in 615/910 in the ivermectin group compared to 169/461 for vehicle in favour of ivermectin (RR 1.84, 95% CI 1.62 to 2.09; P < 0.00001; I^2 = 0%; NNTB = 3, 95% CI 3 to 4). See Analysis 5.3.

Proportion of participants who reported an adverse event throughout the study period

All three studies provided data for this outcome; in the ivermectin group 62/1050 reported adverse events compared to 45/567 with vehicle (RR 0.83, 95% CI 0.54 to 1.28; I^2 = 26%). See Analysis 5.4. Adverse events more frequently reported in the ivermectin group were skin burning, pruritus and dry skin.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

An Investigator's Global Assessment of clear or almost clear (Stein 2014a) was attained by 173/451 in the ivermectin group and 27/232 for vehicle (RR 3.30, 95% CI 2.27 to 4.79; P < 0.00001; NNTB = 4, 95% CI 4 to 5). In Stein 2014b these global

assessment success outcomes were reported in 181/459 of the ivermectin group and 43/229 with vehicle (RR 2.10, 95% CI 1.57 to 2.81; P < 0.00001; NNTB = 5, 95% CI 4 to 8). The results of both studies were in concordance with the assessments of the participants. In EUCTR2010-018319-13-DE a 2 grade improvement on the IGA scale was considered treatment success. In the ivermectin group the success rate was 58/104 versus 36/106 with vehicle (1.64, 95% CI 1.20 to 2.25; P = 0.002; NNTB = 5, 95% CI 3 to 12). The data of the three studies were not pooled (I^2 = 76%).

- Assessment of erythema or telangiectasia, or both, at end of study

  Not assessed.

- Lesion counts

  All three studies provided data for this outcome. The MD of change from baseline in lesion counts was -8.09 lesions (95% CI -9.82 to -6.35; P < 0.00001; I^2 = 52%) in favour of ivermectin. See Analysis 5.5.

- Time needed until improvement

  This was not a predefined outcome, but improvement in both studies was seen after four weeks.

- Duration of remission

  Not assessed.

Topical interventions: studies with topical metronidazole, azelaic acid, and/or other topical treatments

(16) Topical azelaic acid versus topical metronidazole

Three studies assessed as at unclear risk of bias provided data; Elewski 2003, Wolf 2006 and Maddin 1999 (which had a within-participant study design but the trialists did not account for this within their analyses, therefore only summary statistics are presented). See also Summary of findings table 6.
Azelaic acid and metronidazole were applied twice a day in all except Wolf 2006 where metronidazole was applied once daily.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

In Elewski 2003 97/124 participants in the azelaic acid gel group considered themselves to have a good to excellent improvement versus 81/127 with metronidazole gel (RR 1.23, CI 95% 1.04 to 1.44; P = 0.01; NNTB = 8, 95% CI 4 to 34). In Wolf 2006 these frequencies were 57/78 versus 60/82, respectively (RR 1.00, 95% CI 0.83 to 1.21). Pooling of the data was not possible (I^2 = 62%).

In the Maddin 1999 study participants considered the 20% azelaic acid cream more effective than the metronidazole 0.75% cream. Severity was rated on a 5-point scale (0 to 4, higher = worse), the mean score on the azelaic acid treated side was 1.87 (SD 0.76) compared with 2.33 (SD 0.95) on the metronidazole side (investigators reported P = 0.02).

Proportion of participants who reported an adverse event throughout the study period

The number of participants in Elewski 2003 experiencing adverse events was higher and statistically significant in the azelaic acid group with 32/124 as compared to 9/127 with metronidazole (RR 3.64, 95% CI 1.81 to 7.31; P = 0.0003; NNTH = 6, 95% CI 4 to 10). There was no statistically significant difference in adverse events between the groups in Wolf 2006: 29/78 versus 41/82 (RR 0.74, 95% CI 0.52 to 1.07). The adverse events reported in both Elewski 2003 and Wolf 2006 were mild to moderate and mostly transient, with skin dryness, scaling, stinging and burning being the most frequent. Pooling of data of these two studies was not possible due to excessive heterogeneity (I^2 = 94%). In Maddin 1999 only one participant reported an adverse event, that is stinging, on the side of the face which had been treated with azelaic acid cream.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In the azelaic acid group 130/202 participants were considered by physicians to be cleared or nearly cleared versus 114/209 in the metronidazole group (RR 1.18, 95% CI 1.00 to 1.40; P = 0.05; I^2 = 6%; NNTB = 10, 95% CI 5 to 273). See Analysis 6.1

Investigators in the Maddin 1999 study evaluated 'Global Improvement in severity of rosacea' (1 = complete clearance to 6 = exacerbation). At 15 weeks the score for the azelaic acid treated side was 2.7 (SD 1.0) compared with 3.1 (SD 1.0) on the metronidazole treated side; the investigators suggested limited superiority of azelaic acid over metronidazole but they failed to adjust for the within-participant design of their study.

- Assessment of erythema or telangiectasia, or both, at end of study

Improvement in erythema was demonstrated in 70/124 in the azelaic acid group compared to 53/127 with metronidazole in Elewski 2003. A decrease of one point on the four-point Likert scale (none to severe) was considered to be an improvement. In Wolf 2006 33/78 participants in the azelaic acid group attained an erythema score of 0 or 1 (same scale) compared to 35/82 with metronidazole gel. Pooled data showed a RR of 1.19 (95% CI 0.88 to 1.61; P = 0.26; I^2 = 47%; see Analysis 6.2). In Maddin 1999 both participants and investigators assessed erythema. The investigators scored a reduction of 0.83 on the azelaic acid side compared to a reduction of 0.51 on the metronidazole side, whilst the participants scored a greater reduction on the metronidazole side (reduction of 0.23 (SD 0.58) on the azelaic acid side and a reduction of 0.74 (SD 0.57) on the metronidazole treated side).

- Lesion counts

The decrease in inflammatory lesion counts reported in Elewski 2003 was 12.9 in the azelaic acid group versus 10.7 with metronidazole. No SDs were provided, but the

investigators reported a P value of 0.003 and although this was a statistically significant difference, a difference of 2.2 lesions is not considered important. In Maddin 1999 the decrease in lesion count was expressed as a percentage, 78.5% on the azelaic acid treated side versus 69.4% on the metronidazole treated side. In Wolf 2006 this was reported as median change reductions of 80% and 77% respectively.

- Time needed until improvement

An improvement for both arms was seen after four to six weeks in all three studies.

- Duration of remission

Not assessed.

(17) Azelaic acid 20% twice daily versus metronidazole 0.75% twice daily versus permethrin 5% twice daily

Only one study at high risk of bias with a within-participant design compared these interventions (Mostafa 2009). Investigators' conclusions were based on the analysis of skewed and unreliable data.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Side effects included itching, burning sensation, oedema and scales, and were mostly transient. The investigators reported that "there were no statistically significant differences among the three groups and almost decreased at the end visit".

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

The reductions in mean erythema scores (scale unclear) were 0.60 (SD 0.66) for the 16 sites treated with azelaic acid, 0.30 (SD 0.48) for the 16 sites treated with metronidazole, and 0.25 (SD 0.51) for the sites treated with permethrin. The investigators stated that the changes from baseline were statistically significant ($P < 0.05$), but that there was no statistically significant difference between the three treatments.

- Lesion counts

Although the analysis was based on skewed data and unreliable data analysis, all three treatments reduced the mean number of lesion counts, with 3.60 (SD 2.33) for azelaic acid, 3.70 (SD 2.92) for metronidazole and 2.60 (SD 3.24) for permethrin cream.

- Time needed until improvement

Not assessed.

- Duration of remission

Lesion counts and erythema assessments were provided six months after the end of treatment, but the report provided no indication of how long the participants were in remission before they relapsed.

(18) Topical permethrin 5% twice daily versus placebo twice daily

Two studies evaluated this comparison. One had a within-patient design and was assessed at high risk of bias (Raoufinejad 2016). Due to a 40% drop-out in participants, we have presented the data narratively without analysis. The other study had an unclear risk of bias (Koçak 2002, three-arm study, see also comparison 6 and 19). Most data were skewed.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

This outcome was only assessed in Raoufinejad 2016. On the permethrin 5% treated side 14/20 participants that completed the study reported after two weeks (end of study) to be clear or only have mild rosacea severity and 13/20 participants reported to be clear or only have mild rosacea on the side treated with placebo (authors report P = 0.721 comparing two sides of the face).

Proportion of participants who reported an adverse event throughout the study period

Side effects were reported by 18/34 participants in the study of Raoufinejad 2016. Of the 71 reported adverse events, 38 were related to permethrin and the remaining to placebo. Adverse events were mostly mild and in similar in frequency on both sides. These included dryness, burning, itching, scaling, erythema, inflammatory lesions, numbness and oedema. In the study of Koçak 2002 no adverse events were reported in either intervention group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In the 20 people completing the study (Raoufinejad 2016) physicians rated the side treated with permethrin to have a score of absent or mild rosacea in all 20 versus 15 of the 20 sides treated with placebo. This outcome was not assessed in Koçak 2002.

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema had cleared after two weeks (end of treatment) on the side treated with permethrin in the 20 participants that completed the study (Raoufinejad 2016) versus 18 sides that were treated with placebo. In Koçak 2002 the mean change in erythema score (scale 0 to 3, 3 = severe) from baseline to day 60 was -1.26 (SD 2.09) in the permethrin group versus -0.05 (SD 1.39) in the placebo group. Data were skewed. Neither treatment was shown to be more effective than the other for rhinophyma or telangiectasia.

- Lesion counts

At the end of two weeks (end of treatment) the sides treated with permethrin in the 20 participants that completed the study were all considered cleared from lesions or just mild lesions versus 16 sides treated with placebo (Raoufinejad 2016).

In the study of Koçak 2002 the mean change from baseline in number of papules was -4.33 (SD 28.72) in the permethrin group versus +0.25 (SD 11.25) in the placebo group. The mean change from baseline in pustules was -1.74 (SD 13.52) for the permethrin group and -0.20 (SD 9.20) in the placebo group. Data were skewed, but not for pustules. Most of the data that were reported were skewed, but the authors concluded that permethrin 5% cream was more effective than placebo.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(19) Topical permethrin twice daily versus topical metronidazole twice daily

There was a three-armed study (Koçak 2002) assessed as at unclear risk of bias with data for this comparison. Most of the data reported were skewed. The authors, however, concluded that permethrin 5% cream showed comparable effectiveness to metronidazole on both erythema and papules, but indicated that this did not apply to pustules (see also comparison 6 and 18).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in either intervention group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

  The mean change in erythema score (scale 0 to 3, 3 = severe) from baseline to day 60 was -1.26 (SD 2.09) in the permethrin group versus 1.45 (SD 2.00) in the metronidazole 0.75% group. Data were skewed. Neither treatment was shown to be more effective for rhinophyma or telangiectasia.

- Lesion counts

  The mean change from baseline in number of papules was -4.33 (SD 28.72) in the permethrin group versus -5.10 (SD 23.36) in the metronidazole group. The mean change from baseline in pustules was -1.74 (SD 13.52) for the permethrin group and -2.5 (SD 13.65) in the metronidazole group. Data were skewed, but not for pustules.

  Most of the data that were reported were skewed but the authors concluded that permethrin 5% cream showed comparable effectiveness to metronidazole on both erythema and papules, but indicated this did not apply to pustules.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(20) Ivermectin 1% cream once daily versus metronidazole 0.75% cream twice daily

This comparison was evaluated in one study at low risk of bias (Taieb 2015), and one study at unclear risk of bias that was not published but provided data (EUCTR2006-001999-20-HU) see Summary of findings table 7.

Primary outcomes

Change in HRQOL at end of study

DLQI score at baseline (Taieb 2015) was 6.93 in the ivermectin group and 6.05 in the metronidazole group. A reduction of 5.18 on the DLQI was seen in the ivermectin group compared to a reduction of 3.92 in the metronidazole group but no SDs were provided. A DLQI score of 0 to 1 equates to no effect on HRQOL, a score of 2 to 5 a small effect, and a score of 6 to 10 represents a moderate effect. Although the minimal important difference (MID) for the DLQI is yet to be established for the different skin diseases there is general acceptance that this ranges between 2.5 and 5, and therefore the impact of both these treatments was a small improvement in HRQOL but the difference between the groups in terms of reduction of the DLQI scores was not clinically important (Basra 2008; Basra 2015). At the end of the 16 weeks 339/478 in the ivermectin group compared to 310/484 in the metronidazole group reported that the disease had no deleterious effect on their quality of life (RR 1.11, 95% CI 1.01 to 1.21; P = 0.02; NNTB = 15, 95% CI 8 to 100), which was statistically significant in favour of ivermectin. Furthermore, in another publication on this same study (see under primary reference of Taieb 2015), was added that 201/478 in the ivermectin group reached a MID of 5 versus 153/484 in the metronidazole group (RR 1.33, 95% CI 1.12 to 1.57; P = 0.0009; NNTB = 10, 95% CI

6 to 23). In addition, besides the DLQI which is dermatology specific, a generic instrument was also used (the EQ-5D) which confirmed the data of the DLQI. In 16 weeks the EQ-5D score (higher score is better) increased from 0.86 to 0.94 in the ivermectin group and from 0.85 to 0.91 in the metronidazole group. An increase of ≥ 0.074 versus baseline is considered as MID which was met for the ivermectin group. A follow up study demonstrated that the effects on health related quality of life lasted over a period of one year favouring ivermectin.

In EUCTR2006-001999-20-HU only a generic comment was made "The patient's quality of life demonstrated a dose related increase of overall quality of life per DLQI" (see also comparison 14 which referred more closely to ivermectin).

Participant-assessed changes in rosacea severity at end of study

This outcome was only assessed in the study of Taieb 2015. In the ivermectin group 409/478 participants rated their improvement as good or excellent compared to 362/484 in the metronidazole group (RR 1.14, 95% CI 1.07 to 1.22; P < 0.0001; NNTB = 10, 95% CI 7 to 17), which was a statistically significant difference and in concordance with the results on the number of participants that experienced no deleterious effect on their quality of life.

Proportion of participants who reported an adverse event throughout the study period

In the ivermectin group 13/530 experienced an adverse event compared to 7/532 with metronidazole (RR 1.78, 95% CI 0.72 to 4.43; I^2 = 0%; Analysis 7.1). The reactions were mild and consisted of skin irritation, dryness and hypersensitivity.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Based on a composite score of IGA scale ((erythema and inflammatory lesions) 406/478 were clear or almost clear in the ivermectin group compared to 365/484 in the metronidazole group, which was consistent with assessments of participants (Taieb 2015). The other study (EUCTR2006-001999-20-HU) used the same composite score of IGA and 34/52 compared with 30/48 respectively were rated as having treatment success. Pooled data showed a RR of 1.12 (95% CI 1.06 to 1.19; P = 0.0003; I^2 = 0%; NNTB = 11, 95% CI 7 to 26; see Analysis 7.2).

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed in Taieb 2015. In EUCTR2006-001999-20-HU only generic comments were made "Decrease in erythema score were not statistically significant between any of CD5024 concentrations *(ivermectin*) and vehicle or metro. Telangiectasia remained unchanged in all groups".

- Lesion counts

The mean change from baseline in lesion count in Taieb 2015 was -27.70 (SD 8.85) in the ivermectin group compared to -23.60 (SD 8.23) in the metronidazole group, which were both important reductions (MD -4.10, 95% CI -5.18 to -3.02; P < 0.00001). The reductions in EUCTR2006-001999-20-HU were expressed in percentages; the reduction in the ivermectin group was 70% (SD 34.3) and in the

metronidazole group 59.9% (SD 52.2)(MD -10.10 %, 95% CI -27.56 to 7.36; P = 0.26).

- Time needed until improvement

This was not a predefined outcome but clear improvement was observed for both treatment arms around six weeks.

- Duration of remission

A follow-up study (reference under Taieb 2015) reported data on relapse rate in those people that had reached an IgA score of clear or almost clear after the 16 week treatment period. Relapse was defined as IGA ≥ 2 (mild). Three hundred ninety nine people had been treated with topical ivermectin and 358 with topical metronidazole. If a relapse occurred participants received the same treatment as in the first 16 weeks of the study. At week 36 of the follow up period 62.7% (250/399) had experienced a relapse in those initially assigned to topical ivermectin versus 68.4% (245/358) in those initially assigned to topical metronidazole (RR 0.92, 95% CI 0.83 to 1.02; P = 0.09). The mean time to relapse was 147.0 days (SD 4.66) for ivermectin versus 133.6 days (SD 5.13) for metronidazole.

(21) Ivermectin 1% cream once daily versus azelaic acid 15% gel twice daily

Two studies (Stein Gold 2014c; Stein Gold 2014d) which are actually 40-week extension studies of Stein 2014a and Stein 2014b evaluated long-term safety of ivermectin 1% cream versus azelaic acid 15% gel. Participants originally treated for 12 weeks with ivermectin 1% in Stein 2014a and Stein 2014b continued on ivermectin 1% and those originally treated with vehicle switched to azelaic acid 15% gel. Those treated with azelaic acid in this extension study were therefore more affected at baseline than the participants in the ivermectin treatment arm that had been treated with ivermectin in the prior 12 weeks. Therefore there is a clear baseline imbalance between intervention groups for these extension studies and as a result both studies were assessed at high risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

During the 40 week extension period, 11/840 (1.3%) in the ivermectin group experienced a related dermatologic adverse event compared with 22/418 (5.3%) in the azelaic acid group (RR 0.25, 95% CI 0.12 to 0.52; P = 0.0002; I^2 = 0%; NNTH = 25, 95% CI 16 to 60) favouring ivermectin (see Analysis 8.1). Skin irritation, dry skin, pruritus and pain were more frequently reported with azelaic acid.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

At the start of the extension studies more participants were clear or almost clear after 12 weeks treatment with ivermectin than in the vehicle group, resulting in baseline imbalance for the 40 week extension period. In the ivermectin group 330/840 (39.3%) participants had an IGA of clear or almost clear at the start of the extension studies versus 63/418 (15.1%) in the initially treated with vehicle group (which were treated with azelaic acid in the extension period). After 40 weeks 618/840 (73.6%) that continued on ivermectin was considered 'clear or almost clear', an increase of 34.3% whereas in the azelaic acid group 245/418 (58.6%) was considered 'clear or almost clear' which is an increase of 43.5%. Because of the baseline imbalance we did not analyse the data further as it is not a fair comparison, but continued use of ivermectin appeared to yield a greater percentage of treatment success in that group.

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(22) Ivermectin 1% cream once daily in evening plus brimonidine 0.33% gel once daily in the morning versus ivermectin vehicle cream once daily in the evening and brimonidine vehicle gel once daily in the morning

One three-armed study Stein-Gold 2017 at unclear risk of bias evaluated these combined treatments. We have not included the results of the third arm (ivermectin 1% cream once daily in the evening for 12 weeks plus brimonidine vehicle once daily in the morning for four weeks followed by brimonidine once daily in the morning for the remaining eight weeks) as we felt this was less informative for the review.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Of the 49 participants treated with both ivermectin and brimonidine 38 (77.7%) reported to have good to excellent improvement versus 52/95 (55.2%) in the combined ivermectin vehicle and brimonidine vehicle group (RR 1.42, 95% CI 1.12 to 1.80; P = 0.004; NNTB = 4, 95% CI 3 to 13) favouring the combined treatment group.

Proportion of participants who reported an adverse event throughout the study period

The adverse events reported in the two active treatment arms were combined and 4/95 participants in the active treatment arms reported five adverse events versus 2/95 reporting three adverse events in the vehicle group. Adverse events consisted of allergic dermatitis, skin burning and skin irritation in the active treatment groups; while erythema, pruritus and worsening rosacea was mentioned in the vehicle group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

An IGA of clear or almost clear was reached in 30/49 (61.2%) participants that were treated with both ivermectin and brimonidine compared with 35/95 (36.8%) in the vehicle group (RR 1.66, 95% CI 1.18 to 2.35; P = 0.004; NNTB = 4, 95% CI 2 to 13). This is consistent with assessments of participants.

- Assessment of erythema or telangiectasia, or both, at end of study

In the group treated with both ivermectin and brimonidine 37/49 (75%) achieved 'clear or almost clear' on the Clinician Erythema Assessment (CEA) compared with 39/95 (40.7%) in the vehicle group (RR 1.84,1.38 to 2.46; P < 0.0001; NNTB = 3, 95% CI 2 to 5).

- Lesion counts

A reduction of 100% was obtained by 8/49 (16.3%) in the active treatment group and by 4/95 (4.2%) in the vehicle group (RR 3.88, 95% CI 1.23 to 12.24; P = 0.02; NNTB = 8, 95% CI 4 to 99). The percentage reduction from baseline was 78.3% for the active treatment group versus 65.5% for the vehicle group.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(23) Brimonidine 0.05% gel versus azelaic acid 15% gel

Limited data from a poster abstract were reported in the single study at unclear risk of bias comparing these interventions in 70 participants (Kendall 2014).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

After 2 weeks (end of study) 9/35 of the participants reported a two grade PSA improvement on a scale from 0 to 4 (higher indicating worse) in the brimonidine group compared to 7/35 in the azelaic acid group (RR 1.29, 95% CI 0.54 to 3.07).

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

No global assessments were assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

The judgements of the investigators were not in concordance with the judgements of the participants. A two grade CEA improvement (scale 0 to 4, higher indicating worse) was seen in 12/35 in the brimonidine group versus 4/35 in the azelaic acid group (RR 3.00, 95% CI 1.07 to 8.40; P = 0.04; NNTB = 4, 95% CI 2 to 25), which was a statistically significant difference in favour of brimonidine. Chroma Meter readings decreased by 9.64% and 2.35% respectively.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(24) Brimonidine 0.33% gel once daily combined with azelaic acid 15% gel twice daily versus brimonidine 0.33% once daily

A single study assessed at high risk of bias due to a more than 20% drop-out evaluated this comparison (NCT02147691). Data will only be described narratively.

Primary outcomes

Change in HRQOL at end of study

This was assessed with the DLQI (score ranges 0 through 30, 0 being none and 30 worst possible). In the six participants that completed the study on the combined therapy there was a reduction of 1.40 (SD 2.83) and in the brimonidine only group a reduction of 0.10 (SD 1.71), both are minimal improvements in quality of life not meeting the MID (Basra 2008; Basra 2015).

Participant-assessed changes in rosacea severity at end of study

This outcome was assessed with a VAS scale (0 to 10, higher is worse). The combined treatment group had a reduction of 1.70 (SD 1.53) versus a reduction of 1.60 (SD 1.27) in the brimonidine only group.

Proportion of participants who reported an adverse event throughout the study period

Three of the 10 people in the group treated with both brimonidine and azelaic acid reported six adverse events of which only one appeared treatment related (burning at application site). In the brimonidine only group four participants of the 12 reported four adverse events of which one appeared treatment related (worsening of erythema).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

No global assessments were assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema was assessed with the Clinician Erythema Assessment from 0 to 4 (0 = none and 4 = very severe). In the six participants that completed the study treated with brimonidine and azelaic acid the reduction was 1.00 (SD 0.42) and in the brimonidine only group (n = 11) 0.90 (SD 0.59).

- Lesion counts

Lesion count was reduced by 2.60 (SD 0.96) in the combined treatment group after 12 weeks compared with 3.40 (SD 1.93) in the brimonidine only group.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(25) Benzoyl peroxide versus vehicle

Two studies provided data for this comparison. Leyden 2014 was a three-armed study comparing benzoyl peroxide 1% and 5% against vehicle and was assessed as at unclear risk of bias. Only data for our secondary outcomes were provided. Montes 1983 was assessed as at high risk of bias and complete data were only reported for the first four weeks. The lack of baseline values hampered our ability to interpret the data.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

There was no statistically significant difference between the two groups in the number of participants reporting adverse events (Montes 1983): 26/33 in the benzoyl peroxide group versus 18/31 in the vehicle group (RR 1.36, 95% CI 0.96 to 1.92).

Irritation and burning were the most frequently reported side effects in both groups. The rate of adverse events was high in both groups, which the authors indicated could be attributed to the vehicle in that the benzoyl peroxide gel may have a greater dehydrating effect than the newer aqueous gels. This outcome was not assessed in Leyden 2014.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In Leyden 2014 physicians rated 12/32 participants as a treatment success in the benzoyl peroxide 1% group compared to 6/30 in the vehicle group, which was not statistically significant (RR 1.88, 95% CI 0.81 to 4.36). However, the higher concentration did show a statistically significant difference as 16/30 in the benzoyl peroxide 5% group were considered to have a treatment success (RR 2.67, 95% CI 1.21 to 5.88; P = 0.01). There was no statistically significant difference between the 5% and the 1% group (RR 0.70, 95% CI 0.40 to 1.23). In Montes 1983 the overall response score, rated on a scale of 0 to 4 (4 = worst), at the end of four weeks was 2.69 (benzoyl peroxide) versus 3.71 (vehicle). However, no baseline values were reported.

- Assessment of erythema or telangiectasia or both at end of study

In the study of Leyden 2014, investigators reported no changes in persistent erythema or telangiectasia in any of the groups. In Montes 1983 the investigators also reported no statistically significant differences seen in the severity of erythema and telangiectasia.

- Lesion counts

In Leyden 2014 lesion counts reduced by 21.6 (SD 23.31) in the benzoyl 1% group versus 7.4 (SD 17.24) in the vehicle group (MD -14.20, 95% CI -24.36 to -4.04; P = 0.006), which was a statistically significant difference in favour of benzoyl peroxide 1%. The reduction in the 5% group was smaller (14.1 (SD 8.78)) and compared to the vehicle the MD was -6.70 (95% CI -13.62 to 0.22; P = 0.06). There was no statistically significant difference between the 1% and 5% group (MD -7.50, 95% CI -16.17 to 1.17). These were rated on a scale of 0 to 3 (3 = worst) in Montes 1983 and the improvement in scores appeared to favour benzoyl peroxide. The papule scores at four weeks were 0.89 (benzoyl peroxide) compared with 1.91 (vehicle), and pustules scores 0.46 (benzoyl peroxide) versus 1.31 in the placebo group (investigators reported P < 0.05). No baseline values were reported.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(26) Benzoyl peroxide 5% with clindamycin 1% gel versus vehicle

There were two individual reports at unclear risk of bias (Breneman 2004; Leyden 2004) involving the same study participants but focusing on different outcomes measures. Some SDs were lacking, and most data were skewed.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Mean scores, rated as 0 to 4 (4 = worst), at end of the study were 1.54 (much to slightly better) in the benzoyl peroxide with clindamycin group versus 2.50 (slightly better) in the vehicle group (investigators reported P = 0.0002). This outcome was only assessed at 12 weeks.

Proportion of participants who reported an adverse event throughout the study period

There was no statistically significant difference in the number of participants between the groups reporting adverse events; 7/27 participants in the benzoyl peroxide with clindamycin group versus 4/26 in the vehicle group (RR 1.69, 95% CI 0.56 to 5.08). Treatment-related adverse events included localised burning and itching, both well-known side effects of benzoyl peroxide.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Mean scores, rated 0 to 5 (5 = worst), at the end of the study were 1.85 (which was equivalent to a marked improvement) in the active treatment group versus 2.96, indicating minimal improvement in the vehicle group. In the benzoyl peroxide with clindamycin group 11/27 compared with 4/26 in the vehicle group were considered to have a marked improvement or complete clearance (RR 2.65, 95% CI 0.96 to 7.25). The mean percentage change from baseline in overall rosacea severity assessment was -29.3% for benzoyl peroxide with clindamycin and -10.6 for the vehicle group (investigators reported P = 0.01).

Global photographic improvement was assessed on a 7-point scale (−2 to +4, 4 = best) in Leyden 2004. The investigators reported a mean Global photographic comparison rating of 1.6 in the active intervention group versus 0.7 in the vehicle group (P < 0.001, investigator reported).

- Assessment of erythema or telangiectasia, or both, at end of study

Mean erythema score decreased, 0.63 in the benzoyl peroxide with clindamycin group and 0.33 in the vehicle group (investigators reported P = 0.07). There were also no statistically significant differences between the two groups in telangiectasia.

- Lesion counts

Mean reduction in lesion counts in the treatment group was 71.3% (SD 25.3) versus 19.3% (SD 89.6) in the vehicle group (Breneman 2004). Mean papule counts decreased from 15.6 (SD 7.8) to 3.9 (SD 3.6) in the benzoyl peroxide with clindamycin group versus a decrease from 16.8 (SD 10) to 13.4 (SD 14.6) in the vehicle group, and the pustule counts decreased from 2.5 (SD 3.8) to 0.8 (SD 2.4)

versus from 2.5 (SD 4.0) to 2.0 (SD 4.5) respectively. The investigators in this study also concluded that a treatment effect, that is a reduction in the number of lesions, was demonstrated in the benzoyl peroxide and clindamycin group, which we were unable to confirm because the data as reported were skewed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(27) Clindamycin 1% cream or gel twice daily versus vehicle cream or gel twice daily

Two studies evaluated the efficacy of clindamycin in rosacea (Martel 2017a; Martel 2017b). The studies were assessed as unclear risk of bias and we failed to receive a response from the authors about several trial details (see Table 3). In the first study Martel 2017a it appeared that the different concentrations and dosages were no more effective than their vehicles. Therefore, we report only the data for clindamycin 1% twice daily versus vehicle twice daily. In Martel 2017a cream was used and in Martel 2017b gel. See Summary of findings table 8.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Data reporting on adverse events was limited. The authors reported "Overall, 12 participants had AEs considered by the investigator as possibly or probably related to the study treatment: 4.9% in the clindamycin cream 1% twice daily group, 4.6% in the clindamycin cream 1% once daily group, 3.7% in the vehicle cream twice daily group, 1.2% in the clindamycin cream 0.3% once daily group, and 0% in the vehicle cream once daily group". This refers certainly to Martel 2017a but there was no mention of adverse events in Martel 2017b.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The rosacea severity score was used in both studies. Information on this score was explained "Investigator global rosacea severity score: 0=none/clear; 1=mild, detectable erythema with ≤7 papules/pustules; 2 = moderate, prominent erythema with ≥8 papules/pustules; 3 = severe, intense erythema with ≥10 to <50 papules/pustules; 3.5 (study A) or 4 (study B) = very severe, intense erythema with >50 papules/pustules".

In Martel 2017a the rosacea severity score reduced by 0.6 in the clindamycin group (n = 81) compared with 0.7 in the vehicle group (n = 81) (no SDs were provided). In

Martel 2017b the investigators reported that in the clindamycin group 49/109 (45%) achieved treatments success (score of 0 or 1) compared with 40/104 (38%) in the vehicle group (RR 1.17, 95% CI 0.85 to 1.61; P = 0.34). Both studies indicated that clindamycin was not more effective than vehicle.

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema was evaluated with the Erythema Severity Score (ESS). "The ESS is the combined erythema score of 5 facial regions, each assessed on a 7-point scale in increments of 0.5 (from 0 = no erythema to 3.5 = very severe, very intense redness". In Martel 2017a the score reduced by 1.8 in the clindamycin group and by 1.7 in the vehicle group. In the study of Martel 2017b the reductions were 1.5 and 1.9 respectively.

- Lesion counts

In Martel 2017a the lesion count was reduced by 30% in the clindamycin group and by 35% in the vehicle group and in Martel 2017b 32% in the clindamycin group and 29% in the vehicle group demonstrating that clindamycin in both studies was not more effective than vehicle

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(28) Clindamycin phosphate 1.2% + tretinoin 0.025% once daily gel versus placebo once daily

The efficacy of this topical treatment was examined in one study at low risk of bias (Chang 2012), see Summary of findings table 9.

Primary outcomes

Change in HRQOL at end of study

Quality of life was assessed with the disease-specific RosaQoL. However, no means of scores were provided, only percentages of participants that had improved per item on the 21 survey items, making these data less usable. The investigators reported that there were no statistically significant differences for any item.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Twenty-nine adverse events were reported in 43 participants on the combination treatment of clindamycin and tretinoin, compared to 11 adverse events in 40 participants in the placebo group (RR 2.45, 95% CI 1.42 to 4.23; P = 0.001, NNTH =

3, 95% CI 2 to 5). Worsening of rosacea, facial scaling as well as dry skin were reported most often in the active treatment group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

None of the primary features of the Physician's Global Assessment as defined by Wilkin 2004 showed statistically significant differences between the treatment groups except for oedema in favour of placebo.

- Assessment of erythema or telangiectasia, or both, at end of study

Although the inclusion criteria suggested that only people with papulopustular rosacea would have been included, all subtypes were represented. Only the erythematotelangiectatic subtype showed a statistically significant difference in favour of the combination treatment of clindamycin and tretinoin as 12/43 were improved compared to 4/40 in the placebo group (RR 2.79, 95% CI 0.98 to 7.95; P = 0.05; NNTB = 6, 95% CI 3 to 50). Erythema improved in 11/43 on the active treatment versus 6/40 on placebo (RR 1.71, 95% CI 0.70 to 4.18), and telangiectasia in 13/43 compared to 5/40 (RR 2.42, 95% CI 0.95 to 6.17).

- Lesion counts

Both treatments had no or minimal effect on inflammatory lesions. The mean change from baseline in lesion count was 0.83 (SD 10.84) in the group treated with clindamycin and tretinoin and -3.13 (SD 13.28) in the group treated with placebo, with a MD of 3.96 (95% CI -1.28 to 9.20).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(29) Minocycline 1.5% foam once daily versus vehicle foam once daily

One three-armed study at low risk of bias (Mrowietz 2018) evaluated different dosages of minocycline versus vehicle (see also comparison 31 and 32). See Summary of findings table 10.

Primary outcomes

Change in HRQOL at end of study

The RosaQoL was used for evaluating this outcome. There was a reduction in overall score after 12 weeks of 0.4 in the minocycline 1.5% foam group (n = 79) compared with a reduction of 0.2 in the vehicle group (n = 78). No SDs were provided. It is difficult to interpret these data as the MID is not established.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

A total of 46/79 reported an adverse event in the minocycline 1.5% foam group of which two subjects reported treatment related adverse events. In the vehicle group 31/78 reported an adverse event of which five were considered to be treatment related (RR 1.47, 95% CI 1.05 to 2.04; P = 0.02; NNTH = 5, 95% CI 3 to 32). All adverse events resolved during the study. Cutaneous adverse events consisted in the minocycline foam group consisted of eczema, burning sensation or worsening rosacea and in the vehicle group of pruritus and skin burning.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Improvement in IGA scores of at least 2 grades was obtained by 33/79 (41.8%) in the minocycline 1.5% foam compared with 14/78 (17.9%) in the vehicle foam group (RR 2.33, 95% CI 1.35 to 4.00; P = 0.002; NNTB = 4, 95% CI 3 to 10).

- Assessment of erythema or telangiectasia, or both, at end of study

After 12 weeks, 60/79 (76%) in the minocycline 1.5% group had score clear to mild on the Clinician's Erythema Assessment (score 0, 1 or 2) versus 53/78 (68%) in the vehicle foam group (RR 1.12, 95% CI 0.92 to 1.36).

- Lesion counts

Mean lesion count reduction was 21.1 (SD 8.1) in the minocycline 1.5% group versus 7.8 (SD 8.0) for vehicle. This difference favoured minocycline 1.5% (MD -13.30, 95% CI -15.82 to -10.78).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(30) Minocycline 3% foam once daily versus vehicle foam once daily

This is the second comparison of the study of Mrowietz 2018.

Primary outcomes

Change in HRQOL at end of study

The overall score of the RosaQoL demonstrated after 12 weeks a reduction of 0.3 in the minocycline 3% foam group (n = 75) compared with a reduction of 0.2 in the vehicle foam group (n = 78).

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

In the minocycline 3% group 32/75 reported an adverse event compared with 31/78 in the vehicle group (RR 1.07, 95% CI 0.74 to 1.57).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In the minocycline 3% foam group 25/75 achieved a 2 grade improvement in IGA versus 14/78 in the vehicle foam group (RR 1.86, 95% CI 1.05 to 3.29; P = 0.03; N = 7, 95% CI 3 to 58).

- Assessment of erythema or telangiectasia, or both, at end of study

At the end of 12 weeks 64/75 (85%) in the minocycline 3% foam group was rated clear to mild on the CEA compared with 53/78 in the vehicle foam group (RR 1.26, 95% CI 1.05 to 1.50; P = 0.01; NNTB = 6, 95% CI 3 to 23).

- Lesion counts

The mean lesion count reduction was 19.9 (SD 8.0) in the minocycline 3% foam group versus 7.8 (SD 8.0) with vehicle foam (MD -12.10, 95% CI -14.64 to -9.56; P < 0.00001) favouring minocycline 3% foam.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(31) Minocycline 1.5% foam once daily versus minocycline 3% foam once daily

This is the last comparison of the study of Mrowietz 2018 (see also comparison 30 and 31). Both concentrations appeared to be effective with no difference in efficacy or safety.

Primary outcomes

Change in HRQOL at end of study

For the overall score of the RosaQoL there was a reduction after 12 weeks of 0.4 in the minocycline 1.5% foam group (n = 79) compared with a reduction of 0.3 in the minocycline 3% foam group (n = 75). No SDs were provided.

Participant-assessed changes in rosacea severity at end of study

Not assessed

Proportion of participants who reported an adverse event throughout the study period

In the minocycline 1.5% foam group 46/79 reported an adverse event versus 32/75 in the minocycline 3% group (RR 1.36, 95% CI 0.99 to 1.88). There were 2 subjects with treatment related adverse events in the minocycline 1.5% foam group and 4 in the minocycline 3% foam group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

A 2 grade improvement in IGA was achieved by 33/79 in the minocycline 1.5% foam group versus 25/75 in the minocycline 3% foam group (RR 1.25, 95% CI 0.83 to 1.89).

- Assessment of erythema or telangiectasia, or both, at end of study

A score of clear or mild as measured with CEA was obtained by 60/79 participants in the minocycline 1.5% group compared with 64/75 in the minocycline 3% group (RR 0.89, 95% CI 0.76 to 1.04).

- Lesion counts

There was reduction of 21.1 (SD 8.1) in the minocycline 1.5% foam group compared with a reduction of 19.9 (SD 8.0) in the minocycline 3% foam group (MD -1.20, 95% CI -3.74 to 1.34).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(32) Erythromycin 2% gel twice daily versus metronidazole 0.75% gel twice daily

Only one study with a small sample size compared these two interventions (Verea Hernando 1992). A baseline imbalance in severity of the disease at enrolment placed the study at a serious risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

There was no statistically significant difference between the two groups for this outcome: after three months 16 of the 22 participants considered themselves improved with erythromycin gel versus 17 of 18 in the metronidazole gel group (RR 0.77, 95% CI 0.58 to 1.02).

Proportion of participants who reported an adverse event throughout the study period

These were inadequately reported in the study and therefore we have not included any of the data in this review.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Although this was a pre-specified outcome it was not addressed (see 'Risk of bias' under Characteristics of included studies for this study).

- Assessment of erythema or telangiectasia, or both, at end of study

Only one participant in the erythromycin group had an improvement in erythema compared with two in the metronidazole group.

- Lesion counts

Baseline imbalance between the groups with respect to the number of papules and pustules was quite marked and placed the study at serious risk of bias. The total number of papules in the erythromycin group was 571 at baseline, which reduced to 250 after three months, while the number at baseline in the metronidazole group was 476, which reduced to 317. The baseline number of pustules was 160 for the erythromycin group and reduced to 126 after three months, and for the metronidazole group the baseline number of pustules was 63 and the number at the end of the study was 33.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(33) Sodium sulphacetamide 10% and sulphur 5% twice daily versus placebo (vehicle) twice daily

Only one study evaluated these interventions but the overall reporting quality was inadequate: the number of participants in each treatment arm was not reported, improvement as an outcome was ill-defined, and the data reported as continuous outcomes were skewed and largely unusable (Sauder 1997). This study was categorised as at unclear risk of bias. For further details see the 'Risk of bias' tables in 'Characteristics of included studies'.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

A larger percentage of participants (90%) in the active treatment group considered themselves improved as compared with the vehicle group (58%) (investigators reported $P < 0.001$).

Proportion of participants who reported an adverse event throughout the study period

Adverse events were reported as 38% in the active group versus 29% in the vehicle group. Application site reactions such as dryness, erythema and pruritus were the most commonly reported adverse events.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Based on these assessments, 98% in the active treatment group versus 68% of the participants in the placebo group demonstrated an improvement (investigators reported P < 0.001).

- Assessment of erythema or telangiectasia, or both, at end of study

Improvement in erythema was seen in 83% of the active treatment group compared to 31% in the vehicle group (investigators reported P < 0.001).

- Lesion counts

The mean lesion count reductions were reported as 78% versus 36% for the active treatment group and vehicle group respectively, with a corresponding reduction of 30.5 lesions and 9.4 lesions (investigators reported P < 0.001).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(34) Sodium sulphacetamide 10% and sulphur 5% twice daily versus metronidazole 0.75% twice daily

Two studies which we assessed as at unclear to high risk of bias reported data for this comparison (Lebwohl 1995; Torok 2005).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

No exact data were provided in Lebwohl 1995, but the investigators reported there were no statistically significant treatment differences in any of the participant assessments. Although this was a pre-specified outcome in Torok 2005, this was not addressed (see 'Risk of bias' under Characteristics of included studies for this study).

Proportion of participants who reported an adverse event throughout the study period

Fewer participants experienced adverse events in the metronidazole group but the difference between groups was not statistically significant. In Lebwohl 1995 5/31 versus 3/32 (RR 1.72, 95% CI 0.45 to 6.59) and in Torok 2005 48/75 versus 41/77 (RR 1.20, 95% CI 0.92 to 1.57) reported adverse events. Most adverse events were mild and transient and consisted of dryness, pruritus, burning and stinging.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

These assessments indicated that there was some evidence that sodium sulphacetamide 10% with sulphur 5% was more effective than metronidazole 0.75% gel. Although no SDs were provided in Lebwohl 1995 the overall severity reduced from 2.2 to 1.1 on a scale of 0 to 3 (none to severe) in the sodium sulphacetamide 10% with sulphur 5% (investigators reported P < 0.01) and from 2.1 to 0.6 in the metronidazole group (investigators reported P < 0.01). The difference was, according to the investigators, statistically significant (P = 0.002). No baseline values were reported on Physician's Global Assessment but the investigators concluded that "treatment mean contrasts show statistically significant differences favouring sodium sulphacetamide/sulphur at all times points (week eight P = 0.001)".

In Torok 2005 51/75 participants were considered to have been cleared, or to have shown good to excellent improvement, in the sulphacetamide plus sulphur group versus 43/77 in the metronidazole gel group (RR 1.22, 95% CI 0.95 to 1.57).

- Assessment of erythema or telangiectasia, or both, at end of study

In Lebwohl 1995 the mean erythema scores decreased from 2.3 to 1.2 at eight weeks (SDs were missing, investigators reported P < 0.05) in the sulphacetamide plus sulphur group and from 2.2 to 0.7 in the metronidazole group (investigators reported P < 0.05). The difference was reported to be statistically significant in favour the sulphacetamide plus sulphur group (P = 0.017). This difference was not confirmed in Torok 2005 where 45/75 treated with sulphacetamide plus sulphur showed at least one grade improvement on a scale from 0 to 3 compared to 43/77 on metronidazole (RR 1.07, 95% CI 0.82 to 1.41).

- Lesion counts

No SDs were provided for baseline values. The authors reported no statistically significant difference in decrease of papule counts for these interventions in Lebwohl 1995. However, there was a statistically significant difference in decrease in the pustule counts in favour of sodium sulphacetamide plus sulphur (investigators reported P = 0.006). For Torok 2005 the mean reductions in lesion counts were 80% in the sulphacetamide plus sulphur group and 72% in the metronidazole group.

- Time needed until improvement

This was not a predefined outcome but improvement was noted at four to six weeks in both studies.

- Duration of remission

Not assessed.

(35) Pimecrolimus 1% twice daily versus vehicle twice daily

Twice daily applications of pimecrolimus 1% were compared with vehicle in Weissenbacher 2007. The study was assessed as at unclear risk of bias.

Primary outcomes

Change in HRQOL at end of study

The "quality of life impairment" (Dermatology Life Quality Index, score 0 to 30, higher score = more impairment) showed a reduction of the mean absolute value from 5.50 to 3.10 in the pimecrolimus group versus 6.70 to 3.70 in the vehicle group with no significant differences between groups (investigators reported P = 0.75) and both were both small reductions.

Participant-assessed changes in rosacea severity at end of study

The subjective severity score (VAS 0 to 100 mm, higher = worse) indicated an improvement of the mean absolute value from 53.45 to 48.95 in the pimecrolimus group and from 64.75 to 43.35 in the vehicle group (investigator reported P = 0.48).

Proportion of participants who reported an adverse event throughout the study period

Two adverse events were reported, but it was unclear in which group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Mean absolute values for the total rosacea severity score reduced from 6.88 to 4.68 in four weeks in the pimecrolimus group versus 7.00 to 4.33 in the vehicle group. The difference was not statistically significant (investigators stated P = 0.59).

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(36) Metronidazole 1% cream twice daily versus pimecrolimus cream twice daily

One study at high risk of bias compared these interventions (Koca 2010) but there was an appreciable baseline imbalance at enrollment, that is consisting of an increased duration and severity of disease in the pimecrolimus arm compared to the metronidazole arm. The conclusions reached by the investigators did not appear to plausibly reflect the data that were reported as the data were massively skewed.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Four of 24 in the metronidazole group reported adverse events (burning and stinging) compared to 2/25 with pimecrolimus (itching) (RR 2.08, 95% CI 0.42 to 10.34).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

There was no statistically significant difference in global improvement between the two groups. In the metronidazole group all (24/24) of the participants showed a measure of improvement as compared with 22 out of 25 participants in the pimecrolimus group (RR 1.13, 95% CI 0.96 to 1.33).

- Assessment of erythema or telangiectasia, or both, at end of study

On a scale from 0 to 3 (higher = worse), erythema scores reduced by 0.92 (SD 0.24) in the metronidazole group and 0.92 (SD 0.35) in the pimecrolimus group (MD 0.0, 95% CI 0.17 to 0.17). Both treatments failed to show any improvement in telangiectasia.

- Lesion counts

The mean changes in number of lesion counts were from 16.0 (SD 4.6) to 0.6 (SD 1.5) in the metronidazole group and from 26 (SD 14.4) to 3.7 (SD 6.8) in the pimecrolimus group. These data were skewed, and there was an important baseline imbalance in the number of lesions.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(37) Topical ciclosporin ophthalmic emulsion 0.05% twice daily versus artificial tears twice daily for the treatment of ocular rosacea

One study at unclear risk of bias examined this comparison (Schechter 2009), see Summary of findings table 11.

Primary outcomes

Change in HRQOL at end of study

Assessment of changes in quality of life were carried out with the Ocular Surface Disease Index (OSDI) (scale 0 to 100, 100 = worst). Baseline scores were 19.1 (SD 13.9) in the topical ciclosporin group and 16.9 (SD 15.8) in the artificial tears group. The difference between the change scores at completion of the study was -8.6 in favour of topical ciclosporin (95% CI -15.42 to -1.78; P = 0.01), which equated to a moderate improvement in quality of life.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Only one participant in the topical ciclosporin group (n = 21) reported an adverse event and 0/16 in the artificial tears group, which consisted of stinging (RR 2.32, 95% CI 0.10 to 53.42).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The data from these assessments provided evidence for the effectiveness of topical ciclosporin in the treatment of ocular rosacea. The Schirmer's test determines whether the eye produces enough tears to keep it moist. Paper strips are inserted into the eye for several minutes to measure the production of tears, and then the paper is removed and the amount of moisture measured. At baseline the mean Schirmer scores were 9.7 mm (SD 5.1) in the ciclosporin group compared with 10.2 mm (SD 5.8) in the artificial tears group. The mean difference between the groups at the end of the study was 4.1 mm (95% CI 1.66 to 6.54; P = 0.001), which indicates a significant improvement in the ciclosporin group. Furthermore, the change score of 3.6 seconds in the tear break-up time in favour of the ciclosporin group (95% CI 2.59 to 4.61; P < 0.00001) provided an indication of the role played by topical ciclosporin in improving tear quality.

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(38) Rosacea treatment system (RTS) (gentle cleanser, metronidazole 0.75% gel, hydrating complexion corrector and skin balancing sunscreen SPF 30) twice daily versus RTS without metronidazole twice daily

One three-armed study with a small sample size (30 participants) assessed as at unclear risk of bias addressed this comparison (Leyden 2011).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Participant assessments were made with a 5-point Likert scale (0 = none, 4 = severe). No SDs were provided and the investigator was unable to provide these. The mean score in the RTS + metronidazole group decreased from 2.6 to 2.0, whilst the group on RTS without metronidazole had a smaller reduction from 2.5 to 2.2.

In the RTS + metronidazole group 50% were very satisfied and 20% satisfied compared to 30% very satisfied and 40% satisfied in the comparator group.

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in either group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

None had more than moderate improvement on a 7-point Likert scale. In the RTS + metronidazole group 4/10 achieved moderate improvement versus 1/10 in the comparator group (RR 4.00, 95% CI 0.54 to 29.80).

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema decreased on a 5-point Likert scale from 2.8 to 2.4 in the RTS + metronidazole group and from 2.5 to 2.3 in the RTS without metronidazole group. No SDs were provided.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(39) Rosacea treatment system (RTS) (gentle cleanser, metronidazole 0.75% gel, hydrating complexion corrector and skin balancing sunscreen SPF 30) twice daily versus metronidazole 0.75% and standard skin care regimen twice daily

This was the second comparison from the three-armed study of Leyden 2011.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Assessments were made on a 5-point Likert scale. In the RTS + metronidazole group the scores decreased from 2.6 to 2.0, and in the metronidazole group + standard skin care regimen the score remained unchanged at 2.0.

Percentages regarding satisfaction were for the RTS + metronidazole group 50% very satisfied and 20% satisfied, and for the metronidazole group + standard skin care regimen 78% was satisfied.

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in the group on RTS + metronidazole (n = 10), and two participants reported adverse events in the group treated with metronidazole + standard skin care regimen (n = 10) (RR 0.20, 95% CI 0.01 to 3.70).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In the RTS + metronidazole group 4/10 showed moderate improvement versus 1/10 in the metronidazole + standard skin care regimen group (RR 4.00, 95% CI 0.54 to 29.80).

- Assessment of erythema or telangiectasia, or both, at end of study

There was a decrease in erythema from 2.8 to 2.4 in the RTS + metronidazole group, it remained at 2.3 in the metronidazole + standard care regimen group.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(40) Rosacea treatment system (RTS) without metronidazole twice daily versus metronidazole 0.75% and standard skin care regimen twice daily

This was the third comparison in Leyden 2011.

Primary outcomes

Change in health-related quality of life (HRQOL) at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

In the RTS group without metronidazole the score decreased from 2.5 to 2.2, and in the metronidazole group + standard skin care regimen it remained at 2.0.

In the RTS group without metronidazole 30% were very satisfied and 40% satisfied, whilst in the group on the metronidazole and standard skin care regimen 78% were satisfied.

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in the RTS without metronidazole group (n = 10), and two participants reported adverse events in the group treated with the metronidazole + standard skin care regimen (n = 10) (RR 0.20, 95% CI 0.01 to 3.70).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Only 1/10 showed moderate improvement in both groups (RR 1.00, 95% CI 0.07 to 13.87).

- Assessment of erythema or telangiectasia, or both, at end of study

There was a slight reduction from 2.5 to 2.3 in the RTS without metronidazole group and it remained at 2.3 in the metronidazole + standard skin care regimen group.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(41) 4-Ethoxybenzaldehyde 1% twice daily versus vehicle twice daily

The anti-inflammatory effect of this intervention in reducing facial erythema was evaluated in only one study (Draelos 2005b), assessed as at high risk of bias. No SDs were reported.

Primary outcomes

Change in health-related quality of life (HRQOL) at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

There were no adverse events reported in either group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Ten out of 20 participants in the active group had a marked improvement from baseline compared to 0/10 in the vehicle group (RR 11.00, 95% CI 0.71 to 170.64), which was not statistically significant.

- Assessment of erythema or telangiectasia, or both, at end of study

Improvement in erythema was seen in 43.7% of the active treatment group, and a 16.7% improvement in the vehicle group. No exact baseline values or study endpoint values were reported.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(42) Cream containing 1% extract of a flavonoid-rich plant *Chrysanthellum indicum* twice daily versus placebo (vehicle) twice daily

One trial (Rigopoulos 2005) assessed as at high risk of bias reported data for this comparison.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

A larger number of participants in the active intervention than in the vehicle cream group reported improvement in rosacea severity, 60/125 participants with the flavonoid cream and 36/121 in the vehicle arm (RR 1.61, 95% CI 1.16 to 2.24; P = 0.004; NNTB = 6, 95% CI 4 to 17).

Proportion of participants who reported an adverse event throughout the study period

There were no statistically significant differences in number experiencing adverse events: 13/125 in the flavonoid cream group experienced adverse events and 8/121 with vehicle (RR 1.57, 95% CI 0.68 to 3.66).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Based on the final investigators' assessment 64/125 participants in the active treatment group showed improvement, compared to 52/121 with vehicle (RR 1.19, 95% CI 0.91 to 1.56). Clearing or marked improvement on rosacea overall assessment (seven grade scale) was scored as 78/125 in the active treatment group compared to 61/121 on vehicle (RR 1.24, 95% CI 0.99 to 1.55).

- Assessment of erythema or telangiectasia, or both, at end of study

  Reduction in erythema was 53.65% in the flavonoid rich cream group versus 44.23% for the vehicle group.

- Lesion counts

  Not assessed.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(43) Praziquantel 3% ointment twice daily versus vehicle ointment twice daily

This comparison was evaluated in a single study at high risk of bias (Bribeche 2015).

Primary outcomes

Change in HRQOL at end of study

The DLQI decreased in the praziquantel group from 15.8 (very large effect on quality of life) to 4.6 (small effect on quality of life), which was a clinically important reduction (Basra 2008; Basra 2015). The reduction in the vehicle group was smaller, from 14.6 to 7.9 (moderate effect on quality of life), but also clinically important.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

In the praziquantel group 1/43 reported an adverse event versus 2/22 in the vehicle group (RR 0.26, 95% CI 0.02 to 2.67). Dryness was mild in intensity and resolved after using a moisturizer.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Based on the IGA (5-point Likert scale) at baseline 39/43 had a score of mild to moderate in the praziquantel group and at the end of study 35/43 had a score of minimal or clear. Corresponding values for vehicle were 21/22 and 5/22, respectively. RR at end of study 3.58 (95% CI 1.64 to 7.84; P = 0.001).

- Assessment of erythema or telangiectasia, or both, at end of study

  At the start of the study 38/43 had a score of moderate to significant erythema on the 5-point CEA scale, and at the end of the study 38/43 had no or mild erythema. In the vehicle group 19/22 had moderate to significant erythema at the start of study and

after 16 weeks 9/22 had no or mild erythema. RR at end of study 2.16 (95% CI 1.29 to 3.61; P = 0.003).

- Lesion counts

  Not assessed.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(44) BFH772 1% (betamethasone, calcipotriol) ointment versus metronidazole 1% cream

One small sample size (N = 36) three-armed study of participants with erythema consistent with erythematotelangiectatic rosacea reported data for this comparison (NCT01449591). This study was assessed as at unclear risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

The mean participant's assessment of flushing frequency was -0.2 in the BFH772 1% group compared to -0.3 in the metronidazole group.

The mean change in self assessments of erythema, after 12 weeks, in the BFH772 1% group showed no change: 0 (SD 0.7) compared to -0.5 (SD 0.8) in the metronidazole group with a MD of 0.5 (95% CI -0.10 to 1.10).

Proportion of participants who reported an adverse event throughout the study period

Six of 12 participants in the BFH722 1% group reported adverse events compared to 4/12 in the metronidazole group (RR 1.50, 95% CI 0.56 to 4.00). Most adverse events were not drug related (gastrointestinal disorders, psychiatric disorders etc).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Mean change in IGA of rosacea was -0.4 (SD 0.5) in the BFH722 1% group versus -0.5 (SD 0.5) in the metronidazole group (MD 0.10, 95% CI -0.30 to -0.50).

- Assessment of erythema or telangiectasia, or both, at end of study

  IGA of telangiectasia showed a change from baseline of -0.2 (SD 0.4) in the BFH722 1% group compared to 0.4 (SD 1.2) in the metronidazole group with a MD of -0.60 (95% CI -1.32 to 0.12).

- Lesion counts

There was a small increase in mean number of lesion counts of 0.5 (SD 0.1) in the BFH722 1% group compared to a small decrease of 0.5 (SD 1.4) in the metronidazole group (MD 1.00, 95% CI 0.21 to 1.79; P = 0.01).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(45) BFH772 1% (betamethasone, calcipotriol) ointment versus vehicle ointment

This comparison was evaluated in NCT01449591. None of the data showed that BFH772 1% was any better than vehicle ointment.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

In the group treated with BFH722 1% ointment the mean participant-assessed change in flushing frequency was -0.2 compared to -0.7 in the vehicle ointment group.

The change in facial redness was 0 (SD 0.7) for the BFH772 group compared to -0.5 (SD 0.9) in the vehicle ointment group (MD 0.50, 95% CI -0.15 to 1.15).

Proportion of participants who reported an adverse event throughout the study period

In the BFH722 1% group 6/12 reported an adverse event compared to 4/12 with vehicle (RR 1.50, 95% CI 0.56 to 4.00).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The reductions on the IGA scale were 0.4 (SD 0.5) for the BFH772 1% group and 0.5 (SD 0.7) for the vehicle group (MD 0.10, 95% CI -0.39 to 0.59).

- Assessment of erythema or telangiectasia, or both, at end of study

IGA of telangiectasia showed a change from baseline of -0.2 (SD 0.4) in the BFH722 1% group compared to 0.1 (SD 0.6) in the vehicle group with a MD of -0.30 (95% CI -0.71 to 0.11).

- Lesion counts

There were minimal changes in lesion counts: 0.5 (SD 1.0) in the BFH772 1% group and 0.1 (SD 0.4) in the vehicle group (MD 0.40, 95% CI -0.21 to 1.01).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(46) TDT 068 gel twice daily versus vehicle gel twice daily

TDT 068, a topical drug-free gel containing ultra-deformable Sequessome™ vesicles, was evaluated in a single study (Luger 2015) assessed as at low risk of bias. None of the outcomes suggested that TDT 068 gel was more effective than vehicle gel.

Primary outcomes

Change in HRQOL at end of study

The RosaQoL (range 1 to 5) reduced by 0.08 (SD 0.38) in the TDT 068 gel group and by 0.08 (SD 0.37) in the vehicle group (MD 0.00, 95% CI -0.20 to 0.20).

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Adverse events were reported in 5/40 in the TDT 068 gel group versus 4/21 with vehicle. These consisted mostly of skin irritation and pruritus (RR 0.66, 95% CI 0.20 to 2.19).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

This outcome was assessed with the Rosacea Standard Grading System (RSGS) (Wilkin 2004). Investigators stated that there was no statistically significant difference in reduction in the total score at the end of the four week study (investigators reported a difference at 4 weeks of 0.94 (SD 2.03), 95% CI –0.20 to 2.08; P value of 0.11).

- Assessment of erythema or telangiectasia, or both, at end of study

Non-transient erythema decreased from baseline by 0.34 (SD 0.63) in the TDT 068 gel group (n = 38) and 0.05 (SD 0.51) in the vehicle group (n = 20) (MD -0.29, 95% CI -0.59 to 0.01). Transient erythema reduced from baseline by 0.55 (SD 0.66) and 0.35 (SD 0.50) respectively (MD -0.20, 95% CI -0.50 to 0.10). Telangiectasia reduced by 0.26 (SD 0.55) and 0.15 (SD 0.50) respectively (MD -0.11, 95% CI -0.39 to 0.17). All of these differences were not statistically significant.

- Lesion counts

No exact data were provided other than as a graphical representation, which suggested no change.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(47) Crotamiton once daily versus benzyl benzoate once daily

This comparison was examined in a single study that only addressed one of our outcomes, that is adverse events (Rodríguez 2003). The study was assessed as at unclear risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

There were no adverse events in either group.

Secondary outcomes

None of our secondary outcomes were assessed.

(48) Skin care product containing ambophenol, neurosensine and La Roche-Posay thermal spring water twice daily versus vehicle twice daily

This cosmetic was evaluated in one study that provided limited data (Seité 2013). The study was assessed as at unclear risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Global efficacy of rosacea was assessed by the participants to be good or excellent in 10/32 in the test formula group compared to 5/34 in the vehicle group (RR 2.13, 95% CI 0.81 to 5.54).

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Rosacea improved or was cured in 20/32 in the test formula group compared to 11/34 in the vehicle group (RR 1.93, 95% CI 1.11 to 3.37; P = 0.02). A rating of global efficacy of good to excellent was seen in 10/32 in the test formula group compared to 1/34 in the vehicle group (RR 10.63, 95% CI 1.44 to 78.36; P = 0.02). Both these assessments were not in concordance with the participants' judgements, where no statistically significant difference was seen.

- Assessment of erythema or telangiectasia, or both, at end of study

  Not assessed.

- Lesion counts

  Not assessed.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(49) SEI003 cream versus vehicle

One study with a small sample size (Two 2014), assessed as at high risk of bias, evaluated the efficacy of this topical serine protease inhibitor.

Primary outcomes

Change in HRQOL at end of study

Not assessed

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in either group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

IGA decreased by 1.00 (SD 0.57) in the SEI003 group (n = 11) and 0.7 (SD 0.5) in the vehicle group (n = 4), MD of 0.30, however these data were skewed, analysed inappropriately and have not been summarised or reported here.

- Assessment of erythema or telangiectasia, or both, at end of study

  The CEA reduced by 4.10 (SD 1.62) in the SEI003 group and by 3.5 (SD 1.43) in the vehicle group (MD -0.60). However, as with the IGA outcome, these data were skewed.

- Lesion counts

  Not assessed.

- Time needed until improvement

  Not assessed.

- Duration of remission

Not assessed.

(50) P-3075 cream (based on hydroxypropyl chitosan and potassium azeloyl diglycinate) twice daily versus vehicle cream twice daily

This comparison was evaluated in a single study at unclear risk of bias (Berardesca 2012) and which provided limited data, mainly on erythema.

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

No global efficacy assessment was done.

- Assessment of erythema or telangiectasia, or both, at end of study

No exact data per group were provided on the data assessed with the Mexameter (colorimeter, measuring skin colour), but authors state that at end of treatment "the composite erythema index representing the sum of the 4 site-specific erythema indices showed a statistically significant decrease at day 28 of 167.00; P < 0.001)", in favour of P-3075.

Based on a 4-point Likert scale (0 = none, 3 = severe) the investigators concluded "that at day 28 in the P-3075 group, the clinical assessment of erythema showed a statistically significant decrease (P = 0.005 in the chi-square test and P = 0.011 in the Fisher exact test)". At day 28, 27/28 of the participants treated with P-3075 had no erythema, 1/28 had mild erythema, and in the vehicle group 9/14 had no erythema and 5 had mild erythema.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(51) Kanuka honey +10% glycerine 30 to 60 min application twice daily versus cetomacrogol cream 30 to 60 min application twice daily

This comparison was examined in a single study assessed at unclear risk of bias (Braithwaite 2015).

Primary outcomes

Change in HRQOL at end of study

The DLQI was used to measure quality of life and in the kanuka honey group (69) the DLQI decreased by 1.59; in the cetomacrogol cream group (69) there was a reduction of 1.68. Both are small reductions not meeting the minimal important difference.

Participant-assessed changes in rosacea severity at end of study

This outcome was measured with a visual analogue scale (VAS) (0 to 100, higher = worse). The mean change from baseline in the kanuka honey group was -10.55 (SD 12.92) compared with -1.20 (SD 12.11) in the cetomacrogol cream group (MD -9.35, 95% CI -13.53 to -5.17; P < 0.0001) favouring kanuka honey.

Proportion of participants who reported an adverse event throughout the study period

In the kanuka honey group 23/69 reported 31 adverse events versus 27/69 reporting 37 adverse events in the cetomacrogol cream group (RR 0.85, 95% CI 0.55 to 1.33). Reported adverse events in both groups included burning, itching, peeling, stinging, dry skin and pain, which could also be ongoing rosacea symptoms.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

This outcome was assessed with Investigator Global Assessment of Rosacea Severity Score (IGA-RSS)(7 point Likert scale, 0 = clear, 6 = severe). In the kanuka honey group 24/69 had a 2 grade improvement versus 12/69 in the cetomacrogol cream group (RR 2.00, 95% CI 1.09 to 3.67; P = 0.03; NNTB = 6, 95% CI 3 to 33).

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(52) Timolol 1% in oil free base once daily versus placebo (oil free base) once daily

The efficacy of timolol 1% application was investigated in one study at low risk of bias (Jaque 2012). Timolol 1% appeared not be more effective than placebo for any outcome.

Primary outcomes

Change in HRQOL at end of study

The mean DLQI for both groups was 6 (moderate impact on quality of life) at baseline and reduced to 1 (no impact on quality of life) at week 12 with no difference between the two groups.

Participant-assessed changes in rosacea severity at end of study

After 12 weeks participants in both groups indicated on a visual analogue scale (VAS) the percentage of improvement (0-100%). The group treated with timolol (n = 31) improved 70% versus 80% in the group treated with placebo (n = 30). Investigators reported "P = 0.37"

Proportion of participants who reported an adverse event throughout the study period

There were 14/34 participants in the timolol group reporting an adverse event compared with 19/33 in the placebo group (RR 0.72, 95% CI 0.44, 1.18)

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Physicians also used a VAS to rate improvement (0-10, higher is worse). In the timolol group VAS score decreased from 8 to 6 in 12 weeks time versus from 8 to 4 in the placebo group. The investigators report "P =0,062".

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema was evaluated with a colorimeter and showed a mean change of -1.77 (SD 1.90) in the timolol group compared with -2.27 (SD 2.41) in the placebo group (MD 0.50, 95% CI -0.54 to 1.54).

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(53) IncobotulinumtoxinA injections across cheeks up to 20 units versus saline injections

Both treatments were given once in a study assessed at high risk of bias (Dayan 2017). The follow-up was 16 weeks. Only data for the active group were presented and not for the control group. We failed to obtain additional information from the investigators. Investigators reported "Subjects receiving the placebo did not experience improvements in any of the RCS criteria" (*Rosacea Clinical Scorecard*; Wilkin 2004). Primary signs and symptoms (flushing, non transient erythema, papules and pustules and telangiectasia) may be graded as absent, mild, moderate, or severe (0-3), and most secondary features (edema, ocular manifestations, peripheral location) may be graded simply as absent or present. Secondary features

such as burning or stinging, plaques dry appearance and phymatous changes are also graded as absent to severe (0 to 3).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Data of Patient's Global Assessment (RCS) were available for three of the four people treated with the incobotulinumA injections. Based on a Likert scale (0 = absent, 1 = mild, 2 = moderate, 3 = severe) the three participants on active treatment showed a reduction of 1 after 16 weeks.

Proportion of participants who reported an adverse event throughout the study period

Although this was a prespecified outcome in the protocol, no information on adverse events was provided.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The same scoring system was used by the patients and the physicians. The score decreased by 1 for erythematotelangiectatic rosacea and by 1.33 for papulopustular rosacea. Only data of three participants were provided.

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome was also assessed with RSC and showed for the three participants treated with incobotulinumtoxinA injections a decrease of 1.

- Lesion counts

A decrease of 0.96 on the RCS was reported for the 3 participants treated with incobotulinumtoxinA injections.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(54) Tranexamic acid 5% solution twice daily versus vehicle twice daily

This comparison was examined in one within-patient study assessed at high risk of bias (Zhong 2015) and provided very limited data.

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Data had to be estimated from a figure based on chroma meter readings. The "Chroma a value" value (erythema) decreased after two weeks from 22 to 15 on the side treated with tranexamic acid 5% (n = 30) compared with an increase from 20 to 21 on the side treated with vehicle.

- Lesion counts

Although this was not a prespecified outcome it provides some data on lesion count (medians). There was a reduction of 6.5 to 1 after two weeks of treatment on the side treated with tranexamic acid 5% solution versus a decrease from 6.5 to 2.5 on the vehicle side. The investigators report that the difference in score is statistically significant but a difference of one lesion cannot be considered to be important to a patient.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(55) Diclofenac sodium 3 % gel once daily versus placebo gel once daily

One within-patient study at unclear risk of bias examined this comparison (EUCTR2011-002057-65-DE) and diclofenac 3% did not appear to be effective

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

There were eight adverse events in the side (n = 20) treated with diclofenac 3% gel of which two were dermatological adverse events and there were seven adverse events on the side treated with placebo gel (n = 20) of which one was a dermatological adverse event.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

After four weeks there was absolutely no change on both sides when compared to baseline.

- Lesion counts

No precise data were provided but the investigators reported that there was no difference between the two treatments in lesion count.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Systemic interventions: studies with oral antibiotics

(56) Tetracycline versus placebo

Two trials at unclear risk of bias were included (Marks 1971; Sneddon 1966), see Summary of findings table 12.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Only one of the studies provided data for this outcome (Marks 1971). Based on these participant-assessed outcomes there was insufficient evidence to demonstrate that tetracycline was more effective than placebo. In the tetracycline group 14/20 participants considered they were better to much better versus 9/19 in the placebo group (RR 1.48, 95% CI 0.85 to 2.57).

Proportion of participants who reported an adverse event throughout the study period

In Marks 1971 only one adverse event was reported in each group, diarrhoea in the tetracycline group and maculopapular erythema in the placebo group (RR 0.95, 95% CI 0.06 to 14.13). This outcome was not assessed in Sneddon 1966.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In contrast with the participant-assessed changes these assessments indicated that tetracyclines appeared to be significantly more effective than placebo in the treatment of rosacea. In the Marks 1971 study 17 out of 20 participants in the tetracycline group were considered to be improved versus 4 of 19 in the placebo group (RR 4.04, 95% CI 1.66 to 9.83; P = 0.002; NNTB = 2, 95% CI 2 to 3). In Sneddon 1966 28 of 36 participants in the tetracycline group improved versus 19 of 42 in placebo (RR 1.72, 95% CI 1.18 to 2.50; P = 0.005; NNTB = 4, 95% CI 2 to 9). Data from the two studies could not be pooled (I^2 = 70%).

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome was not assessed in Sneddon 1966, and there were no significant changes in erythema in Marks 1971.

- Lesion counts

The mean reduction in number of lesions in Marks 1971 was 16.05 (SD 13.45) in the tetracycline group (n = 17) compared to 1.41 (SD 9.52) in the placebo group (n = 17) but these data were skewed (MD -14.64).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(57) Anti-inflammatory dose doxycycline 40 mg versus placebo

Two studies assessed as at low risk of bias (Del Rosso 2007a; Del Rosso 2007b), and two studies at unclear risk of bias (Di Nardo 2016; NCT00560703) evaluated this comparison. See Summary of findings table 13. Study duration in Del Rosso 2007a and Del Rosso 2007b was 16 weeks, but in Del Rosso 2007b the participants were re-evaluated at 20 weeks. Only the data from the 16 week assessment was analysed for this review. Di Nardo 2016 focused on biomarkers (cathelicidin and protease activity) and of NCT00560703 focused on ocular blepharitis in patients with rosacea.

Primary outcomes

Change in HRQOL at end of study

This outcome was only addressed in NCT00560703 and the Ocular Surface Disease Index (OSDI) was used. The overall OSDI score defined the ocular surface as normal (0-12 points) or as having mild (13-22 points), moderate (23-32 points), or severe (33-100 points) disease. No baseline data were provided but in the 46 participants treated with doxycycline a change from baseline in OSDI was seen of -5.15 (SD 14) compared with -8.7 (SD 17.7) in the 24 participants on placebo (MD 3.55, 95% CI -4.61 to 11.71).

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

The number of participants reporting adverse events in the four studies was 181/399 in the doxycycline group versus 139/378 in the placebo group (RR 1.27, 95% CI 1.08 to 1.49; P = 0.003; I^2 = 0%; NNTH = 12, 95% CI 6 to 59; see Analysis 9.1). The majority of these adverse events were considered mild or moderate in severity.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Three of the studies (Del Rosso 2007a; Del Rosso 2007b; Di Nardo 2016) reported on IGA data as clear or near clear (IGA 0 or 1). Ninety-one participants in the

doxycycline group (n = 353) achieved an IGA score of 0 (clear) or 1 (near clear) versus 53 in the placebo group (n = 354) (RR 1.69, 95% CI 1.26 to 2.28; P = 0.0005; I^2 = 0%; NNTB = 9, 95% CI 6 to 20). See Analysis 9.2.

In NCT00560703 the physicians assessed the change in bulbar conjunctival hyperemia using a categorical scale of 0 (clear) to 4 (severe). The mean change from baseline was -0.61 (SD 0.80) in the 46 participants on doxycycline versus -0.60 (SD 0.71) in the placebo group (n = 24)(MD -0.01, 95% CI -0.38 to 0.36).

- Assessment of erythema or telangiectasia, or both, at end of study

In three studies this outcome was measured with Clinician's Erythema Assessment scale (range 0 to 4, 0 = none and 4 is severe redness). The MD between the two groups was -0.48 (95% CI -0.97 to 0.00; P = 0.05; I^2 = 28%; Analysis 9.3) in favour of doxycycline 40 mg.

- Lesion counts

As the number of lesions at baseline was much lower in the study of Di Nardo 2016 we have not included the data from this study in the pooled the data (I^2 = 70%). The MD of pooled data of Del Rosso 2007a and Del Rosso 2007b was -5.51 lesions (95% CI -7.81 to -3.21; P < 0.00001; I^2 = 0%; Analysis 9.4). For the study of Di Nardo 2016 the reduction in lesion count in the 84 participants in the doxycycline group was 4.3 (SD 7.9) compared with 3.2 (SD 8.6) in the 86 participants in the placebo group (MD -1.10, 95% CI -3.58 to 1.38).

- Time needed until improvement

The data from two studies (Del Rosso 2007a; Del Rosso 2007b) were presented in the reports as graph plots, which did not permit accurate data to be extracted. However, the steepest changes in the graph plots occurred within the first three weeks in the doxycycline group, which provided an indication of the time needed for improvement of inflammatory lesions relative to placebo.

- Duration of remission

Not assessed.

(58) Anti-inflammatory dose doxycycline 40 mg once daily versus placebo once daily as maintenance therapy during 40 weeks

This study at high risk of bias evaluated the efficacy in preventing relapse and safety of long-term treatment with doxycycline after a 12 week treatment with doxycycline 40 mg and topical metronidazole. Only participants that achieved an IGA of clear or near clear entered the second, randomised phase (NCT01426269).

Primary outcomes

Change in HRQOL at end of study

The RosaQoL scores (1 to 5) were 3.3 for both groups at the end of the first open phase of the study and decreased to 2.8 in the participants that continued with

doxycycline (n = 65), while the participants that switched to placebo (n = 65) had a smaller reduction to 3.1.

Participant-assessed changes in rosacea severity at end of study

This outcome was assessed with a satisfaction questionnaire which reported the percentages of participants that were not bothered by or did not experience symptoms. The percentages for tightness of the skin were 64.6% for the doxycycline group and 60% for the placebo group, sensitivity of the skin 64.6% versus 55.4%, stinging and burning 66.1% versus 47.7%, roughness 55.4% versus 49.3%, and itchy skin sensation 58.4% versus 52.3%, indicating that higher percentages not experiencing symptoms were in the doxycycline group.

Proportion of participants who reported an adverse event throughout the study period

Adverse events were reported in 8/65 of the participants in the doxycycline group and 9/65 in the placebo group (RR 0.89, 95% CI 0.37 to 2.16).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

At the start of the randomised second phase all 65 participants in both groups had an IGA of clear or near clear. At the end of 40 weeks 41/65 were still clear to near clear in the doxycycline group, while in the placebo group this number had dropped to 33/65.

- Assessment of erythema or telangiectasia, or both, at end of study

The mean change in CEA score was -0.50 (SD 2.14) for the doxycycline group and 0.40 (SD 2.36) for the placebo group (MD -0.90, 95% CI -1.67 to -0.13; P = 0.02), which was a statistically significant difference in favour of doxycycline.

- Lesion counts

The mean number of lesion counts increased by 0.90 (SD 1.61) in the doxycycline group and 0.30 (SD 1.20) in the placebo group (MD 0.60, 95% CI 0.11 to 1.09; P = 0.02), which was a statistically significant difference in favour of placebo; but such a small difference in lesion count is unlikely to be important. However, it suggested that when treatment success had been achieved with doxycycline there was a prolonged, sustained and relevant effect which was shown to continue up to 40 weeks in the placebo group.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

During the 40 weeks, 9/65 relapsed (return to the baseline lesion count or return to the baseline IGA score) in the doxycycline group compared to 18/65 in the placebo group (RR 0.50, 95% CI 0.24 to 1.03).

(59) Minocycline 100 mg once daily versus doxycycline 40 mg once daily

A non-inferiority study assessed as at unclear risk of bias examined these interventions (van der Linden 2017). The study lasted 16 weeks with a follow-up to week 28. See Summary of findings table 14

Primary outcomes

Change in HRQOL at end of study

This outcome was measured with the disease specific RosaQoL (range 1 to 5). In the group treated with minocycline 100 mg (n = 40) the reduction was 0.86 (SD 0.14) versus a reduction of 0.62 (SD 0.13) in the doxycycline 40 mg group (MD -0.24, 95% CI -0.30 to -0.18; P < 0.00001) favouring minocycline.

Participant-assessed changes in rosacea severity at end of study

The Patient's Global Assessment (PaGA) was used to assess this outcome (1 = excellent improvement, 5 = worse). In the minocycline 100 mg group 22/40 participants achieved an excellent or good improvement (PaGA 1 or 2) compared with 20/40 in the doxycycline 40 mg group (RR 1.10, 95% CI 0.72 to 1.67).

Proportion of participants who reported an adverse event throughout the study period

In the minocycline 100 mg group 27/40 reported an adverse event versus 23/40 in the doxycycline 40 mg group (RR 1.17, 95% CI 0.83 to 1.65). The adverse events reported were quite similar in both groups (e.g. gastro-intestinal side effects and headache).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The physicians used the Investigator's Global Assessment scale (0 = clear, 4 = severe). IGA success was defined as a score of 'clear' or 'near clear' (IGA 0–1). In the minocycline 100 mg group 24/40 achieved treatment success versus 7/40 in the doxycycline 40 mg group (RR 3.43, 95% CI 1.67 to 7.04; P = 0.0008; NNTB = 2, 95% CI 2 to 4).

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome was assessed with the Clinician's Erythema Assessment (CEA)(0 to 4, clear to severe). CEA success (at least one-point decrease) was obtained in 16/40 participants in the minocycline 100 mg compared with 13/40 participants in the doxycycline 40 mg (RR 1.23, 95% CI 0.68 to 2.21).

- Lesion counts

In the minocycline 100 mg group a reduction of 14 (SD 14.3) was observed versus a reduction of 13 (SD 17.3) in the doxycycline 40 mg group (MD -1.00, 95% CI -7.96 to 5.96).

- Time needed until improvement

Not assessed.

- Duration of remission

At week 28, 13/24 patients still had an IGA of ‘clear’ or ‘near clear’ in the minocycline 100 mg group and 4/7 in the doxycycline 40 mg group (RR 0.95, 95% CI 0.45 to 1.99). Only 2/30 had a relapse (an increase in inflammatory lesion count by ≥ 50% of the lesion count reduction observed at week 16) in the minocycline 100 mg group versus 12/25 in the doxycycline group (RR 0.14, 95% CI 0.03 to 0.56; P = 0.006; NNTB = 2, 95% CI 2 to 5).

(60) Azithromycin 500 mg three times a week then tapered versus doxycycline 100 mg once daily

Only one study assessed as at high risk of bias addressed this comparison (Akhyani 2008). See Summary of findings table 15.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Although there was no measurable difference in change in severity between the two treatment groups, 29/37 participants in the azithromycin group considered themselves improved after three months versus 24/30 in the doxycycline group (RR 0.98, 95% CI 0.77 to 1.25).

Proportion of participants who reported an adverse event throughout the study period

Diarrhoea was reported in 4/37 participants in the azithromycin group, and 2/30 in the doxycycline group experienced epigastric burning (RR 1.62, 95% CI 0.32 to 8.26).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

At baseline these were 19.24 (SD 9.67) in the azithromycin group and 1.90 (SD 3.28) at 3 months, and similarly in the doxycycline group 18.86 (SD 8.95) and 2.34 (SD 3.47) at three months. However, in addition to having large SDs these data were skewed.

- Time needed until improvement

Not assessed.

- Duration of remission

No data were available for the duration of remission, but both groups showed no statistically significant change between the third month of treatment and the second month post-treatment in the mean inflammatory lesion counts.

(61) Ampicillin versus placebo

One study at unclear risk of bias provided data for this comparison (Marks 1971). The dosage of ampicillin was not reported.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

These assessments demonstrated significant improvements in favour of ampicillin over placebo, such that 14/17 participants treated with ampicillin versus 9/19 in the placebo group (RR 1.74, 95% CI 1.03 to 2.93; P = 0.04; NNTB = 3, 95% CI 2 to 17) considered themselves improved.

Proportion of participants who reported an adverse event throughout the study period

Three of 17 participants treated with ampicillin reported adverse events versus 1/19 in the placebo group (RR 3.35, 95% CI 0.38 to 29.26). The adverse events were mild and transient, and one participant in the ampicillin group experienced diarrhoea.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

These were generally in line with the participant-assessed changes but there was no statistically significant difference between the groups. Nine of 17 participants treated with ampicillin reported improvement compared with 4/19 in the placebo group (RR 2.51, 95% CI 0.94 to 6.70).

- Assessment of erythema or telangiectasia, or both, at end of study

  There were no significant changes in erythema.

- Lesion counts

  Mean change from baseline was -11.2 (SD 19.23) in the ampicillin group (n = 15) and 1.41 (SD 9.52) in the placebo group, but these had large SDs and skewed data (MD -9.79, SD 14.86; P = 0823).

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(62) Oral tetracycline versus ampicillin

Only one study at unclear risk of bias provided data for this comparison (Marks 1971).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

These assessments did not indicate any difference in efficacy between the two interventions: 14/20 participants treated with tetracycline considered themselves improved versus 14/17 in the ampicillin group (RR 0.85, 95% CI 0.59 to 1.22).

Proportion of participants who reported an adverse event throughout the study period

Most side effects were mild and transient, 3/17 participants in the ampicillin group reported adverse events compared with 1/20 in the tetracycline group (RR 0.28, 95% CI 0.03 to 2.48).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

These were in line with the participant-assessed changes, 17/20 in the tetracycline group reported they had improved versus 9/17 in the ampicillin group (RR 1.61, 95% CI 0.99 to 2.61).

- Assessment of erythema or telangiectasia, or both, at end of study

There were no significant changes in erythema.

- Lesion counts

Mean change from baseline was -16.45 (SD 8.83) in the tetracycline group and -11.53 (SD 15.96) in the placebo group, but these had large SDs and skewed data (MD -4.86 (SD 16.4); P = 0.4249).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(63) Oral oxytetracycline versus oral metronidazole

Only one study assessed as at unclear risk of bias provided data for this comparison (Saihan 1980).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

These were combined with the physician assessments and reported as unified scores.

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in either group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Combined scores of the participants and physicians ((scale - 1 = worse to 3 = much improved) demonstrated no statistically significant difference between the two groups in rosacea severity at the completion of the study. The mean severity scores (scale -1 to 3, with 3 = much improved) were 2.60 (SD 0.70) in the tetracycline group (n = 20) versus 2.30 (SD 1.00) in the metronidazole group (n = 18) with a MD of 0.30 (95% CI -0.25 to 0.85).

- Assessment of erythema or telangiectasia or both at end of study

Not assessed.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(64) Clarithromycin and omeprazole versus placebo in *Helicobacter pylori* positive patients with rosacea

The data from the single study at unclear risk of bias evaluating these interventions were skewed, had large SDs and were considered to be unusable (Bamford 1999). There were 22 participants in the clarithromycin and omeprazole group and 22 in the placebo group.

Primary outcomes

Change in HRQOL at end of study

Participant-assessed changes in rosacea severity at end of study

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event throughout the study period

One participant in the treatment group reported headaches during treatment, but no adverse events were reported in the placebo group (RR 3.00, 95% CI 0.13 to 69.87).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Mean change in total rosacea severity score was -4.50 (SD 2.12) in the active treatment group compared to -3.20 (SD 2.95) in the placebo group, but these data were very skewed. It should be noted that 25% of the participants in the active treatment group were still positive for *Helicobacter pylori* on the urea breath test despite having reported completing the antibiotic therapy.

- Assessment of erythema or telangiectasia, or both, at end of study

The mean reductions in erythema intensity were 2.00 (SD 1.55) in the active treatment group and 1.80 (SD 1.71) in the placebo group.

- Lesion counts

The mean reduction in pustule count was 15.30 (SD 9.56) in the active treatment group and 9.30 (SD 12.03) in the placebo group, and the data were very skewed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Systemic interventions: studies with oral antibiotics combined with topical treatments

(65) Anti-inflammatory dose doxycycline 40 mg and metronidazole gel 1% versus doxycycline 100 mg and metronidazole gel 1%

Only one study assessed as at unclear risk of bias evaluated these interventions (Del Rosso 2008). SDs were missing, some of which we were able to calculate. See Summary of findings table 16.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Four times as many adverse events were reported in the higher dose group compared with the 40 mg dose group. Six of the 44 participants treated with the anti-inflammatory dose of 40 mg had adverse events versus 26/47 participants in the 100 mg group (RR 0.25, 95% CI 0.11 to 0.54; P = 0.0005; NNTH = 3, 95% CI 2 to 5). The majority of these adverse events were gastrointestinal complaints.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Mean reduction in IGA was 1.6 (SD 0.27) in the 40 mg doxycycline group (n = 44) and also in the 100 mg doxycycline group (n = 47) (MD 0.00, 95% CI -0.11 to 0.11).

- Assessment of erythema or telangiectasia, or both, at end of study

Change in CEA from baseline (0 to 4, 0 = no redness present, 4 = severe redness) was -4.2 for the 40 mg group and -4.0 for the 100 mg group (investigators stated P = 0.50).

- Lesion counts

The mean change from baseline in lesion count was -12.5 (SD 6.64) for the 40 mg group versus -12.2 (SD 6.64) for the 100 mg group (MD -0.30, 95% CI -3.03 to 2.43).

- Time needed until improvement

Although this was not a pre-specified outcome a clear improvement was seen from week four in both groups.

- Duration of remission

Not assessed.

(66) Anti-inflammatory dose doxycycline 40 mg and azelaic acid 15% gel versus anti-inflammatory dose doxycycline 40 mg and metronidazole gel 1%

These treatments were evaluated in one study at unclear risk of bias (Del Rosso 2010). See Summary of findings table 17.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Excellent improvement was reported by 52/106 of the participants in the doxycycline + azelaic acid group compared to 47/101 in the doxycycline + metronidazole group (RR 1.05, 95% CI 0.79 to 1.40). The improvement score (1 = excellent, 4 = worse) was 1.6 in the doxycycline + azelaic acid group and 1.7 in the comparator group.

Proportion of participants who reported an adverse event throughout the study period

Very few participants reported adverse events: 2/106 in the doxycycline + azelaic acid group and 7/101 in the doxycycline + metronidazole group (RR 0.27, 95% CI 0.06 to 1.28).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Treatment responses based on an IGA score of 0, 1 or 2 (clear, minimal or mild) were seen in 83/106 in the doxycycline + azelaic acid group and in 73/101 in the doxycycline + metronidazole group (RR 1.08, 95% CI 0.93 to 1.27). Assessments of

treatment success (IGA 0 or 1) were 66/106 versus 53/101 participants respectively (RR 1.19, 95% CI 0.94 to 1.50). Investigators' overall rating of improvement was 1.8 for both groups.

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

Mean reductions in lesion counts were 10.5 (SD 9.14) for the doxycycline + azelaic acid group and 9.4 (SD 9.38) in the comparator group (MD -1.10, 95% CI -3.62 to 1.42).

- Time needed until improvement

Although this was not a pre-specified outcome, improvement could be seen for both treatment arms after four weeks.

- Duration of remission

Not assessed.

(67) Anti-inflammatory dose doxycycline 40 mg combined with topical metronidazole 1% gel twice daily versus placebo capsules combined with topical metronidazole 1% gel twice daily

A single study assessed as at unclear risk of bias was included but provided very limited outcome data for this comparison, and SDs were missing (Fowler 2007). After week 12 metronidazole was discontinued, therefore we have reported data at 12 weeks. The combination of doxycycline with topical metronidazole performed better than topical metronidazole alone but with more adverse events.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Participants in the doxycycline with metronidazole group (n = 30) reported 39 adverse events compared to 23 in the placebo with metronidazole group (n = 32), however the report was unclear about how many participants actually experienced these adverse events.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The IGA score reduced by 1.3 in the doxycycline + metronidazole group (n = 30) compared to 0.8 in the placebo + metronidazole group (n = 32) (investigators reported P = 0.01).

- Assessment of erythema or telangiectasia, or both, at end of study

The mean reduction in erythema (Clinician's Erythema Assessment) in the doxycycline + metronidazole group was 0.91 and in the comparator group 0.66 (investigators reported P = 0.01).

- Lesion counts

At 12 weeks the mean reduction in inflammatory lesion counts was 13.86 in the doxycycline + metronidazole group and 8.47 in the comparator group (investigators reported P = 0.002).

- Time needed until improvement

Improvement in the lesion counts was seen within four weeks in the doxycycline + metronidazole group as compared to within eight weeks for the placebo + metronidazole group.

- Duration of remission

Not assessed.

(68) Combined effect of anti-inflammatory dose doxycycline with metronidazole gel versus metronidazole gel alone

Only one study (Sanchez 2005) assessed as at unclear risk of bias provided data for this comparison. The combination therapy appeared to perform better, based on physicians assessed improvement as well as on reduction of lesion count, than metronidazole alone.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Thirty-three adverse events were reported: 14 in the doxycycline plus metronidazole group versus 19 in the metronidazole gel alone group, but it was unclear in how many participants these occurred.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Numeric data were not provided and both of these outcome measures had to be estimated from figures in the report, and SDs were calculated. The mean change

from baseline in Global Severity score was -1.43 (SD 1.6) for the doxycycline combined with metronidazole group (n = 20) compared to -0.42 (SD 1.6) for the metronidazole gel only group (n = 20) (MD -1.01, 95% CI -2.00 to -0.02; P = 0.05).

- Assessment of erythema or telangiectasia, or both, at end of study

  Mean changes from baseline also had to be estimated from figures, but the investigators reported that they "failed to demonstrate a change in Clinician's Global erythema scale due to disparity in location number of affected facial sites".

- Lesion counts

  Changes from baseline in lesion counts at week 12 were -15.6 (SD 9.5) for the doxycycline with metronidazole group and -7.9 (SD 9.5) for the metronidazole gel only group with a MD of -7.70 (95% CI -13.59 to -1.81; P = 0.01), which was an important difference.

- Time needed until improvement

  Improvements were seen between four and eight weeks.

- Duration of remission

  Not assessed.

(69) Minocycline 45 mg versus minocycline 45 mg and topical azelaic acid 15% gel

This comparison was evaluated in a single study assessed as at unclear risk of bias (Jackson 2013). There was no statistically significant difference for any outcome between the treatment arms. See Summary of findings table 18.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Although only two adverse events were related to the study medication (upset stomach and urticaria), 11/30 in the minocycline only group reported an adverse event compared to 16/30 in the combined treatment group (RR 0.69, 95% CI 0.39 to 1.22).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The mean change from baseline in the IGA (0 = clear, 5 = very severe) was -2.00 (SD 0.63) for both groups (MD 0.00, 95% CI -0.32 to 0.32).

- Assessment of erythema or telangiectasia, or both, at end of study

  Erythema was evaluated with the CEA scale (0 = none, 4 = severe fiery redness) and scored -3.00 (SD 2.68) in the minocycline only group compared to -4.00 (SD 1.90) in the minocycline with azelaic acid group (MD 1.00, 95% CI -0.18 to 2.18).

- Lesion counts

  In both groups there was an important reduction in lesion counts of 11.00 (SD 4.49) in the minocycline group and 12.00 (SD 3.00) in the comparator group (MD 1.00, 95% CI -0.93 to 2.93).

- Time needed until improvement

  Although this was not a pre-specified outcome, improvement was seen in both arms at four weeks.

- Duration of remission

  Not assessed.

(70) Oral metronidazole and topical hydrocortisone 1% cream versus oral placebo and topical hydrocortisone 1% cream

Only one study (Pye 1976) assessed as at unclear risk of bias provided outcome data for these interventions.

Primary outcomes

Change in HRQOL at end of study

Not assessed

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Adverse events were confined to two participants in the metronidazole plus hydrocortisone group and one participant in the placebo group (RR 1.87, 95% CI 0.19 to 18.38).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Although the study was inadequately reported, the data available for this outcome indicated that oral metronidazole appeared to be almost four times more effective than placebo. Ten of the 15 participants treated with oral metronidazole plus hydrocortisone showed an improvement in severity scores compared with only 2/14 in the placebo plus hydrocortisone group (RR 4.64, 95% CI 1.23 to 17.68; P = 0.02; NNTB = 2, 95% CI 2 to 5).

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(71) Dapsone 5% gel twice daily plus 100 mg/day doxycycline versus metronidazole 0.75% gel twice daily plus 100 mg/day doxycycline

These treatments were evaluated in a study (Faghihi 2015) assessed as high risk of bias as two of the predefined outcomes in the protocol were not addressed in the publication.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Participants used a VAS scale (0 to 10 with higher being worse) to rate the severity of their rosacea. The mean change from baseline after 12 weeks in the group (28) treated with dapsone gel and doxycycline was -0.90 (SD 1.17) compared with -1.60 (SD 1.30) in the group treated with metronidazole gel and doxycycline (MD 0.70, 95% CI 0.05 to 1.35; P = 0.03) which favoured treatment with metronidazole gel and doxycycline.

Proportion of participants who reported an adverse event throughout the study period

This outcome was prespecified in the protocol but not addressed in the reference (selective reporting see Assessment of risk of bias in included studies for this specific study).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Mean change from baseline in IGA was -0.60 (SD 0.57) in the dapsone gel plus doxycycline group and similar reduction (-0.60, SD 0.80) was seen in the control group (MD 0.00, 95% CI -0.36 to 0.36; P = 1.00).

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed.

- Lesion counts

The reduction in lesion count was 3.90 (SD 4.44) in the group treated with dapsone gel and doxycycline versus a reduction of 5.10 (SD 4.78) in the group treated with metronidazole gel and doxycycline (MD 1.20, 95% CI -1.22 to 3.62; P = 0.33).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Systemic interventions: studies with oral antibiotics compared with topical treatments

(72) Topical metronidazole versus oral (oxy)tetracycline

Four studies at unclear risk of bias were included in this comparison. Nielsen 1983b investigated the effects of metronidazole 1% cream versus oral oxytetracycline for the treatment of rosacea. The other two studies, Veien 1986 and Schachter 1991, utilised tetracycline instead of oxytetracycline. In Monk 1991 metronidazole gel 0.75% was compared with oxytetracycline.

Although the quality of reporting of these studies was generally poor, they indicated that there was no statistically significant difference in effectiveness between metronidazole cream and (oxy)tetracycline. The Schachter 1991 study was assessed as being at high risk of bias and provided only very limited data. See Summary of findings table 19.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Based on these assessments no statistically significant difference in efficacy could be demonstrated. Data from two pooled studies (Monk 1991; Nielsen 1983b) showed that 30/41 participants in the topical metronidazole group considered themselves improved versus 33/40 in the oxytetracycline group (RR 0.90, 95% CI 0.66 to 1.23; I^2 = 33%; see Analysis 10.1). In Schachter 1991 no exact data were provided other than that "both groups considered their condition much improved".

Proportion of participants who reported an adverse event throughout the study period

No adverse events were reported in Nielsen 1983b. In both groups in Monk 1991 two participants reported flaking of the skin and two experienced gastrointestinal problems. It was unclear how many participants were randomised in Schachter 1991 to each group, but 12 participants reported an adverse event in the metronidazole group and nine in the tetracycline group. In Veien 1986 7/38 participants in the metronidazole group reported an adverse event (skin irritation (4), skin dryness (1), stinging (2)) and 10/38 in the tetracycline group (skin irritation (4), skin dryness (4), stinging (2)). Pooled data for Monk 1991; Nielsen 1983b; Veien 1986 demonstrated a RR of 0.80 (95% CI 0.40 to 1.62; I^2 = 0%; see Analysis 10.2)

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

These were in agreement with the participants' assessments and showed no statistically significant difference between the two interventions RR (0.95, 95% CI 0.70 to 1.29; I^2 = 43%; see Analysis 10.3). No baseline data were provided in Schachter 1991, making the data unusable.

- Assessment of erythema or telangiectasia, or both, at end of study

In Monk 1991 all participants (16) showed improvement in erythema in the metronidazole group compared to 9/17 in the oxytetracycline group. The mean erythema score reduced from 2.5 to 1.1 in the metronidazole group and from 2.4 to 1.1 in the oxytetracycline group. No exact data were provided in Nielsen 1983b but it was stated that "the reduction of erythema was the same in both groups, and the number and extent of telangiectases were unchanged". In Schachter 1991 no differences in erythema nor telangiectasia were seen in either group. In Veien 1986 the percentages of no improvement of erythema after 8 weeks were 11.1% in the metronidazole group versus 12.5% in the tetracycline group.

- Lesion counts

In Monk 1991 at baseline the metronidazole group had a mean papule and pustule count of 25 (mean grade 3.7) versus a mean count of 20 (mean grade 2.9) in the oxytetracycline group. By week nine both treatment groups had shown a reduction of more than 50%, with 100% clearing in 75% versus 66% respectively; while the mean papule and pustule grade had fallen to 1.3 versus 1.1. In Nielsen 1983b the investigators stated that "the reduction of papules and pustules was the same in both groups". In Schachter 1991 a decrease of 68% in papule count was seen in the metronidazole group and 77% in the tetracycline group; for pustules the percentage decrease was 53% and 61% respectively. In Veien 1986 only medians were provided, and at week eight the median for inflammatory lesions was 11.1 for metronidazole versus 0 in the tetracycline group.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(73) Topical ciclosporin emulsion twice daily vs doxycycline 100 mg twice daily first month followed by two months once daily for ocular rosacea

One study assessed as at high risk of bias evaluated this comparison in participants with ocular rosacea with a study duration of three months (Arman 2015). For all outcomes ciclosporin emulsion performed better than doxycycline. See Summary of findings table 20

Change in HRQOL at end of study

The Ocular Surface Disease Index (OSDI) (scale 0 to 100, 100 = worst) was used. The mean change from baseline was -20.04 (SD 8.06) for the 19 participants in the ciclosporin group versus -11.22 (SF 9.20) for the 19 participants in the doxycycline group (MD -8.82, 95% CI -14.32 to -3.32; P = 0.002).

Participant-assessed changes in rosacea severity at end of study

Participants used the Symptom score (0 to 9, higher is worse) to assess ocular rosacea severity. In the ciclosporin group a score reduction of 5.32 (SD 1.25) was seen, compared to a reduction of 3.47 (SD 1.12) in the doxycycline group (MD -1.85, 95% CI -2.60 to -1.10; P < 0.00001).

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Several instruments were used to assess this outcome. The Eyelid score (0 to 9, higher is worse) showed a reduction of 2.68 (SD 0.82) in the ciclosporin group versus a reduction of 1.58 (SD 0.96) in the doxycycline group (MD -1.10, 95% -1.67 to -0.53; P = 0.0001). The Cornea/conjunctival sign score was also used (0 to 9, higher is worse) and showed reductions of 2.58 (SD 0.69) versus 2.05 (SD 0.52)(MD -0.53, 95% CI -0.92 to -0.14; P = 0.007). The Schirmer's test (higher is better) showed an increase of 4.58 mm (SD 2.46) in the ciclosporin group compared to 2.47 mm (SD 1.47) in the doxycycline group (MD 2.11, 95% CI 0.82 to 3.40; P = 0.001). The last test was the tear break up time (TBUT) (higher is better) and the TBUT in the ciclosporin group increased by 5.00 seconds (SD 2.69) compared to an increase of 2.68 (SD 2.00) in the doxycycline group (MD 2.32, 95% CI 0.81 to 3.83; P = 0.003).

- Assessment of erythema or telangiectasia, or both, at end of study

  Not assessed.

- Lesion counts

  Not assessed

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

Studies with other systemic treatments

(74) Isotretinoin 0.3 mg/kg per day versus doxycycline 100 mg once daily for 14 days and then tapered to 50 mg once daily

One study assessed as at low risk of bias evaluated this comparison (Gollnick 2010), see Summary of findings table 21. This study consisted of two phases, the first phase was a dose finding study for isotretinoin, and the second phase compared 0.3 mg isotretinoin with doxycycline 100 mg 14 days and then tapered to 50 mg per day. We have noted and reported that there was inconsistency in the denominators used by the investigators in the per-protocol analyses for the different outcomes. See 'Characteristics of included studies' and 'Table 3'.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Data were presented, as reported, in a per-protocol analysis. In the group treated with isotretinoin 0.3 mg/kg daily 102/129 participants considered themselves to have achieved a good to excellent improvement compared to 85/132 in the doxycycline group (RR 1.23, 95% CI 1.05 to 1.43; P = 0.009; NNTB = 7, 95% CI 4 to 25), which was a statistically significant difference in favour of isotretinoin.

Proportion of participants who reported an adverse event throughout the study period

In the isotretinoin group 30/147 participants reported adverse events compared to 26/152 in the doxycycline group (RR 1.19, 95% CI 0.74 to 1.92). There were more gastrointestinal and respiratory complaints reported in the doxycycline group; and cheilitis, dry mouth and lips were more frequent occurrences in the isotretinoin group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Data were presented based on a per-protocol analysis. A complete remission or marked improvement was observed in 105/129 participants in the isotretinoin group compared to 91/132 in the doxycycline group (RR 1.18, 95% CI 1.03 to 1.36; P = 0.02; NNTB = 9, 95% CI 5 to 50), which was in concordance with the participant-assessed changes.

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema was improved or "healed" in 105/142 participants in the isotretinoin group compared to 112/143 in the doxycycline group (RR 0.94, 95% CI 0.83 to 1.08).

Telangiectasia improved or were "healed" in 56/142 of the participants isotretinoin group versus 55/143 in the doxycycline group (RR 1.03, 95% CI 0.77 to 1.37).

- Lesion counts

There was an overall reduction of 16 lesions in the isotretinoin group compared to a reduction of 13 in the doxycycline group.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(75) Isotretinoin 0.25 mg/kg per day versus placebo once daily

One study at unclear risk of boas compared these treatments in difficult-to-treat papulopustular rosacea (Sbidian 2016). Difficult-to-treat was defined as "cycline-refractory or frequently relapsing" papulopustular rosacea. See Summary of findings table 22.

Primary outcomes

Change in HRQOL at end of study

The Skindex-29 was used to measure this outcome (29-item dermatology specific questionnaire with each item scoring from never bothered (0) to always bothered (100)). After four months the Skindex scores showed median relative variations of -49.4% of the 108 participants treated with isotretinoin compared with -18.0% of the 48 participants in the placebo group (investigators reported "P = 0.002").

Participant-assessed changes in rosacea severity at end of study

Participants did not assess rosacea severity but did assess satisfaction on a VAS scale from 0 to 100 (higher being better) and showed median values of 80 in the isotretinoin group versus 9 in the placebo group.

Proportion of participants who reported an adverse event throughout the study period

Treatment related adverse events were more frequently reported in the group treated with isotretinoin (75/108 (69.4%)) than with placebo (21/48 (43.4%))(RR 1.59, 95% CI 1.12 to 2.24; P = 0.009; NNTH = 4, 95% CI 2 to 11). Eczema, cheilitis, dry skin, abdominal pain, myalgias/arthralgias and dry eyes, which are well known side effects of isotretinoin, were reported in the active treatment group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Dermatologist’s assessment scale to evaluate treatment efficacy was used for this outcome (0 = thorough disappearance of the lesions and 6 = very high number of papules and/or pustules, possible presence of extended inflammatory lesions/moderate-to-severe erythema/moderate-to-severe telangiectasia). The number of participants that had score 0 (thorough disappearance of the lesions) or score 1 (minor-few papules and/or pustules/slight-to-moderate residual erythema/slight-to-moderate telangiectasia) was 66/108 (61.3%) in the isotretinoin group compared to 6/48 (12.5%) in the placebo group (RR 4.89, 95% CI 2.28 to 10.49; P < 0.0001; NNTB = 2, 95% CI 2 to 3).

- Assessment of erythema or telangiectasia, or both, at end of study

No detailed data were provided but the investigators reported "No difference between the 2 groups (isotretinoin vs. placebo group) was observed for the associated symptoms (telangiectasia and erythema)".

- Lesion counts

After four months 62/108 (57.4%) the participants treated with isotretinoin reached a 90% reduction in inflammatory lesion count versus 5/48 (10.4%) in the placebo group RR 5.51 (95% CI 2.37 to 12.83; P < 0.0001; NNTB = 2, 95% CI 2 to 3). The median reduction in lesion count was 13 lesions (92% reduction) in the isotretinoin-treated group and 6 lesions in the placebo group (36%).

- Time needed until improvement

Not assessed.

- Duration of remission

Of the 62 participants in the isotretinoin-treated group who achieved at least a 90% reduction of inflammatory lesions, 51 of them (82.3%) agreed to a four month continued follow-up after end of treatment. In 27/51, rosacea relapsed with a median of 15 weeks.

(76) Zinc sulphate versus placebo

Two studies provided data for this comparison (Bamford 2012; Sharquie 2006). No SDs or exact data were reported in follow-up assessments in the study of Sharquie 2006 (study assessed as at high risk of bias). In Bamford 2012 (assessed as at unclear risk of bias) there were no statistically significant differences for any outcome between zinc sulphate 220 mg twice daily, whilst in Sharquie 2006 the authors reported that zinc sulphate 100 mg three times a day was effective for rosacea.

Primary outcomes

Change in HRQOL at end of study

This was assessed with the RosaQoL (rated 1 to 5) in Bamford 2012. The baseline value for the group treated with zinc sulphate (n = 22) was 3.10 (95% CI 2.88 to 3.50) and for the placebo group (n = 22) 3.29 (95% CI 3.06 to 3.53). At the end of three months the score reduced to 2.90 (95% CI 2.67 to 3.12) in the zinc sulphate group and to 2.99 (95% CI 2.73 to 3.26) in the placebo group. The adjusted MD between the groups was 0.07 (95% CI -0.14 to 0.27; P = 0.53).

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

The number of participants experiencing adverse events in Bamford 2012 was 17/27 in the group treated with zinc sulphate and 14/26 in the placebo group (RR 1.17, 95% CI 0.74 to 1.85). In Sharquie 2006 the number of participants who reported an adverse event in the zinc sulphate group was 3/13 compared to 0/12 for the placebo group (RR 6.50, 95% CI 0.37 to 114.12). Most of the adverse events reported in the zinc sulphate group were gastric upset, nausea, discomfort and diarrhoea.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

In Bamford 2012 this was assessed with the Standard Grading System for Rosacea, with a total severity score ranging from 0 to 12. At baseline, mean score for the zinc

sulphate group was 6.32 (95% CI 5.76 to 6.87), and reduced to 5.09 (95% CI 4.18 to 6.00). For the placebo group, he corresponding were 6.91 (95% CI 6.31 to 7.50), and at 3 months 4.06 (95% CI 4.07 to 5.65). The adjusted MD between groups was 0.57 (95% CI 0.47 to 1.62; P = 0.28).

In Sharquie 2006

the physicians used the Disease severity score (Sharquie score). This scale gives an individual score for the severity of erythema (as measured according to a colour chart), the number of papules, pustules and telangiectasia, and the presence or absence of rhinophyma. In the zinc sulphate group decreased from 8 (SD 2.0) at baseline to 1.6 (no SD provided) and in the placebo group an increase from 7 (SD 1.3) at baseline to 7.6 (no SD provided) was reported. Although no details were provided the investigators reported that for the nine participants with ocular rosacea "all eye involvement disappeared after 3 months' treatment with zinc sulphate".

- Assessment of erythema or telangiectasia, or both, at end of study

This was not assessed in Bamford 2012. In Sharquie 2006 the authors reported an improvement in the zinc sulphate group but no exact data were provided.

- Lesion counts

This outcome was not assessed in Bamford 2012. The numbers of papules and pustules were not reported in Sharquie 2006 and although the investigators reported improvements in the zinc sulphate group this was not supported by the data in the figures.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(77) Oral ivermectin with oral metronidazole versus oral ivermectin

These treatments were assessed in Salem 2013 but the report only provided limited data and was assessed as at high risk of bias.

Primary outcomes

None of our primary outcomes were assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

A marked improvement or complete remission was seen in 47/60 participants in the oral ivermectin only group compared to 59/60 in the combined treatment group (RR 0.80, 95% CI 0.69 to 0.91; P = 0.001; NNTB = 5, 95% CI 4 to 12). This was statistically significant in favour of the combined treatment. Although no details were provided regarding signs and symptoms of ocular rosacea, the investigators reported that "combined therapy was superior in decreasing the D. folliculorum count in all

groups and in reducing the mite count to the normal level in rosacea and in anterior blepharitis".

- Assessment of erythema or telangiectasia or both at end of study

  Not assessed.

- Lesion counts

  Not assessed.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(78) Rilmenidine 1 mg once daily versus placebo

Only one study assessed as at unclear risk of bias examined this comparison (Grosshans 1997).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Six out of 15 participants in the rilmenidine group considered their rosacea improved compared with 6/19 in the placebo group (RR 1.27, 95% CI 0.51 to 3.14). Based on these data rilmenidine appeared to be of limited effectiveness when compared to placebo.

Proportion of participants who reported an adverse event throughout the study period

Although only mild adverse events were reported, there was no statistically significant difference in the number of participants experiencing adverse events, that is 8/15 (rilmenidine) versus 8/19 (placebo) (RR 1.27, 95% CI 0.62 to 2.57).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

The physicians' assessments indicated that 5/15 participants in the rilmenidine group versus 1/19 in the placebo group showed improvement (RR 6.33, 95% CI 0.83 to 48.59), which was in line with the participants' assessments that rilmenidine was not considered to be effective. There was a tendency towards fewer flushing episodes in the rilmenidine group. The mean decrease in number of flushes was 13 versus 5 (rilmenidine and placebo respectively). No SDs were reported in this study.

- Assessment of erythema or telangiectasia, or both, at end of study

There was no apparent difference in facial redness between the groups but no exact data were reported.

- Lesion counts

The number of participants with at least a 50% reduction in lesion count was 10/15 in the rilmenidine group versus 11/19 with placebo (decrease in lesion count 1 versus 2 and no SDs were provided).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(79) Dark sulphonated shale oil versus placebo

One study assessed as at unclear risk of bias evaluated the effectiveness of this intervention but it was only available as an abstract, which provided very limited and largely unusable data (Koch 1999).

Primary outcomes

Change in HRQOL at end of study

Participant-assessed changes in rosacea severity at end of study

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event throughout the study period

No side events were reported in any group.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

No data were provided but the authors reported that there was a statistically significant difference in favour of dark sulphonated oil.

- Assessment of erythema or telangiectasia, or both, at end of study

It was reported by the investigators that there was a statistically significant difference in reduction of erythema in favour of the active treatment group.

- Lesion counts

Lesion counts reduced from 15.9 to 4.3 in the treatment group and 16.1 to 14.1 in the placebo group (investigators reported $P < 0.0001$).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(80) Omega 3 fatty acids (180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA) in one capsule) twice daily versus placebo twice daily for dry eyes in rosacea

One study assessed as at unclear risk of bias examined this comparison in participants with rosacea and suffering from dry eyes (Bhargava 2016). For all outcomes that were addressed, omega 3 fatty acids performed better than placebo. See Summary of findings table 23.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Participants in this study used the Dry Eye questionnaire and Scoring System (DESS) to evaluate this outcome (score of 0–6 was mild, 6.1–12 moderate, and 12.1–18 severely symptomatic dry eye). The mean change from baseline was -5.30 (SD 1.52) in the 65 participants treated with omega 3 fatty acids compared with -0.20 (SD 1.59) in the 65 participants treated with placebo (MD -5.10, 95% CI -5.63 to -4.57; P < 0.00001).

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

This outcome was assessed using several instruments. The mean change from baseline in Meibom gland score (lower score is better) was -1.30 (SD 0.63) in the omega 3 fatty acid group versus -0.02 (SD 0.80) in the placebo group (MD -1.28, 95% CI -1.53 to -1.03; P < 0.00001) favouring omega 3 fatty acids. The tear break up time (TBUT) (higher is better) was also assessed and showed an increase of 3.1 seconds (SD 1.15) in the group treated with omega 3 fatty acids and a change of -0.20 seconds (SD 1.39) in the placebo group (MD 3.30 seconds, 95% CI 2.86 to 3.74; P < 0.00001). The last instrument used was the Schirmer's score (higher is better) and demonstrated an increase of 1.40 mm (SD 3.1) in the group treated with omega 3 fatty acids compared with a reduction of 0.30 mm (SD 3.2) in the placebo group (MD 1.70 mm, 95% CI 0.62 to 2.78; P = 0.002).

- Assessment of erythema or telangiectasia, or both, at end of study

Not assessed

- Lesion counts

Not assessed.

- Time needed until improvement

  After one month there was already a small improvement seen, but improvement clearly increased over time.

- Duration of remission

  Not assessed.

(81) Ondansetron 8 mg twice daily versus placebo

A single study assessed as at unclear bias was not published but provided some data for this comparison (EUCTR2006-003707-40-DE). Ondansetron did not appear to be more effective than placebo in participants with erythematotelangiectatic rosacea.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

After four weeks 7/24 participants treated with ondansetron considered themselves to be moderately to markedly improved compared with 10/26 in the placebo group (RR 0.76, 95% CI 0.34 to 1.67).

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

  This outcome was assessed with the erythema score (0 = none to 3 = severe). The reduction in the group treated with ondansetron was 1.13 (SD 1.60) versus a reduction of 1.69 (SD 0.88) in the placebo group (MD 0.56, 95% CI -0.16 to 1.28).

- Lesion counts

  Participants did not have inflammatory lesions at baseline and median lesion count remained zero for both groups.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed as no effect could be demonstrated.

(82) Famotidine 40 mg twice daily versus placebo twice daily

One study assessed as at unclear risk of bias evaluated these treatments in participants with erythematotelangiectatic rosacea (EUCTR2009-013111-35-DE). The conclusion of the study report was that both famotidine 10 mg twice daily and famotidine 40 mg twice daily did not demonstrate superior efficacy to placebo. We report here only the data of famotidine 40 mg twice daily versus placebo twice daily.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

In the 24 participants treated with famotidine 40 mg twice daily 16 reported adverse events versus 17/27 treated with placebo (RR1.06, 95% CI 0.71 to 1.59). Gastro-intestinal complaints were reported most often.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome was assessed with the cheek-combined severity score (total sum score of 4 areas: cheeks, chin and forehead; scores from 0 to 4 for each area with higher being worse). The reduction in the famotidine group was 1.96 (SD 1.5) versus a reduction of 2.07 (SD 1.5) resulting in a MD of 0.11 (95% CI -0.71 to 0.93).

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(83) Laropiprant 100mg once daily versus placebo once daily

These treatments were evaluated in participants with erythematotelangiectatic rosacea in a single study assessed as at unclear risk of bias (Krishna 2015). The investigators concluded "Laropiprant in comparison to a placebo did not alleviate the symptoms of erythematotelangiectatic rosacea".

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Participants used the Patient Self-Assessment (PSA) Questionnaire to evaluate this outcome. The mean change from baseline was -14.81 (SD 14.43) in the 27 participants of the laropiprant group versus -13.0 (SD 13.67) in the 29 participants in the placebo group (MD -1.81, 95% CI -9.18 to 5.56).

Proportion of participants who reported an adverse event throughout the study period

The investigators reported "The only adverse event reported for more than one subject was nasopharyngitis, which was reported for three subjects in the placebo group and no subjects in the laropiprant group. All adverse events were considered unlikely to be related to study medication. All adverse events except one were considered to be mild".

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome is assessed with Clinician's Erythema Assessment scale for 5 facial areas with a maximum score of 20. The reduction was 2.70 (SD 2.06) in the 27 participants of the laropiprant group compared with 3.20 (SD 2.10) in the 29 participants of the placebo group (MD 0.50, 95% CI -0.59 to 1.59).

- Lesion counts

Not reported, although this was a prespecified outcome (see 'Risk of Bias' under Characteristics of included studies for this study).

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Other interventions: studies with laser or light-based treatment

(84) Dual wavelength laser system (595 + 1064 nm) versus 595 nm pulsed dye laser (PDL) or Nd:YAG laser

One study (Karsai 2008) assessed as at unclear risk of bias evaluated the efficacy of these treatments for telangiectasia on the nose. Dual wavelength laser was allocated to one side of the nose, and PDL or Nd:YAG on the other side. As only limited data were available we have not reported the data for these three treatments based on the individual comparisons.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Adverse events included transient purpura and immediate post-treatment erythema. The investigators stated "there was no significant between-group difference in the incidence of treatment related adverse effects".

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Dual wavelength laser resulted in an improvement in 18/20 sides of the nose versus 2/10 sides treated with PDL and 2/10 sides treated with Nd:YAG, an RR of 4.5 in favour of the dual wavelength treatment over both single wavelength therapies.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(85) Pulsed dye laser (PDL) versus dual wavelength long-pulsed 755-nm alexandrite/1,064-nm Nd:YAG laser (LPAN)

Treatments with these lasers were examined in a single study assessed as at high risk of bias (Seo 2016). There was no to little difference in efficacy and safety between the two lasers for each outcome.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Participants did not evaluate rosacea severity but did comment on treatment satisfaction. In the group treated with PDL 16/25 reported that satisfaction was good or excellent versus 14/24 in the dual wavelength laser group (RR 1.10, 95% CI 0.70 to 1.72).

Proportion of participants who reported an adverse event throughout the study period

Erythema as adverse event was seen in 10/19 in the PDL group versus 12/18 in the comparator group (per-protocol analysis)(RR 0.79, 95% CI 0.46 to 1.35)

Crusts were reported in 6/19 in the PDL group and 2/18 in the dual wavelength laser group (RR 2.84, 95% CI 0.66 to 12.30). The remaining adverse events such as crusts, hyperpigmentation, vesicles, dryness, itch and tightening were mentioned in 18/19 participants in PDL group and 17/18 in the dual wave length laser group (RR 1.00, 95% CI 0.86 to 1.17).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Physicians considered 17/25 in the PDL group to be improved or much improved versus 16/24 in the comparator group (RR 1.02, 95% CI 0.69 to 1.51).

- Assessment of erythema or telangiectasia, or both, at end of study

The erythema index reduced by 0.51 (SD 1.70) in the PDL group and 0.63 (SD 1.16) in the dual wavelength laser group (MD 0.12, 95% CI -0.69 to 0.93).

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(86) Pulsed dye laser (PDL) versus Nd:YAG laser

In this within-participant study assessed as at unclear risk of bias, the cheek on one side of the face was treated with PDL and the other side with Nd:YAG (Alam 2013). See Summary of findings table 24.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

According to the participants, redness improved by a mean of 52% on the PDL treated site and 34% on the Nd:YAG treated site with a MD of -16.33% (95% CI -34.6 to -1.94; P = 0.03).

Proportion of participants who reported an adverse event throughout the study period

Two participants experienced post-treatment swelling and dropped out of the trial. A VAS was used to assess pain, and a score of 3.87 was recorded on the PDL treated

side and 3.07 on the Nd:YAG side, which according to the investigators was statistically significant in favour of Nd:YAG (P = 0.0028).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Erythema was assessed with a spectrophotometer and there was a reduction of 8.9% on the PDL treated side compared to a lower reduction of 2.5% on the Nd:YAG treated side, with a MD of -6.4 (95% CI -11.6 to -1.2; P = 0.02).

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(87) Pulsed dye laser (PDL) versus intense pulsed light therapy (IPL) versus no treatment

Very limited and largely unusable data were reported in this single within-participant study which addressed these interventions (Neuhaus 2009). The investigators concluded that both PDL and IPL were equally effective for erythematotelangiectatic rosacea. The study was assessed as at high risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

The efficacy of treatment and improvement in symptoms was assessed on a VAS. The participants rated a reduction of 3.2 for erythema on the side treated with PDL, and a reduction of 3.6 on the IPL treated side. The investigators reported that this was statistically significant compared to no treatment (P < 0.05), however no data were provided for the untreated group. They also concluded that there was no statistically significant difference between PDL and IPL.

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

No statistically significant reduction in erythema, compared to no treatment, was seen in the spectrophotometer assessments for PDL and IPL, except for IPL on the cheek (investigators reported P = 0.04).

The investigators also graded telangiectasia and erythema on a 4-point Likert scale and, although they did not provide specific data, stated that compared to the untreated control there were statistically significant differences in favour of PDL and IPL of the overall telangiectasia score and erythema score (P < 0.01), but not between PDL and IPL.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(88) Long pulsed dye laser (LPDL) versus intense pulsed light (IPL) therapy

Whilst in the previous comparison the emphasis was on comparing LPDL or IPL to no treatment, in this within-participant study with 40 participants these treatments were compared against each other (Nymann 2010). See also Summary of findings table 25. The study was assessed as at high risk of bias.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Satisfaction with treatment was scored on a VAS with 0 being a poor and 10 an excellent result. The median score (with 10% and 90% percentiles) at end of treatment was 8 (2, 10) for LPDL treatment and 7 (2, 10) for the IPL treated side (investigators reported P = 0.05).

Proportion of participants who reported an adverse event throughout the study period

Pain was also assessed on a VAS with 0 being no pain and 10 worst imaginable pain. The median scores and their 10% and 90% percentiles were 4 (2, 6) for LPDL and 7 (2, 10) for IPL, indicating that LPDL was less painful (investigators reported P < 0.001).

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

For the LPDL treated side 18 had an excellent response (75% to 100% vessel clearance) and 12 a good response (50% to 74% clearance), while for the IPL treated side 11 had an excellent response and 19 a good response.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Other treatments or treatment combinations

(89) Pulsed dye laser (PDL) combined with tacrolimus ointment versus tacrolimus ointment

These treatment modalities were evaluated in one study (Huang 2012) assessed as at high risk of bias.

Primary outcomes

Change in HRQOL at end of study

Participant-assessed changes in rosacea severity at end of study

Neither of the above outcomes were assessed.

Proportion of participants who reported an adverse event throughout the study period

The data for this outcome were inadequately reported. Four participants reported local reactions to tacrolimus, and in the combined treatment group erythema and purpura, which are well known side effects of PDL therapy.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Treatment was rated to be very effective (effective rate 60% to 89%) or cured (effective rate ≥ 90%) in 24/30 participants treated with PDL combined with tacrolimus and in 18/30 of the participants treated with tacrolimus only (RR 1.33, 95% CI 0.95 to 1.88).

- Assessment of erythema or telangiectasia or both at end of study

Not assessed separately.

- Lesion counts

  Not assessed separately.

- Time needed until improvement

  Not assessed.

- Duration of remission

  Not assessed.

(90) Pulsed dye laser (PDL) combined with pretreatment of niacin cream versus PDL

A single within-participant study assessed as at high risk of bias provided data for this comparison (Kim 2011).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Satisfaction with treatment was scored on a VAS (10 highest satisfaction). At the end of treatment, VAS score was 5.06 (SD 2.73) for the combined treatment on the halves of 18 faces compared to 3.67 (SD 2.06) on the PDL only treated other halves of 18 faces. The data were aggregated and analysed as PDL with combined treatment versus PDL alone, but because no adjustments were made to account for the within-participant variation we have only presented the summary statistics.

Proportion of participants who reported an adverse event throughout the study period

All participants experienced transient erythema and oedema after exposure to laser, but without scarring, infections, crusting or hyperpigmentation in the treated areas.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

  Objective assessments of erythema were made using polarization colour imaging, rated on an erythema scale (100 to 1000), in addition to subjective improvement of erythema which was assessed on a 4-point Likert scale.

  The reduction on the objective erythema scale was 29.2 for the PDL + niacin cream and 18.4 for the PDL only group, which were both important, but according to the investigators the difference was not statistically significant. In the subjective assessments where improvement was scored on a Likert scale from 0 to 3 (with 3 being an excellent improvement), 76% to 100% showed a score of 1.65 (SD 1.01) for the combined treatment group versus 0.87 (SD 0.76) for the PDL only group.

On the combined treatment side, 10 sides showed an improvement of more than 50% and three showed a > 75% improvement whilst on the side treated with only PDL just three showed an improvement of more than 50% and none an improvement of more than 75%.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(91) Hydroxychloroquine 0.2 gram twice daily and after 4 weeks a single treatment with PDL versus hydroxycloroquine 0.2 gram twice daily

This comparison was evaluated in a single study assessed as at high risk of bias (Zhang 2017) which provided very limited data for our review.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Not assessed.

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Not assessed.

- Assessment of erythema or telangiectasia, or both, at end of study

Of the 32 participants that received the combined treatment, 28 were markedly improved and 2 cured, compared with 21/33 that were markedly improved in the hydroxychloroquine only group (RR 1.47, 95% CI 1.12 to 1.94; P = 0.005; NNTB = 3, 95% CI 2 to 9).

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(92) Radiofrequency versus PDL

This comparison was evaluated in one within-patient study assessed as at unclear risk of bias (Kim 2017).

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Rosacea severity was not assessed by the participants but they did assess satisfaction. About the side of the face that was treated with radiofrequency 16/30 (53%) participants were satisfied to very satisfied compared with 15/30 (51%) that were satisfied to very satisfied about the PDL treated side (crude RR 1.07)

Proportion of participants who reported an adverse event throughout the study period

Pain was assessed on a VAS scale (0-10, higher is worse). No SD's were provided but radiofrequency scored 1.8 and PDL 2.3. Furthermore the authors reported "There were no noticeable adverse events such as pigmentation or scarring in either of the treated areas. All patients experienced transient erythema and edema immediately after each treatment, which resolved within a few hours without special management".

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Rosacea severity was scored with the scorings system of the National Society Expert Committee's guideline of symptoms (Wilkin 2004). For each symptom the score ranged from 0 (absent) to 3 (severe). The physicians considered that 21 sides of 30 had at least a 50% clearance with radiofrequency treatment compared with 22 sides of 30 treated with PDL (crude RR 0.95). The total score of the rosacea severity went from 13.9 to 8.2 on the radiofrequency side and from 13.8 to 7.2 on the PDL treated side.

- Assessment of erythema or telangiectasia, or both, at end of study

This outcome was assessed with the erythema index and there was a reduction of 27% on the side treated with radiofrequency and a reduction of 31% on the side treated with PDL.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

(93) Fractional microneedling radiofrequency treatment versus no treatment

The study of Park 2016 was also a within-participant study assessed as at unclear risk of bias. evaluated the efficacy of this treatment in 21 participants.

Primary outcomes

Change in HRQOL at end of study

Not assessed.

Participant-assessed changes in rosacea severity at end of study

Subjective therapeutic effectiveness (0 = no effect and 10 = most effective) was used by the participants to rate this outcome. And at the treated side they scored 5.9 (SD 1.7) which was considered to be moderate subjective effectiveness.

Proportion of participants who reported an adverse event throughout the study period

Not assessed.

Secondary outcomes

Physician-assessed changes in rosacea severity at end of study

Physicians considered that 17/21 sides treated with fractional microneedling radiofrequency were improved. The IGA score was 2 which indicated a 11% to 20% improvement. For the untreated side it was 0.38 which was somewhere between no improvement and 10% improvement.

- Assessment of erythema or telangiectasia, or both, at end of study

Reduction in erythema was evaluated with the erythema index which decreased by 13.6% on the treated side versus no decrease on the contralateral and untreated side.

- Lesion counts

Not assessed.

- Time needed until improvement

Not assessed.

- Duration of remission

Not assessed.

Discussion

Summary of main results

One hundred and fifty two studies were included in this updated version of the review. There was a small increase in the number of studies which reported our first primary outcome 'change in quality of life' and the improvements reported were mostly small, and did not meet the minimal important difference. There was little change in the number of studies (approximately half) addressing participants' assessments of improvement in rosacea severity, which was one of the other primary outcomes in this review. These participants' assessments were generally in concordance with those of the physicians, with minimal differences between the ratings. Adverse events were reported in more than half of the studies, although the data were often very limited and frequently incomplete.

More than half the studies focused on papule and pustule counts which, although they may provide a quantifiable, objective and a readily visible outcome, are generally considered to be a clinician reported outcome. Rosacea is a chronic skin disease and the importance of self-assessments by the participants of the effectiveness of the interventions should not be underestimated because rosacea is easily evaluable by patients. Almost three quarter of the studies evaluated erythema, using a variety of scales, principally Likert scales, but there was a lack of uniformity in their ratings making interpretations in any of the relevant comparisons more difficult.

In day-to-day practice, clinicians and patients need to know how rapidly lesions will respond to treatment and, once an optimal response has been achieved, how long this will last. Although these are key issues in clinical decision making, the time to response (which was one of our secondary outcomes) was not a pre-specified outcome in any of the included studies. However, in a few instances it was possible to estimate this from interim reported data. Duration of remission was only assessed and reported in eleven of the studies.

Pooling of data was not feasible for most of the treatment options, and was only feasible for several outcomes in the trials which evaluated:

- topical brimonidine versus placebo (see Summary of findings table 1) showing high certainty evidence for efficacy of brimonidine when compared with placebo and moderate certainty evidence that there was little to no difference in safety
- topical oxymetazoline versus placebo (see Summary of findings table 2) showing moderate certainty evidence for efficacy of oxymetazoline when compared with placebo and and moderate certainty evidence that there was little to no difference in safety
- topical metronidazole versus placebo (see Summary of findings table 3) showing low to moderate certainty evidence for efficacy of metronidazole when compared with placebo and moderate certainty that there was little to no difference in safety
- topical azelaic acid versus placebo (see Summary of findings table 4) demonstrating high certainty for efficacy of azelaic acid when compared with placebo and moderate certainty that there was little to no difference in safety
- topical ivermectin versus placebo (see Summary of findings table 5) demonstrating moderate to high certainty evidence for efficacy of topical ivermectin when compared with placebo and moderate certainty evidence that there was little to no difference in safety. Furthermore, topical ivermectin increases the number of

participants experiencing their rosacea had no effect on quality of life (high certainty evidence).

- oral doxycycline versus placebo (see Summary of findings table 13) showing low to high certainty evidence for efficacy of oral doxycycline when compared with placebo and moderate certainty that oral doxycycline 40 mg probably increases the number of participants reporting an adverse event slightly
- whether azelaic acid or topical metronidazole is most effective still needs to be established because the results from three of the studies (Elewski 2003; Maddin 1999; Wolf 2006) were contradictory (moderate certainty evidence, see Summary of findings table 6)
- topical ivermectin was slightly more effective than topical metronidazole (moderate to high certainty evidence) with no difference in safety (moderate certainty evidence, see Summary of findings table 7)
- oral (oxy)tetracycline was compared with topical metronidazole in four studies (Monk 1991; Nielsen 1983b; Schachter 1991; Veien 1986) and showed no statistically significant difference between the two treatment modalities for any outcome, with the certainty of the evidence rated as low for the outcomes listed (see Summary of findings table 19)

Although most comparisons were evaluated in single studies, we provide 'Summary of findings' tables for the most current and more frequently prescribed therapies as we considered these the most useful for clinical decision making. We did not provide 'Summary of findings' tables for treatments that are not favoured or no longer favoured, as their data would be of limited to no use.

Topical clindamycin was not more effective than placebo (see Summary of findings table 8) and also with no difference in safety (low to moderate certainty evidence). Topical clindamycin phosphate combined with tretinoin was not considered to be effective compared to placebo (moderate certainty of the evidence) (see Summary of findings table 9).

Minocycline foam was more effective based on physician-assessments and in reduction of lesion counts than placebo foam with no or little difference in number of participants experiencing an adverse event (moderate certainty evidence)(see Summary of findings table 10).

For the comparisons assessing oral treatments, there was low certainty evidence that tetracycline is effective but this was based on two older studies which were of short duration (Summary of findings table 12). The newer tetracyclines such as doxycycline and minocycline were evaluated in several comparisons but mainly at the lower dose. The anti-inflammatory dose of 40 mg doxycycline was shown to be as effective as 100 mg doxycycline but with one quarter of the side effects (low certainty evidence) (see Summary of findings table 16). There was no statistically significant difference in effectiveness or safety when low dose doxycycline was combined with either topical metronidazole or azelaic acid (Summary of findings table 17). There was very low certainty evidence from one study assessed as at high risk of bias that doxycycline 100 mg was as effective as azithromycin (Summary of findings table 15). Unfortunately we were unable to locate and include further studies evaluating the effectiveness of azithromycin, even though this is a frequently prescribed drug for rosacea. Minocycline 100 mg was non-inferior to doxycycline 40 mg based on a non-inferiority trial (low to moderate certainty evidence; Summary of findings table 14). Low dose minocycline 45 mg either combined with topical azelaic

acid gel or as stand-alone therapy was effective for papulopustular rosacea (low certainty evidence)(see Summary of findings table 18).

Isotretinoin is frequently prescribed 'off-label' for rosacea, and we were able to include two RCTs evaluating low dose oral isotretinoin. One study was conducted in "difficult-to-treat cases" (cycline refractory or frequently relapsing) and demonstrated that 0.25 mg/kg of isotretinoin was more effective but with probably more adverse events than placebo (very low to high certainty evidence for the various outcomes; Summary of findings table 22). Another study compared the effectiveness of isotretinoin 0.3 mg/kg with doxycycline 100 mg. Low dose isotretinoin was considered by both participants and physicians to be slightly more effective than doxycycline 50 to 100 mg (moderate to high certainty of the evidence; see Summary of findings table 21). Although there was no statistically significant difference in the number of adverse events between the two treatment groups, isotretinoin has a well known risk profile (e.g. teratogenicity) and should only be prescribed in women of child bearing age following the Risk Management Programme of the FDA and American Medical Association (AMA).

Pulsed dye laser (PDL) was slightly more effective than Nd:YAG laser based on one study (certainty of evidence rated low) (see Summary of findings table 24), and long PDL appeared to be as effective as intense pulsed light therapy (certainty of the evidence rated low to moderate) (see Summary of findings table 25).

For ocular rosacea, topical ciclosporin ophthalmic emulsion demonstrated effectiveness with the certainty of the evidence rated as low (see Summary of findings table 11). A further study which compared ciclosporin emulsion versus doxycycline 200 mg per day (after one month tapered to 100 mg per day) for ocular rosacea showed that ciclosporin was slightly more effective than doxycycline (low certainty evidence; Summary of findings table 20). Intake of omega 3 fatty acids was likely to improve ocular signs and symptoms of dry eyes in rosacea (moderate certainty evidence) when compared with placebo (Summary of findings table 23).

Overall completeness and applicability of evidence

Study duration was less than eight weeks in 43/152 studies, which is an inadequate period to demonstrate an optimal treatment effect for some of the interventions. Because rosacea is a chronic disease there is a pressing need for further studies that evaluate strategies focused on therapies that can maintain remission. The evidence was noticeably incomplete for interventions such as patient education and avoidance of triggering factors (i.e. certain foods, exposure to heat and sunlight, or use of non-irritating cosmetics). The review also failed to identify any eligible studies addressing dietary adjustments or sun protective measures for the treatment of rosacea. Nonetheless, most included studies provided sufficient evidence to draw conclusions on the effectiveness of the various treatment options for the different features. At the same time most people with rosacea suffer from more than one feature, which may require a combination of treatments in order to reach satisfactory results.

Treatments for flushing, erythema and telangiectasia

For flushing, beta-blockers such as nadolol, propanolol and carvedilol are frequently prescribed, as is the α_2-adrenergic agonist clonidine, yet these treatments were not addressed by any RCT. Flushing can elicit feelings of embarrassment, low self-

esteem, emotional distress and feelings of stigmatisation (Halioua 2017) and therefore RCTs evaluating treatments that reduce flushing are warranted.

Erythema or telangiectasia, or both, were addressed in 109 studies. The use of different scoring systems to assess improvements of erythema and telangiectasia, and the paucity and variability of evidence on the effects of interventions on erythema and telangiectasia, did not in most cases permit firm conclusions to be made. Clinician's Erythema Assessment (CEA) tool which rates erythema on a 5-point Likert scale (from 0 = clear to 4 = severe erythema, fiery redness) was used in 31/152 studies included in this review. The CEA has been validated and is reported to have high inter-rater and good intra-rater reliability when used by experienced and trained raters (Tan 2014). Applying the same scale in future studies will enable more accurate and directly quantifiable comparisons of erythema between the different interventions. Except for laser and other light based therapies, no other treatments were effective for telangiectasia.

Topical treatments

Robust evidence based on data using the CEA scale came from several studies which had evaluated brimonidine (Fowler 2012a; Fowler 2012b; Fowler 2013a; Fowler 2013b; Kendall 2014; Layton 2015). There was high certainty of the evidence that brimonidine was effective for erythema over a 12 hour period, with a peak effect occurring between three and six hours (Fowler 2013a; Fowler 2013b). There was moderate certainty of the evidence that oxymetazoline probably reduces erythema (Baumann 2018; Kircik 2018). There were limited data indicating that P-3075 cream (based on hydroxypropyl chitosan and potassium azeloyl diglycinate) twice daily was effective in reducing erythema (Berardesca 2012). A study, assessed as at high risk of bias, demonstrated that praziquantel 3% ointment twice daily reduced erythema as well (Bribeche 2015).
None of the data showed that BFH772 1% (betamethasone and calcipotriol) was any better than vehicle in reducing erythema (NCT01449591). The same was true for TDT 068 gel (ultra-deformable Sequessome™ vesicles) (Luger 2015), diclofenac sodium 3% gel (EUCTR2011-002057-65-DE) and timolol 1% oil free base (Jaque 2012).

More than half of the included studies assessed the effects of interventions on erythema or telangiectasia, or both, in participants with 'papulopustular rosacea'. Whilst these participants were classified as having 'papulopustular rosacea', the reports were unclear whether the assessed erythema was perilesional in nature, background erythema or both. However, these studies were conducted principally to evaluate effect on improvement of papules and pustules, not erythema.

Based on the data reported in Bjerke 1989, Bleicher 1987, Breneman 1998, Dahl 1998, Elewski 2003, Koçak 2002, Monk 1991, Nielsen 1983a, Tan 2002, Tirnaksiz 2012 and Wolf 2006, topical metronidazole appears to be effective in reducing erythema. Azelaic acid (Draelos 2015; Elewski 2003; Thiboutot 2003a; Thiboutot 2003b) and sulphacetamide combined with sulphur (Lebwohl 1995; Sauder 1997; Torok 2005) are equally effective in reducing erythema. Two studies provided some evidence for effectiveness of permethrin on erythema (Koçak 2002; Mostafa 2009), however further research is required. The scales used in the assessments of these treatments varied widely and the reporting was mostly incomplete, thus it remained unclear if these treatments had an effect on perilesional erythema or additionally improved background persistent erythema. More evidence is needed on the

effectiveness of five other topical interventions for erythema, as included studies were inadequately powered: P-3075 cream (Berardesca 2012); 4-ethoxybenzaldehyde (Draelos 2005b); praziquantel (Bribeche 2015); a skin care product containing ambophenol, neurosensine and La Roche-Posay thermal spring water (Seité 2013); and SEI003 cream (serine protease inhibitor) (Two 2014). A rosacea treatment consisting of a combination of a gentle cleanser, metronidazole 0.75% gel, hydrating complexion corrector and skin balancing sunscreen SPF 30 was not more effective than metronidazole + the standard care regimen of rosacea treatment without metronidazole; yet, data reporting was incomplete and SDs were missing. Improved reporting might have led to more robust findings (Leyden 2011). Cream containing a 1% extract of a flavonoid-rich plant *Chrysanthellum indicum* was not more effective than placebo in reducing erythema (Rigopoulos 2005).

Systemic treatments

Several systemic treatments investigated effect on erythema, telangiectasia or both; famotidine 40 mg twice daily (EUCTR2009-013111-35-DE), ondansetron 8 mg twice daily (EUCTR2006-003707-40-DE) and laropiprant 100 mg once daily (Krishna 2015), but these did not appear to be more effective than placebo.

As with topical treatments. there were quite a number of studies evaluating oral treatments on erythema in participants with 'papulopustular rosacea'. Oral doxycycline (Del Rosso 2007a; Del Rosso 2008; Di Nardo 2016; Fowler 2007; NCT01426269), (oxy)tetracycline (Monk 1991; Nielsen 1983b; Veien 1986), minocycline (Jackson 2013; van der Linden 2017) and isotretinoin (Gollnick 2010) appeared to be effective for reducing erythema, but further research is needed to confirm these findings. These outcomes were reported incompletely, on different scales, and it remains unclear if erythema only diminished around the lesions because of a satisfactory response to treatment of the 'papulopustular rosacea' or if this treatment reduced background persistent erythema.

Laser and light therapies

Lasers and light therapies would appear to have a major clinical role to play in the treatment of erythema and telangiectasia but these treatment modalities are not underpinned sufficiently by RCTs. There was low to moderate certainty of the evidence that (long) PDL, Nd:YAG laser and intense pulsed light therapy are capable of reducing erythema and telangiectasia on the face (Alam 2013; Nymann 2010). This was supported by Karsai 2008, Kim 2011, Neuhaus 2009 and Seo 2016. Clearance of erythema and telangiectasia on the face is highly desirable, as both can be a source of personal embarrassment and lead to low self esteem. Therefore, further randomised studies of laser- and light-based treatments with blinded assessment of outcomes should be prioritised (Menezes 2009).

Treatments for inflammatory papules and pustules

Topical treatments for papules and pustules

Data from eight RCTs (Beutner 2005; Bitar 1990; Bjerke 1989; Bleicher 1987; Breneman 1998; Dahl 1998; Koçak 2002; Nielsen 1983a) provided moderate certainty of the evidence that metronidazole likely reduces lesion counts when compared with placebo. These data were supported by global physician assessments based on pooled data from three studies (Bjerke 1989; Breneman 1998; Nielsen 1983a). There was high certainty of the evidence based on three

studies (Draelos 2013a, Draelos 2015, NCT00617903) that azelaic acid reduced lesion counts but the difference compared to vehicle was small indicating that vehicle also appeared effective.

When comparing effectiveness of azelaic acid to metronidazole, azelaic acid appeared more effective than metronidazole albeit with more side effects, based on the findings of Elewski 2003 and Maddin 1999. Yet, as the more recent study of Wolf 2006 assessing the same comparison failed to demonstrate superior effectiveness of one of these two treatments over the other (moderate certainty of the evidence), further evidence is still required.

No difference in effect was found between the two used concentrations of topical metronidazole (0.75% and 1%) or when different vehicles were used, as was compared in three studies (Beutner 2005; Dahl 2001; Dreno 1998). Topical metronidazole was also shown to be effective in maintaining remission (Dahl 1998).

A once daily dose of azelaic acid appears as effective as the twice daily dose, and is also likely to result in improved compliance (Thiboutot 2008). This comparison warrants further investigation as the study was assessed at high risk of bias.

The results in Thiboutot 2009 illustrate that there is insufficient evidence to conclude that azelaic acid is either effective or ineffective for maintenance treatment.

Topical ivermectin was shown to be more effective than placebo in reducing lesion counts (high certainty of the evidence) (Stein 2014a; Stein 2014b) and slightly more effective than metronidazole (high certainty of the evidence), but the difference in lesion counts is unlikely to be important (Taieb 2015).

Minocycline 1.5% and 3% foam likely results in a large reduction of lesion counts based on a single study at low risk of bias in 80 participants with the certainty of the evidence rated moderate (Mrowietz 2018).

The effectiveness of benzoyl peroxide in the treatment of papules and pustules remains unclear, due to the conflicting results in Leyden 2011, and the inadequate study design and short study duration (four weeks) of Montes 1983. Benzoyl peroxide combined with clindamycin was investigated in Breneman 2004 but the data were incomplete; no standard deviations were reported and the data were skewed, which did not permit to make firm conclusions about the efficacy of this combined intervention.

Sodium sulphacetamide 10% in combination with sulphur 5% appears to be more effective than metronidazole, but further research is warranted, as two of the studies for this intervention were assessed as being at high risk of bias (Lebwohl 1995; Torok 2005) and one study (Sauder 1997) at unclear risk of bias.

The evidence for the effectiveness of permethrin for inflammatory lesions in rosacea was inconclusive, and therefore further trials with a robust study design are needed (Koçak 2002; Mostafa 2009; Raoufinejad 2016).

There was no evidence to support the effectiveness of pimecrolimus although this was based on very limited and largely unusable data presented in two studies (Koca 2010; Weissenbacher 2007). Several other studies which examined topical calcineurin antagonists (i.e. pimecrolimus, tacrolimus) could not be included as they were not RCTs or did not match the pre-specified inclusion criteria for this review (Chu 2005; Chu 2007; Crawford 2005; Garg 2008; Lee 2008). Therefore well-

designed, double-blind RCTs which examine the potential benefits of calcineurin antagonists for rosacea are required.

No eligible studies were identified for topical dapsone or topical tretinoin, although these treatments are in use for treatment of rosacea (Jansen 1997; Thiboutot 2000; Wilkin 1994). Dapsone 5% gel was only evaluated in combination with 100 mg doxycycline in a study assessed as at high risk of bias where it was shown to be not more effective than the combination of oral doxycycline 100 mg plus topical metronidazole gel (Faghihi 2015). Topical tretinoin combined with clindamycin was not shown to be effective compared to placebo in treating papulopustular rosacea (Chang 2012). Clindamycin 1% cream or gel was not more effective than placebo in reducing lesion counts (Martel 2017a; Martel 2017b). The same holds true for diclofenac sodium 3% gel (EUCTR2011-002057-65-DE) and tranexamic acid 5% solution (Zhong 2015).

One study at unclear risk of bias evaluated the effectiveness of kanuka honey applications versus cetomacrogol cream with the Rosacea Severity Score (RSS) which is a composite score addressing inflammatory lesions as well as erythema (Braithwaite 2015). Participants and physicians were in concordance that kanuka honey was more effective.

Systemic treatments for papules and pustules

Two studies (Marks 1971; Sneddon 1966) evaluated the effects of tetracycline. In both, of these studies the physicians' assessments indicated an improvement in severity, but only Marks 1971 provided data on participants' assessments of treatment. While the six week study duration may have been too short, assessments by participants failed to provide any evidence of a difference in effectiveness between tetracycline and placebo. The data from these two studies are further supported by Monk 1991, Nielsen 1983b, Schachter 1991 and Veien 1986, which compared (oxy)tetracycline with topical metronidazole. Oral tetracycline is used extensively for the treatment of inflammatory lesions in rosacea, and although its presumed efficacy may be widely accepted by clinicians, this practice is currently not supported by high level evidence from robust and methodologically sound clinical trials. Moreover, the certainty of evidence for the various outcomes in these comparisons was low.

Whilst five studies included in this review (Del Rosso 2007a; Del Rosso 2007b; Del Rosso 2010; Fowler 2007; Sanchez 2005) reported the efficacy of an anti-inflammatory dose of doxycycline as a reduction in physician-assessed lesion counts, rather surprisingly the participants' views and satisfaction with the effects of this intervention were not assessed. Furthermore, while a decrease in physician-assessed lesion counts because of the intervention was reported (moderate certainty of the evidence), it was unclear if these counts were continuing to decrease or had stabilised by the time the studies were completed.

There is low certainty of the evidence from one study that the 40 mg dose of doxycycline is at least as effective as the 100 mg dose but with a lower risk of adverse events (Del Rosso 2008). Although these events may be mild to moderate, more were reported with the 100 mg of doxycycline than the 40 mg dose.

Minocycline 45 mg is another tetracycline with demonstrable effectiveness in reducing inflammatory lesions in papulopustular rosacea (Jackson 2013)(low certainty of the evidence), but it has not been established whether this dosage has a

non antimicrobial effect. Minocycline 100 mg probably results in little to no difference in reduction in lesion counts when compared with doxycycline 40 mg (van der Linden 2017)(moderate certainty of the evidence).

Although a number of studies examining the effects of azithromycin were retrieved in our searches, they were excluded from this review because they were not RCTs (Bakar 2004; Bakar 2006; Bakar 2009; Dereli 2005). Only one study comparing azithromycin with doxycycline (Akhyani 2008), assessed as at high risk of bias, was included but the data were skewed and consequently more research is required on the effects of this intervention. Both treatments reduced inflammatory lesions but the certainty of the evidence was very low.

Low dose isotretinoin 0.3 kg/kg was slightly more effective for reducing inflammatory lesions than doxycycline 50 to 100 mg but it may not be an important difference. Both treatments showed important reductions in lesion counts (moderate certainty of the evidence) (Gollnick 2010). Low dose isotretinoin 0.25 mg/kg per day results in far more participants with at least a 90% reduction in lesion counts when compared with placebo in difficult-to-treat papulopustular rosacea (Sbidian 2016). Difficult-to-treat was defined as "cycline-refractory or frequently relapsing" papulopustular rosacea (high certainty of the evidence).

Several studies examined other interventions such as rilmenidine and ampicillin (Grosshans 1997; Marks 1971). Although the latter showed some evidence of effectiveness, neither are now considered as effective treatment options. There were contradictory results for oral zinc (Bamford 2012; Sharquie 2006) and limited data on oral ivermectin (Salem 2013). Famotidine 8 mg did not appear to be effective in reducing inflammatory lesions (EUCTR2006-003707-40-DE).

Treatments for phyma

Surgical therapies as well as ablative laser therapies have been used with reportedly good results for clinically noninflamed phyma, but no eligible RCTs were identified. For clinically inflamed phymas both doxycycline and isotretinoin are recommended, but no supporting evidence based on RCTs is available (Schaller 2017).

Treatments for ocular features

The symptoms of ocular rosacea are often mild but can also be severe and debilitating. Although ocular involvement occurs in 60% of people with rosacea, only eight studies included in this review examined the treatment of ocular rosacea (Arman 2015; Barnhorst 1996; Bhargava 2016; NCT00560703; Salem 2013; Schechter 2009; Sharquie 2006; Wittpenn 2005). Of those, only the studies of Arman 2015, Barnhorst 1996, Bhargava 2016, NCT00560703 and Schechter 2009 provided usable data.

There was low certainty of the evidence of a consistent improvement in all outcomes and that ciclosporin 0.05% ophthalmic emulsion was more effective than artificial tears in the treatment of ocular rosacea (Schechter 2009). Ciclosporin 0.05% was also shown to be more effective than doxycycline 200 mg for the first month and 100 mg for the following two months for all the addressed outcomes (low certainty of the evidence) (Arman 2015). Omega 3 fatty acids improve the symptoms of dry eyes and also improve tear gland function (moderate certainty evidence)(Bhargava 2016).

There was insufficient evidence to support the efficacy of topical metronidazole for ocular rosacea (Barnhorst 1996). The study of NCT00560703 did not show that

doxycycline 40 mg improves quality of life nor bulbar conjunctival hyperemia more than placebo.

Adverse events

The adverse events reported for topical treatments were mostly mild and transient, and comprised of skin irritation, pruritus, tingling or burning, or dry skin. With both topical brimonidine and topical oxymetazoline worsening of erythema was also reported in few cases. In the studies evaluating oral treatments, the reported adverse events varied from gastro-intestinal complaints associated with the antibiotics, to dry skin and mucosae when on oral isotretinoin. In most of the studies the number and characteristics of adverse events did not differ significantly between the intervention and control groups, however adverse events were not always reported consistently, adequately and completely.

Combination of treatments

If the clinical presentation involves several features, a combination of treatments should be considered to address these concurrently. Presently, few RCTs evaluate such combinations of treatments. One study (unclear risk of bias) examined the combination of brimonidine 0.33% gel in the morning with ivermectin 1% cream in the evening (to address both persistent erythema and inflammatory lesions) versus their vehicles (Stein-Gold 2017). According to both participants' assessments (good or excellent) and the physician's global assessment (clear or almost clear), combined treatment was effective in treating both features, with reported reductions of erythema and inflammatory lesions. One study assessed at unclear risk of bias that examined combining doxycycline 40 mg with topical metronidazole versus metronidazole alone was not specifically designed to treat more than one feature (more focused on inflammatory lesions than on erythema: Fowler 2007). The results of this study indicated that combining treatments had a beneficial effect on more than one feature. Having identified this evidence gap, it needs to be mentioned that some of the ongoing studies are indeed examining a combination of treatments for those participants who have more than one feature of rosacea, and those studies will be published in the near future (see Characteristics of ongoing studies).

Maintenance treatments

Rosacea is a chronic disease. At end of treatment, when remission is achieved and symptoms have become well-controlled, maintenance therapy is common practice (Schaller 2017; van Zuuren 2017). However, few RCTs have addressed the effectiveness of the various (combinations of) treatments for this maintenance phase. Based on the studies of Dahl 1998, Stein Gold 2014c and Stein Gold 2014d, topical metronidazole 0.75%, ivermectin 1% and azelaic acid 15% gel seemed effective and safe for maintenance therapy, in order to keep the inflammatory lesions under control.

Quality of the evidence

Limitations in study design and implementation

Although the overall clinical design of the included studies appeared adequate, our risk of bias assessments revealed limitations in the quality of current interventional studies.

1. There was considerable variation in how thorough the studies reported on methods used. These included: generating the randomisation sequence, concealing the allocation, and measures taken to blind investigators and participants. Combined with unsuccessful attempts to contact many of the investigators for additional information, these shortcomings created difficulties in establishing accurate risk of bias assessments in some of the included studies.
2. A significant proportion of the outcome data was not normally distributed (skewed). SDs were frequently missing from study reports, which meant that in many instances continuous outcome data could not be used for quantitative meta-analysis. For most treatment comparisons it was not possible to pool data for our prespecified outcomes.

However, whilst recognising these limitations the authors consider that the body of evidence summarised in this review is sufficient to allow certain conclusions about the effectiveness of several of the interventions used in the treatment of rosacea.

Indirectness of the evidence

The participants included in the studies were largely representative of the population as pre-specified in 'Types of participants'. Almost half of the studies (73) included in this review were placebo-controlled trials, which may only provide limited evidence on the advantages or disadvantages of new treatments compared to existing interventions. However, 60 active-controlled studies were also included, and these gave access to data not only on the risks and benefits of individual interventions but also on comparative efficacy of these interventions. The latter, these head-to-head trials are more likely to have provided evidence that is both relevant and direct. Nineteen of the studies included a placebo in addition to an active treatment arm.

Patient-relevant primary outcomes are a pre-requisite for informing evidence-based clinical decision making, but the importance of patient-reported outcomes (PRO), specifically those evaluating impact of interventions on quality of life, appears to have been overlooked in most of the included studies. Improvement in symptoms may not necessarily equate with or translate into measurably significant changes in quality of life for the individual. For example, while a clinically detectable change in some of the features, such as background erythema or inflammatory lesions, may be interpreted by clinicians as evidence of an effective treatment it does inadequately address the wider psychological distress or impact that may occur in those with rosacea.

Inconsistency of results

The results for specific outcomes were consistent across the limited number of studies and interventions where pooling of data was feasible. Significant heterogeneity between the studies did not permit pooling of data for participant-assessed disease severity of topical metronidazole versus placebo and physician-assessed disease severity in the comparison of topical ivermectin versus placebo. There was also inconsistency across studies for the number of participants experiencing an adverse event in the comparison azelaic acid versus topical metronidazole.

Imprecision of results

The rather limited number of studies that were included in this review examining similar interventions did not permit any substantive assessment of the degree of precision of effect. Small sample sizes were responsible for most of the imprecision.

Publication bias

A large number of abstracts to conference proceedings were identified. Some were published in full but a number were not otherwise available. There is a possibility that some reports, particular those with negative outcomes or involved more adverse effects, and sponsored by parties with potentially vested interests, may have been unpublished.

Potential biases in the review process

Attempts to limit bias in the review process included ensuring a comprehensive search for potentially eligible studies. The authors' independent assessments of eligibility of studies for inclusion in this review and the extraction of data minimised the potential for additional bias beyond that detailed in the 'Risk of bias' tables. Incomplete reporting on methods, results, or both in some of the included studies, and our inability to obtain satisfactory clarification from the investigators, may have contributed to some bias in assessment during the review process. Where these conditions applied this was explicitly stated in the text of our review.

Agreements and disagreements with other studies or reviews

Since the last update of this review in 2015 (van Zuuren 2015), a limited number of other reviews or guidelines have been published. The Canadian Clinical Practice guidelines for rosacea were published in 2016 (Asai 2016). These guideline authors used the 2015 version of this review as a source of clinical evidence and as the basis for making recommendations. Therefore this guideline is in concordance with the conclusions of the 2015 version of this review. The GRADE approach was used to establish the strength and direction of the recommendations and facilitated by a Delphi voting process.

In the 2015 update, we discussed the S1 guideline of the German Society of Dermatology (Reinholz 2013). More recently a Swiss S1 guideline for the treatment of rosacea has been published (Anzengruber 2017). In the latter, guideline assessments of the levels of evidence (A-E) was used, and 13 national experts on rosacea reached consensus on the recommendations provided. The Swiss guideline included all relevant studies which included open label studies as well. Although we are in broad agreement with the conclusions reached overall, the guideline authors concluded that there was level A evidence (no major design flaws and at least 1 double-blind RCT) for the treatments of pimecrolimus, topic retinoids, topical permethrin, topical benzoyl peroxide/clindamycin, topical erythromycin and topical dapsone, oral zinc sulphate and oral ampicillin, on which we clearly disagree. The developers provided no details on the selection criteria for studies to be included, nor the basis of appraisal of methodological quality nor judgements on the risk of bias in the included studies. Neither of the two guidelines included patients or patient advocacy groups but appeared solely reliant on the contribution of expert panels. In contrast, and in terms of recognising the significant impact of this condition on patients, we have tried to ensure that we received timely, patient-relevant input at all stages of conducting and reporting this review and include two consumers as co-authors.

The guidelines produced by the American Acne and Rosacea Society (AARS) (Del Rosso 2013b; Del Rosso 2014a; Del Rosso 2014b; Del Rosso 2014b; Tanghetti 2014) have already been discussed in the former version of the review (van Zuuren 2015) as was also the consensus document proposing an evidence-based treatment approach by the Rosacea International Expert Group (ROSIE)(Elewski 2011).

Guidelines should provide balanced information on the benefits, harms and limitations of the therapeutic interventions being evaluated. Their development process should be transparent, robust and reproducible, and should clearly demonstrate that the supporting evidence was systematically reviewed. The strength of clinical recommendations of the Swiss guideline did not correspond to the widely-recognised GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) approach to develop and present recommendations for the appropriate treatment for specific clinical conditions or circumstances (Guyatt 2008). In contrast, in this review we used the GRADE method to examine and categorise the quality level of a body of evidence and to explain our confidence in the effect estimates for several of the interventions, which we have presented in the 'Summary of findings' tables.

The global ROSacea COnsensus panel (ROSCO), the sole international panel of dermatologists and ophthalmologists to develop consensus based recommendations for classifying and treating rosacea, published in 2017 a much needed report on (re)classifying and treating rosacea (Schaller 2017). The 2015 version of our review (van Zuuren 2015) was the starting point and basis for the Delphi-based consensus process for this report. The ROSCO panel agreed on using the phenotype-based approach, instead of the previously used subtypes, and subsequently provided treatment algorithms for these phenotypes, as well as for phyma and ocular rosacea. These treatment algorithms were based on the quality (nowadays certainty) of the evidence of our 2015 review but adjusted to the phenotype-based approach. The recommendations and algorithms from this ROSCO consensus report were successively adopted by us in this update, and were incorporated in the section on Overall completeness and applicability of evidence.

Topical ivermectin has attracted considerable interest recently. Three reviews on this intervention have been published (Deeks 2015; Ebbelaar 2018; Siddiqui 2016). The review of Deeks 2015 was a narrative review describing the pharmacological properties of ivermectin as well as the available data on efficacy and tolerability from the studies of Stein 2014a, Stein 2014b, Stein Gold 2014c, Stein Gold 2014d and Taieb 2015. As this was a narrative review of previous published studies, no critical appraisal of studies has been carried out. A systematic review on ivermectin with clinical guideline recommendations was recently published (Ebbelaar 2018). The authors used the Jadad score to assess risk of bias of the included studies. This score covers three items (randomisation, double blinding and dropouts) but does not include concealment of treatment allocation, which is a key criterion in the Cochrane risk of bias tool. This review included the same studies as in Deeks 2015 but also identified the 2015 update of our review (van Zuuren 2015) and the review of Siddiqui 2016. Furthermore, recommendations regarding ivermectin in guidelines as well as one consensus report were reviewed in three publications (Anzengruber 2017; Asai 2016; Reinholz 2013; Schaller 2017) and the conclusions drawn are in concordance with our review. However, in our systematic review no recommendations are made. Head-to-head studies comparing various topical treatments are lacking in general. Siddiqui 2016 et al carried out a network meta-

analysis comparing the efficacy, safety and tolerability of topical ivermectin with other currently available topical agents. This study "expanded and built upon" earlier versions of our review (van Zuuren 2011; van Zuuren 2015) and was conducted and reported in a robust methodological way. They concluded that topical ivermectin appeared to be more effective than other topical treatment options for inflammatory lesions in rosacea, with similar safety and tolerability.

Authors' conclusions

Implications for practice

Based on only those studies which are most likely to have provided reliable results, meaning those that are reproducible, repeatable and therefore valid, and by selecting the most rigorously described and conducted studies, we have drawn several conclusions. Evidence of treatment effect could be demonstrated for several of the interventions studied. In daily practice often a single or combination treatments should be considered, based on rosacea features presenting in the individual patient (phenotype).

For erythema and telangiectasia

- There is high certainty evidence to support the effectiveness and safety of brimonidine topical gel and moderate certainty evidence for oxymetazoline topical cream that background erythema reduces over 12 hours after application.
- There was low to moderate certainty evidence of the effectiveness of (long) pulsed dye laser, Nd:YAG laser and intense pulsed light therapy for background erythema and telangiectasia.
- There was moderate certainty evidence that both topical brimonidine as well as oxymetazoline probably results in little to no difference in number of participants experiencing an adverse event when compared with vehicle. Adverse events were mild and transient and consisted of application site pruritus, burning and erythema. Pulsed dye laser was slightly more painful than Nd:YAG laser (low certainty evidence), but long pulsed dye laser was less painful than intense pulsed light therapy (low certainty evidence).

For inflammatory lesions

- There is high certainty evidence that topical azelaic acid and ivermectin reduce lesion counts, and moderate certainty evidence for topical metronidazole and topical minocycline. It still needs to be established whether topical azelaic acid is more effective than topical metronidazole, but topical ivermectin appeared slightly more effective than topical metronidazole (moderate certainty evidence).

- There is low certainty evidence that oral tetracycline is effective in reducing inflammatory lesions. Of the other oral antibiotics there was moderate certainty evidence that the anti-inflammatory dose of doxycycline (40 mg) was effective in reducing lesion counts. There is low certainty evidence that 40 mg doxycycline is at least as effective as 100 mg, with fewer adverse events when using 40 mg. There is low certainty evidence for the effectiveness and safety of low dose minocycline 45 mg and very low certainty evidence for azithromycin in reducing inflammatory lesions. Minocycline 100 mg probably results in little to no difference in reducing

lesion counts when compared with doxycycline 40 mg (moderate certainty evidence).

- There is high certainty evidence that low dose isotretinoin 0.25 mg/kg results in far more participants with at least a 90% reduction in lesion counts when compared with placebo. When compared to 100 mg (after two weeks tapered to 50 mg) doxycycline, low dose isotretinoin 0.3 mg/kg probably results in a small effect that may not be an important difference in reduction in lesion counts. Both oral isotretinoin and oral doxycycline showed important reductions in lesion counts (moderate certainty evidence).

- For most of these treatments, or a combination of them, there is no clear evidence that any has an advantage in higher remission rates or fewer adverse events. However, more participants experienced an adverse event with topical azelaic acid, topical minocycline and oral isotretinoin, when compared with vehicle or placebo.

For phyma

- No studies could be included that addressed treatment of phymatous rosacea.

For ocular features

- For ocular rosacea, ciclosporin 0.05% ophthalmic emulsion was shown to be more beneficial than artificial tears (low certainty evidence). Ciclosporin 0.05% was also shown to be more effective than doxycycline 200 mg for the first month and 100 mg for the following two months for all the addressed outcomes (low certainty evidence). Omega 3 fatty acids improve the symptoms of dry eyes and improved tear gland function (moderate certainty evidence).
- Ciclosporin ophthalmic emulsion may result in little to no difference in number of participants reporting adverse events when compared with artificial tears (low certainty evidence). The other comparisons did not evaluate adverse events.

For combination of treatments

- There is evidence from one study (assessed as at unclear risk of bias) that combined treatment of brimonidine gel in the morning and ivermectin cream in the evening was effective in treating both erythema and inflammatory lesions when compared with their vehicles.
- Both treatment arms showed less than 1% adverse events. Adverse events consisted of allergic dermatitis, skin burning and skin irritation in the active treatment group; while erythema, pruritus and worsening rosacea was mentioned in the vehicle group.

For maintenance treatments

- Topical metronidazole 0.75%, ivermectin 1% and azelaic acid 15% gel seem effective and safe as a maintenance therapy regarding inflammatory lesions. Other maintenance treatments for rosacea have not been addressed in RCTs yet.

Clinical decision making on the choice of intervention for rosacea should be based on high-level evidence if available. In its absence these decisions should continue to be guided by clinical experience and patients' individual characteristics and preferences until further evidence becomes available.

Implications for research

Non-pharmacologic interventions, such as dietary modifications, avoidance of trigger factors, use of sunscreens and patient education, in addition to trials investigating effective treatment for phymas, are further areas of much needed research. Combinations of treatments that address more than one feature of rosacea (such as erythema, telangiectasia and inflammatory papules and/or pustules) need to be evaluated further. Conceivably some of the studies listed in the 'Characteristics of ongoing studies' section of this review will be able to provide answers to these remaining questions. The impact of available treatment on ocular signs and symptoms of rosacea warrants further examination, and this might include the removal of Meibomian cysts.

There was wide variability in not only the conduct but also the quality of reporting of many of the trials. A major area for improvement would be in the standardisation of outcome reporting in any future research, as suggested by the COMET (Core Outcome Measures in Effectiveness Trials) Initiative (http://www.comet-initiative.org/). The use of proprietary severity scales and non-standardised erythema scales significantly hampered our ability to combine study results for meta-analysis. Outcomes collected in future trials should be primarily based on a standardised scale of the participant's assessment of the treatment efficacy, and also have a greater emphasis on measures of quality of life. Standardised and uniform scales should be developed for individual features and used for physicians' assessments. These should reliably reflect reflect dimensions in the feature of interest including global evaluations and assessments for any one of lesion counts, background erythema, telangiectasia and phyma as appropriate to the intervention. Scales should be developed with greater focus on specific features rather than conflation of multiple features into a single scale as previously done with the subtype approach. This focus will provide greater clarity on the effect of interventions on distinct rosacea features. As an example, this would avoid the current conundrum of extracting the effect on background erythema versus perilesional erythema of inflammatory lesions in studies on "papulopustular rosacea".

Time needed for a response and response duration should be addressed more completely, and adverse events reported more rigorously. Furthermore, to ensure improved clinical decision making, future research should place a greater emphasis on the management and treatment of rosacea based the phenotype approach.

Future randomised controlled trials must be well-designed, well-conducted, and adequately delivered with subsequent reporting, including high-quality descriptions of all aspects of methodology. Rigorous reporting needs to conform to the Consolidated Standards of Reporting Trials (CONSORT) statement, and this will enable appraisal and interpretation of results and accurate judgements to be made about the risk of bias and the quality of the evidence of the selected outcomes. Although it is uncertain whether the reported quality mirrors actual study conduct, it is noteworthy that studies with unclear methodology have been shown to produce biased estimates of treatment effects (Schulz 1995). Adherence to guidelines, such as the CONSORT statement, would help ensure complete reporting.

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Contributions of authors

EvZ co-ordinated the contributions from the co-authors and together with ZF wrote the final draft of the protocol.
EvZ and ZF screened papers against eligibility criteria.
EvZ and ZF obtained data on ongoing and unpublished studies.
EvZ, ZF, and BC updated the Methods sections.
EvZ and ZF extracted data for the review and sought additional information about papers.
EvZ and ZF entered data into RevMan and in the Result section
EvZ, ZF and BC analysed and interpreted data.
All drafted the clinical sections of the Background, Discussion and Conclusions and responded to the clinical comments of the referees.
EvZ, ZF, BC responded to the methodology and statistics comments of the referees.
LC and BA were the consumer co-authors and checked the review for readability and clarity.
EvZ is the guarantor of the final review.

Declarations of interest

Zbys Fedorowicz, Ben Carter, Bernd Arents and Lyn Charland have no declarations of interest.

Esther van Zuuren serves on the global rosacea consensus panel (ROSCO) and received non-financial support and other from Galderma in October 2016

Mireille van der Linden received non-financial support and other from Galderma in October 2016, she received speaker fees of Janssen Cilag and Abbvie. Furthermore, she was investigator in the following trial: van der Linden MMD, van Ratingen AR, van Rappard DC, Nieuwenburg SA, Spuls PI. DOMINO, doxycycline 40 mg vs. minocycline 100 mg in the treatment of rosacea: a randomized, single-blinded, noninferiority trial, comparing efficacy and safety. British Journal of Dermatology 2017;176(6):1465-74.

Jerry Tan has been an advisor, consultant, investigator and/or speaker for Allergan, Bayer, Cipher, Galderma and Valeant. He was a co-author of the Canadian Rosacea Clinical Practice Guidelines and is the co-chair of the global rosacea consensus panel (ROSCO) and serves on the expert panel of the National Rosacea Society (NRS).

He was an investigator in the following trials:

Stein L, Kircik L, Fowler J, Tan J, Draelos Z, Fleischer A, et al. Efficacy and safety of ivermectin 1% cream in treatment of papulopustular rosacea: results of two randomized, double-blind, vehicle-controlled pivotal studies. Journal of Drugs in Dermatology 2014;13(3):316-23.

Stein Gold L, Kircik L, Fowler J, Jackson JM, Tan J, Draelos Z, et al. Long-term safety of ivermectin 1% cream vs azelaic acid 15% gel in treating inflammatory lesions of rosacea: results of two 40-week controlled, investigator-blinded trials. Journal of Drugs in Dermatology 2014;13(11):1380-6.

Stein-Gold L, Papp K, Lynde C, Lain E, Gooderham M, Johnson S, et al. Treatment of Rosacea With Concomitant Use of Topical Ivermectin 1% Cream and Brimonidine 0.33% Gel: A Randomized, Vehicle-controlled Study. Journal of Drugs in Dermatology 2017;16(9):909-16.

Tan JKL, Girard C, Krol A, Murray HE, Papp KA, Poulin Y, et al. Randomized placebo-controlled trial of metronidazole 1% cream with sunscreen SPF 15 in treatment of rosacea. Journal of Cutaneous Medicine and Surgery 2002;6(6):529-34.

Differences between protocol and review

For the 2015 update we have revised all of the search strategies and added a search of the LILACS database. LILACS is now a standard resource used in Cochrane Skin Group reviews. The Cochrane randomised control trial filters for MEDLINE and EMBASE have been refined since the previous version of this review, and the latest versions have been used for this update. We also removed many terms that were symptoms of rosacea rather than being synonyms for the disease itself. We checked the new strategies against the previous ones to ensure they were robust enough to capture relevant RCTs.

For the 2018 update we did not search the Skin Group Specialised Register. We did adjust the age of including participants to ≥ 18 years, as 18 years are already adults.

For the 2015 update we added an additional physician-assessed outcome 'assessment of erythema or telangiectasia, or both, at end of study'. In previous versions these data were in part reflected in 'Other data' tables, but we thought it would be more appropriate to have this outcome as a separate listed outcome, as erythema is very bothersome to people with rosacea. We have removed 'dropout rates' as an outcome as this is already listed in the 'Characteristics of included studies' tables, as well as under attrition bias in the risk of bias tables. Adverse events moved to primary outcomes as these should include events that are of potential harm (MECIR C14).

We also revised the 'Methods' section in 2015 to meet the latest requirements of the *Cochrane Handbook for Systematic Reviews of Interventions* as well as the MECIR reporting standards. As it is unlikely we will encounter cluster trials we removed this item under 'units of analysis issues'.

For the 2015 update the additional comparisons of interventions of within-participant studies have been included after extracting the RR or MD and SE for those that appropriately accounted for the variability. These studies were then included in meta-analyses (where appropriate) with the other studies using a generic inverse-method of analysis in Revman.

In the former 2011 update, at the request of the Skin Group odds ratios have been changed into risk ratios. Because risk and odds are different when events are common, the risk ratio and the odds ratio also differ when events are common. The Skin Group recommends that because many of the outcomes of trials of skin conditions are common events risk ratios should be used.

In the protocol (published in 2001) we had planned, under the section Types of studies, to include randomised controlled trials in people with moderate to severe rosacea. By the time the review was first published 2004 'Types of studies' had been amended to randomised controlled trials (RCTs) that met the methodological criteria. This remained the same for the substantial update that was published in 2005. We had previously excluded trials that were RCTs and otherwise matched our inclusion criteria if they were assessed to be of low methodological quality. Following the advice of the Skin Group's editors, we re-assessed all of the excluded RCTs and those which matched the inclusion criteria were included in the former update of this review (2011) and the participant data were analysed (if appropriate).

For the 2011 update we rewrote the Methods section, especially the 'Data collection and analysis' section after comments from our referees. We added a part on 'Assessment of heterogeneity of studies'.

Characteristics of studies

Characteristics of included studies

Akhyani 2008

Methods	RCT, prospective, active-controlled, open-label Date of study Unreported Setting Department of Dermatology, Razi Hospital; Department of Ophthalmology, Farabi Hospital, Teheran, Iran
Participants	**Randomised:** 67 participants (mean age 47.93 years (SD 14.18), 37 male, 30 female) **Inclusion criteria** • Participants with diagnosis of papulopustular rosacea (persistent central facial erythema with transient central facial papules, or pustules, or both) **Exclusion criteria** • Use of topical rosacea treatment or systemic treatment in last month • Use or isotretinoin in the last 6 months • Pregnancy, breastfeeding • Hypersensitivity to macrolides or tetracyclines Neither ocular involvement nor phymas **Dropouts and withdrawals**

	• 9/67 (13.4%); azithromycin group (5), doxycycline group (4) • Non-compliance; azithromycin group (3), doxycycline group (4) • Diarrhoea; azithromycin group (2), doxycycline group (0) **Baseline data mean (SD)** Lesion counts; azithromycin group 19.24 (9.67), doxycycline group 18.86 (8.95)
Interventions	Three months **Intervention** Azithromycin - first month 500 mg 3 times a week, second month 250 mg 3 times a week, third month 250 mg twice a week (37) **Comparator** Doxycycline - 100 mg once daily (30)
Outcomes	Assessments (5): baseline, month 1, 2, 3, and 5 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean percentage decrease in inflammatory lesions (from baseline to third month and from baseline to second month post-treatment)✶ 2. Participant's own assessment of their treatment at the end of the third month (1 = no change, 2 = mild improvement, 3 = moderate improvement, 4 = good improvement)✶ **Secondary outcomes** 1. Side effects✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 288): "The authors wish to acknowledge Pakhshe Razi Co. (Tehran, Iran) for providing azithromycin (azithromycin, 250 mg capsule, Chemiedaru)."
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) Skewed data for lesion counts

	See comparison 60 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 285): "Patients were allocated to the trial using a randomized numbers table in a one-to-one fashion" Comment: Probably done
Allocation concealment (selection bias)	High risk	Following extensive e-mail contact with the investigators we were informed that the providers of care had access to the computer-generated list Comment: We judged this as at high risk of bias
Blinding of participants and personnel (performance bias)	High risk	Quote (page 284): "....an open clinical trial." The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	Quote (page 284): "....an open clinical trial." Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	9/67 (13.4%); 5 in azithromycin group, 4 in doxycycline group. Analysis followed ITT principle, withdrawals were balanced across groups, reasons were reported, all participants were accounted for and included in the analysis Comment: We considered this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration and wash-out period adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Alam 2013

Methods	RCT, prospective, active-controlled, double-blind, within-patient comparison Date of study January to July 2012 Setting Department of Dermatology, Northwestern University, Chicago, IL, US

Participants	**Randomised:** 16 participants (mean age 42 years (range 24 to 52), 8 male, 8 female) **Inclusion criteria** • Participants aged 18 to 55 years with erythematotelangiectatic rosacea **Ocular involvement:** Unclear **Exclusion criteria** • Acute inflammatory papules, pustules, or vesicles of the central aspect of face • Facial telangiectasis greater than 2 mm in diameter **Dropouts and withdrawals** • 2/16 (12.5%); both post-treatment swelling **Baseline data mean (SD)** Nothing reported
Interventions	Six months **Intervention** Pulsed dye laser - four treatments were delivered per side, at three to four week intervals **Comparator** Nd:YAG laser - four treatments were delivered per side, at three to four week intervals
Outcomes	Assessments (2): baseline, month 7 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Standard digital photographs and erythema measurements with spectrophotometer (Dermatospectrometer, Cortex Technology, Hadsund, Denmark)✶ **Secondary outcomes** 1. The side that blinded subjects selected as having greater improvement, and the results of the post-treatment subject satisfaction questionnaire✶ 2. Procedure-associated pain scores✶

	3. Patient-reported adverse events, and events observed by the investigator✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 438): "Funded by the Northwestern University Department of Dermatology"
Declaration of interest	Quote (page 438): "None declared"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 86 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 439): "This was a randomized controlled split-face study with allocation ratio 1:1, using random block size of 2" and "A random number generator was used to generate 0s and 1s, which were designated as left or right" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 440): "Each random assignment was sealed individually in an opaque, sequentially numbered envelope (M.A.). Assignments were made consecutively, with subjects receiving PDL to the left or right side of the face, and Nd:YAG laser to the contralateral side" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 440): "Subjects were blinded as to which facial side received which laser treatment. They were laser naive before the study, and both laser treatments were performed (N.V.) in the same room after subjects donned occlusive eye-protective goggles. The investigator obtaining spectroscopy measurements (M.W.) was not present during treatments and blinded regarding allocation" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome	Low risk	Outcomes were investigator and participant assessed

assessment (detection bias)		Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	2/16 (12.5%) dropped out reporting post-treatment swelling. Per-protocol analysis Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available on clinicaltrials.gov (NCT01529996) and the pre-specified primary outcome "rating on global improvement scale" has not been assessed, nor mentioned anymore in the methods section of present publication Comment: We judged this as at unclear risk of bias
Other bias	Low risk	Study duration adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Arman 2015

Methods	RCT, prospective, active-controlled, open label Date of study Unreported Setting Dermatology and Ophthalmology Outpatient Clinics of Ankara Atatürk Training and Research Hospital, Ankara Turkey
Participants	**Randomised:** 38 participants (mean age 49.6 years (SD 11.8) in ciclosporine group group, 53.8 years (SD 12.6) in doxycycline group, 15 male, 23 female) **Inclusion criteria:** • Participants with rosacea, and associated eyelid and ocular surface changes **Ocular involvement:** Yes **Exclusion criteria** • Pregnancy, breast-feeding • Eyelid defects • Lagophthalmos • Active ocular infections and allergies • History of hypersensitivity to ciclosporin and/or doxycycline • Ocular surgery within the past 6 months **Dropouts and withdrawals:** Not reported **Baseline data mean (SD)**

	Mean symptom score; ciclosporin group 7.16 (1.21), doxycycline group 6.79 (1.08) Mean eyelid sign score; ciclosporin group 3.89 (0.74), doxycycline group 3.79 (0.79) Mean Corneal/conjunctival sign score; ciclosporin group 3.16 (0.77), doxycycline group 3.05 (0.78) Ocular Surface Disease Index; ciclosporin group 34.76 (7.70), doxycycline group 29.64 (10.30) Schirmer score; ciclosporin group 4.21 (2.69), doxycycline group 4.05 (2.40) Tear Break Up Time; ciclosporin group 3.68 (1.63), doxycycline group 4.0 (1.63)
Interventions	Three months **Intervention** Topical ciclosporin emulsion - BID (19) **Comparator** Doxycycline - first month 100 mg BID, second and third month QD (19) All patients were instructed about lid hygiene and given artificial eye drops four times daily
Outcomes	Assessments (2): baseline, month 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Symptom panel included burning, stinging or foreign body sensation, photophobia, itching, redness, blurring, watering, pain and lid swelling (symptoms and signs are recorded as present or absent (1/0) at each visit, maximum 9)✴ 2. Eyelid sign panel included blepharitis, meibomian gland inspissation, erythema and telangiectasia, chalasia and lid margin irregularity (symptoms and signs are recorded as present or absent (1/0) at each visit, maximum 5)✴ 3. Corneal and conjunctival sign panel included conjunctival hyperemia, episcleritis or scleritis, punctate epithelial keratopathy, corneal infiltration, corneal vascularisation and corneal thinning or perforation (symptoms and signs are recorded as present or absent (1/0) at each visit, maximum 6)✴ 4. Schirmer test 5. Tear Break Up Time

	6. Ocular Surface Disease Index (OSDI)) on a scale of 0 to 100 (100 = worst) **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 549): "Arman A, None; Demirseren DD, None; Takmaz T, None."
Notes	Two of our primary outcomes was addressed (quality of life and participant-assessed changes in rosacea severity) See comparison 73 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 544): "randomly divided into two groups" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "We used “Restricted Randomisation Technique “ to divide the patients into two treatment groups" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding. Outcomes were investigator- and participant assessed Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	There were no losses to follow up Comment: We judged this as at low risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, no wash-out period described, groups treated equally Comment: The study appeared to be free of other forms of bias

Bamford 1999

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Screening and enrolment between February 1996 and June 1997 Setting Dermatology Section, St Mary's - Duluth Clinic Health System, Duluth, Minnesota, US
Participants	**Randomised:** 44 participants (mean age 56.9 years (SD 12.9) in treatment group, 58.9 years (SD 11.9) in control group, gender unreported) **Inclusion criteria** • Participants > 25 years with active rosacea, who tested positive for *Helicobacter pylori* (UBT, RWBT) **Ocular involvement:** Unclear **Exclusion criteria** • Allergy to clarithromycin or omeprazole • UBT ^{13}C, negative RWBT results, negative UBT results • Pregnancy, breast-feeding • Antibiotics within past 2 months, topical treatments 3 weeks prior to start of study **Dropouts and withdrawals** • 2/44 (4.5%); 2 withdrawals in clarithromycin and omeprazole group, death due to myocardial infarction (1), incapacitating headaches (1) **Baseline data mean (SD)** Duluth Rosacea score; clarithromycin group 10.8 (3.5), placebo group 11.1 (4.2)
Interventions	Two weeks **Intervention**

	Clarithromycin - 500 mg TID and omeprazole 40 mg QD (22) **Comparator** Placebo - QD (22)
Outcomes	Assessments (2): baseline, day 60 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Extent and intensity of rosacea at follow-up as measured by the number of papules and pustules✴ 2. Extent and intensity of erythema and telangiectasia✴ Method: Duluth Rosacea Scoring Instrument **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
	Quote (page 663): "Astra Merck, Wayne, PA, provided the major funding for the study as well as omeprazole (Prilosec) and matching placebos. Abbott laboratories, North Chicago, Ill, supplied the clarithromycin. Cortecs Diagnostics Ltd, London, England, donated the Helisal Rapid Whole Blood Test. Meretek Diagnostics, Inc, Houston, Tex, donated the ^{13}C urea breath tests."
Declaration of interest	None reported
Notes	None of our primary outcomes were addressed. Follow-up 2 months; 25% in the treatment group tested positive still for *Helicobacter pylori* after treatment. For the N of pustules the data are quite skewed and for the total score very skewed See comparison 64 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 660): "Patients were randomly assigned to groups receiving active treatment or placebo. Dispensing of study medications according to a randomised registry list provided by the project programmer." Comment: Probably done

Allocation concealment (selection bias)	Unclear risk	Quote (660): "Treatment status was not disclosed to investigators, coordinators or patients throughout study." The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 660): "Double-blind, placebo medication resembled active treatment." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator-assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	2/44 (4.5%); 2 withdrawals in clarithromycin group, reasons reported Comment: Low number of dropouts at follow-up, and although per-protocol analysis considered to be at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, no wash-out period described, groups treated equally Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship and support represented any additional bias

Bamford 2012

Methods	RCT, prospective, active-controlled, double-blind Date of study August 2006 to July 2008 Setting Essentia Health Duluth Clinic, MN, US

Participants	**Randomised:** 53 participants (mean age 47.3 years, 14 male, 39 female) **Inclusion criteria** • Facial rosacea with severity 'greater than mild' (scores 5 to 12 on the rosacea severity scale) **Ocular involvement:** Unclear **Exclusion criteria** • Used zinc dietary supplements (> 25 mg/day) • Oral or topical treatment for rosacea three months prior to study entrance **Dropouts and withdrawals** • 9/53 (17%); zinc group (5), placebo group (4) • Adverse events; zinc group (3), placebo group (4) • Did not attend 3 month visit; zinc group (1), placebo group (0) • Withdrawal without reason; zinc group (1), placebo group (0) **Baseline data mean** Rosacea severity; zinc group 6.30 (95% CI 5.83 to 6.76), placebo group 6.77 (95% CI 6.22 to 7.32)
Interventions	Three months **Intervention** Zinc sulfate 220 mg - BID (27) **Comparator** Placebo - BID (26) Subjects were required to refrain from using oral or topical treatments for rosacea while participating in the trial
Outcomes	Assessments (2): baseline, month 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Rosacea severity score (transient erythema (flushing), non-transient erythema, papules, pustules, and telangiectasia; each feature was measured on a 4-point scale from absent (0) to severe (3))✴ **Secondary outcomes**

	1. Subject-reported rosacea-related quality of life (RosaQoL, Nicholson 2007)✶ 2. Laboratory data (haemoglobin (g/dl), zinc level (µg/ml), and ceruloplasmin (units/l)) 3. Adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 462): "thank the Duluth Clinic Foundation for grant support that made this study possible"
Declaration of interest	Quote (page 459): "None declared"
Notes	Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 76 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 460): "Randomization was carried out following a sequence of random numbers using random block size created by a biostatistician and maintained at the research pharmacy of the healthcare organization" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 460): "Randomization was carried out following a sequence of random numbers using random block size created by a biostatistician and maintained at the research pharmacy of the healthcare organization" Comment: Form of central allocation, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 459-60): "double-blind" and "Treatment was masked from participants, investigators, and study staff". Capsules probably of identical appearance Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken

		Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	9/53 (17%); zinc group (5), placebo group (4), reasons reported. Per-protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT00395226). Only the primary outcome was listed in the protocol. The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Barnhorst 1996

Methods	RCT, prospective, placebo-controlled, investigator-blinded, within-patient comparison Date of study Unreported Setting Department of Ophthalmology, Cleveland Clinic Foundation, Cleveland, US
Participants	**Randomised:** 13 participants (mean age 72.8 years (range 40 to 90), 7 male, 6 female) **Inclusion criteria** • Participants with ocular rosacea and previous diagnosis of facial rosacea (≥ 18 years) **Exclusion criteria** • Age < 18 years, pregnancy, antibiotic use, inability to provide informed consent **Dropouts and withdrawals** • 3/13 (23%) at metronidazole site • Stinging of the eye (1) • Non-compliance (2) **Baseline data mean (SD)** Eye and eyelid grading: metronidazole site 4.5 (1.1), control site 4.5 (1.0)
Interventions	12 weeks **Intervention**

	Lid hygiene plus warm compresses plus metronidazole 0.75% gel - BID **Comparator** Lid hygiene and warm compresses - BID
Outcomes	Assessments (3): baseline, week 6 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Eye and eyelid grading by physician✴ Method: grading sheet (1 to 5) (higher score is worse) Pre-treatment scores were compared with post-treatment scores with respect to ocular surface, eyelid margin, and combined eyelid plus ocular surface **Secondary outcomes** 1. Patient questionnaire evaluating patient compliance with the treatment regimen and any side effects noted✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	Withdrawals were not included in the analysis by the review authors. Because it is a within-patient study, patients can make errors with which eye to treat or treat both eyes. One of our primary outcomes was addressed (adverse events) See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1881): "One eye was assigned randomly to receive lid hygiene and warm compresses twice daily, while the other eye received lid hygiene and compresses twice daily." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1881): "An observer who was masked to the treated and control eye completed a physician data sheet." Participants were not blinded Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator as well as participant-assessed Quote (page 1881): "An observer who was masked to the treated and control eye completed a physician data sheet." Comment: We judged this at unclear risk of bias
Incomplete outcome data (attrition bias)	High risk	3/13 (23%), reasons reported Quote (page 1881): "Those patients reporting noncompliance were removed from the study." Comment: We considered this as at high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate Comment: The study appeared to be free of other forms of bias

Baumann 2018

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study June 2014 to May 2015 Mulicentre (24) in US
Participants	**Randomised:** 445 participants (mean age 50.3 years, 95 male, 350 female) **Inclusion criteria**

	• > 18 years of age with a diagnosis of moderate to severe persistent facial erythema associated with rosacea, defined as grade 3 or higher on both the CEA scale with photonumeric guide and the Subject Self-Assessment for rosacea facial redness (SSA) scale with photo guide **Ocular involvement:** Unclear **<u>Exclusion criteria</u>** • 3 inflammatory lesions on the face • Facial hair, tattoos, or other characteristics that would interfere with erythema assessments • Other dermatologic conditions within the treatment area • Uncontrolled systemic disease • Raynaud syndrome • Narrow-angle glaucoma • Orthostatic hypotension • Cerebral or coronary insufficiency • Thromboangiitis obliterans • Scleroderma • Sjögren's syndrome • History of current or past drug or alcohol abuse • Severe, unstable, or uncontrolled cardiovascular disease • Known hypersensitivity to oxymetazoline • Current treatment with monoamine oxidase inhibitors or niacin (2500 mg/d) • Treatment with oxymetazoline-containing products, topical glucocorticosteroids applied to the face, systemic or nasal corticosteroids, or any product for the treatment of acne, rosacea, or facial redness in the past 14 days • Systemic antibiotics for rosacea in the past 28 days • Isotretinoin, laser light, or other energy-based therapy to the face in the past 180 days • Currentty receiving or with a history of receiving brimonidine **<u>Dropouts and withdrawals</u>** • 16/445 (3.6%); oxymetazoline group (11), vehicle group (5) • Adverse event; oxymetazoline group (6), vehicle group (1) • Lost to follow-up; oxymetazoline group (2), vehicle group (2)

	• Personal reasons; oxymetazoline group (1), vehicle group (2) • Randomised in error; oxymetazoline group (1), vehicle group (0) • Conflict of interest; oxymetazoline group (1), vehicle group (0) **Baseline data (n)** Clinician's Erythema Assessment (CEA) 3: oxymetazoline group 187, vehicle group 187 Clinician's Erythema Assessment (CEA) 4: oxymetazoline group 37, vehicle group 34 Subject Self Assessment (SSA) 3: oxymetazoline group 207, vehicle group 200 Subject Self Assessment (SSA) 4: oxymetazoline group 16, vehicle group 21
Interventions	29 days **Intervention** Oxymetazoline hydrochloride cream 1% - QD (224) **Comparator** Vehicle cream - QD (221)
Outcomes	Assessments (4), baseline, day 1, 15 and 29 (and 28-day posttreatment for worsening and rebound) **Outcomes of the trial** (as reported) **Primary outcomes** 1. 2-grade or greater decrease (improvement) from baseline on both CEA and SSA (SSA: 0 = no signs of unwanted redness and 4 = severe redness) **Secondary outcomes** 1. At least a 2-grade decrease (improvement) from baseline on the individual components, CEA and SSA (scale 0 to 4, higher is worse)✴ 2. Percent change from baseline in facial erythema assessed using digital image analysis of photographs (Canfield Scientific, Inc, Fairfield, NJ) 3. Patient satisfaction (Satisfaction Assessment for Rosacea Facial Redness questionnaire) 4. Patients' assessed symptoms (Symptom Assessment for Rosacea Facial Redness questionnaire)✴ 5. Patients' assessment of impacts associated with rosacea facial erythema (Impact Assessment for Rosacea Facial Redness questionnaire)✴

	6. Safety and tolerability✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 298): "This study was sponsored by Allergan plc, Dublin, Ireland"
Declaration of interest	Quote (page 298): "L Baumann, DJ Goldberg, L Stein Gold, EA Tanghetti, E Lain, and J Kaufman are investigators for Allergan plc. E Weng, DR Berk, and G Ahluwalia are employees of Allergan plc and may own stock/stock options in that company"
Notes	Two of our outcomes are addressed (participant-assessed changes of rosacea severity and adverse events) See comparison 5 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 294): "Randomization was stratified by baseline score on the Clinician Erythema Assessment (CEA) scale and by study site, and managed by an interactive voice or web response system" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 294): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement

Incomplete outcome data (attrition bias)	Low risk	16/445 (3.6%); oxymetazoline group (11), vehicle group (5) Comment: Low number of drop-outs. We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on www.clinicaltrials.gov (NCT02132117). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	All authors were investigators of employees for Allergan Comment: We judged this as at an unclear risk of bias

Benkali 2014

Methods	RCT, prospective, within-patient comparison Date of study Unreported Setting Multicentre in US
Participants	**Randomised:** 102 participants (mean age 41.6 years, 40 male, 62 female) **Inclusion criteria** • Adult male or female subjects, with a clinical diagnosis of rosacea with a Clinician's Erythema Assessment (CEA) scale score ≥ 3 (moderate) on the 5-point scale **Ocular involvement:** Unclear, probably not **Exclusion criteria** • Abnormal intraocular pressure (IOP) (< 11 mm Hg or > 21 mm Hg) • Active rosacea • History of glaucoma or ocular hypertension • Prior eye surgery • Raynaud's syndrome • Thromboangiitis obliterans • Orthostatic hypotension • Severe cardiovascular disease • Cerebral or coronary insufficiency • Renal or hepatic impairment • Scleroderma • Sjögren's syndrome • Depression • Concomitant treatment with monoamine oxidase (MAO) inhibitors, tricyclic antidepressants, barbiturates,

	opiates, sedatives, systemic anaesthetics, alpha-agonists, beta blockers, antihypertensive agents, cardiac glycosides, or any topical or systemic agent used for the treatment of ocular hypertension **Dropouts and withdrawals** • 6/102 during ophthalmic dosing, and an additional 8/102 during dermal dosing, unclear from which group, reasons unreported **Baseline data (number)** CEA score 3 (moderate); 0.07% group 22, 0.18% QD group 22, 0.18% BID group 21, 0.5% group 24 CEA score 4 (severe); 0.07% group 5, 0.18% QD group 3, 0.18% BID group 5, 0.5% group 0
Interventions	Four weeks **Intervention** Brimonidine tartrate 1 gram 0.07% gel - BID (27) **Comparator 1** Brimonidine tartrate 1 gram 0.18% gel - QD (25) **Comparator 2** Brimonidine tartrate 1 gram 0.18% gel - BID (26) **Comparator 3** Brimonidine tartrate 1 gram 0.5% gel - QD (24) Each subject received one drop of brimonidine tartrate 0.2% ophthalmic solution in each eye every 8 hours over a 24 hour period, as proposed in the US prescribing information. After a 2 day wash-out period they received the dermal applications as described above
Outcomes	Assessments (47): day 1 (10x), after 2 days wash-out day 4 (10x), 5, 10, 18 (10x), 19, 24 and 32 (13x) **Outcomes of the trial** (as reported) **Primary outcomes** 1. Plasma concentrations of brimonidine (validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) analytical method) 2. Pharmacokinetic parameters (Cmax, Tmax, Ctrough, AUC (0-24 h) (non-compartmental method with

	KineticaTM software (version 4.3, InnaPhase Corporation, Philadelphia, USA) **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 162): "Funding for this study was provided by Galderma R&D, SNC. Funding for writing assistance was provided by Galderma Laboratories, L.P."
Declaration of interest	Quote (page 162): "K. Benkali, F. Rony, R. Bouer, and N. Wagner are employees of Galderma R&D, Sophia Antipolis, France. M. Leoni, A. Fernando, and M. Graeber are employees of Galderma R&D, Princeton, NJ, USA"
Notes	None of our primary nor secondary outcomes were addressed (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 163): "One hundred and two (102) subjects were randomly assigned to 1 of the 4 brimonidine gel regimens" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "Regarding the allocation sequence generated for the 4 subsequent groups consisting of different doses or regimen for topical applications, the randomization list was created before the study started, with a 1:1:1:1 ratio and block size of 4. This randomization list was generated by a designated biostatistician and was distributed to the clinical supply team in a sealed envelope" Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: "This randomization list was generated by a designated biostatistician

		and was distributed to the clinical supply team in a sealed envelope" Comment: Adequate, probably done
Blinding of participants and personnel (performance bias)	High risk	No blinding reported Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding reported Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	14/102 (13.7%); 6/102 during ophthalmic dosing, and an additional 8/102 during dermal dosing, unclear from which group, reasons unreported. Per-protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate Comment: The study appeared to be free of other forms of bias

Berardesca 2012

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Between April and June 2009 Setting Multicentre in Europe (Italy, Switzerland and Belgium)
Participants	**Randomised:** 42 participants (mean age 39.8 years (range 20 to 60), 11 male, 31 female) **Inclusion criteria** • Participants aged 18 to 60 years, with stage I and II rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** None

	Baseline data mean Nothing reported
Interventions	Four weeks **Intervention** P-3075 cream (Polichem SA, Lugano, Switzerland) containing 5% potassium azeloyl diglycinate (Azeloglicina; Sinerga S.p.A., Milan, Italy) and 1% hydroxypropyl chitosan (HPCH) - BID (28) **Comparator** Placebo (vehicle) cream - BID (14)
Outcomes	Assessments (5): baseline, day 7, 14, 28 and 42 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Instrumental evaluations of erythema (forehead, cheeks and chin by assessing the erythema index (Mexameter; C+K electronic, Cologne, Germany))✶ 2. Instrumental evaluations of stratum corneum hydration (forehead, cheeks and chin by assessing skin capacitance (Corneometer CM 825; C+K electronic)) 3. Assessment of flushing, erythema, oedema, itching, burning and stinging (0 = none, 1 = mild, 2 = moderate and 3 = severe)✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed See comparison 50 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 38): " were randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

		After e-mail communication: "according to a computer generated randomization list".. "with a 2:1 ratio using blocks of 3" Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: Form of central allocation, "the randomization list was generated by the statistician and kept under lock and key until the data base lock, as usual" and "Patients were sequentially assigned to the next available randomization number, starting from the lowest number provided to each investigational site" Comment: Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 37): "double-blind" Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "placebo cream units, which were identical to the active product in terms of size, shape, volume, color. The tubes (P-3075 and placebo) were identically labeled for clinical use as it is in a double-blind procedure." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 37): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: "placebo cream units, which were identical to the active product in terms of size, shape, volume, color. The tubes (P-3075 and placebo) were identically labeled for clinical use as it is in a double-blind procedure." Outcomes were investigator-assessed

		Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	No losses to follow up Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	No exact data were provided regarding assessment of sign and symptoms of rosacea, only generic comments were made Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Study duration adequate, no wash-out period described, groups treated equally Comment: The study appeared to be free of other forms of bias

Berlin 2015

Methods	RCT, prospective, placebo-controlled, 2-phase study (only second phase is randomised) Date of study Unreported Setting The Berlin Center for Medical Aesthetics, Boynton Beach, FL, US
Participants	**Randomised:** unclear number of participants (age and gender unreported) **Inclusion criteria** • Participants with moderate to severe papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** Not reported **Baseline data (mean)** Nothing reported
Interventions	Forty weeks **Intervention** Doxycycline 40 mg modified release - QD **Comparator**

	Placebo - QD First phase 12 week combination regimen of doxycycline 40 mg modified release and metronidazole 1% gel in subjects with moderate to severe rosacea. At the end of phase 1, subjects who achieved an investigator global assessment (IGA) score of clear or near clear, or whose IGA score improved 2 grades from baseline, were eligible for enrolment in phase 2
Outcomes	Assessments (2): baseline, week 40 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Relapse rate (IGA score or inflammatory lesion count that returned to baseline, or if the investigator determined that the subject warranted a change in rosacea therapy)✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page AB11): "Study was funded by Galderma Laboratories, L.P."
Declaration of interest	None declared. One investigators was employed by Galderma Laboratories, L.P., Fort Worth, TX, United States, the manufacturer of doxycycline 40 mg modified release
Notes	None of our primary outcomes was addressed. Abstract, few data presented. Received no further data of principal investigator, no exact data are provided (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page AB11): "were randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported

		Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding reported Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding reported Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	No information on dropouts and withdrawals Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Beutner 2005

Methods	RCT, prospective, active- and vehicle-controlled, investigator-blinded Date of study March 2003 to January 2004 Setting Multicentre study in the US
Participants	**Randomised:** 1299 participants (557 in metronidazole gel group, 553 in metronidazole cream group, and 189 in vehicle gel group) (mean age 48.4 ± 13.02 years, range 18 to 92 for metronidazole gel group; 48.3 ± 13.04 years, range 18 to 88 for metronidazole cream group; 47.8 ± 12.05 years, range 22 to 81 for vehicle gel group; sex 149 male, 408 female for metronidazole gel group; 143 male, 410 female in metronidazole cream group; and 48 male, 141 female in vehicle gel group) **Inclusion criteria** • Adults with rosacea, 8 to 50 inflammatory lesions and no more than 2 nodules. All enrolled participants had IGA of 3 = moderate at baseline **Ocular involvement:** Unclear **Exclusion criteria** • Pregnant or lactating female • Female unwilling to use oral contraceptives

	• Subjects unwilling to minimise external factors that might produce an exacerbation of their rosacea **Dropouts and withdrawals** • 156/1299 (12%); 57 (10.2%) discontinued in metronidazole gel group, 72 (13.0%) in metronidazole cream, and 27 (14.3%) in vehicle gel group • Adverse events; metronidazole gel group (11), metronidazole cream group (12), vehicle group (5) • Lack of efficacy; metronidazole gel group (0), metronidazole cream group (2), vehicle group (2) • Subject request; metronidazole gel group (15), metronidazole cream group (21), vehicle group (8) • Protocol violation; metronidazole gel group (9), metronidazole cream group (9), vehicle group (2) • Lost to follow-up; metronidazole gel group (11), metronidazole cream group (12), vehicle group (5) • Pregnancy; metronidazole gel group (3), metronidazole cream group (0), vehicle group (0) • Other reasons; metronidazole gel group (1), metronidazole cream group (2), vehicle group (0) **Baseline data (mean)** Lesion count: metronidazole gel group (18.3), metronidazole cream group (18.1) vehicle group (18.4)
Interventions	10 weeks **Intervention** Metronidazole gel - 1% QD (577) **Comparator 1** Metronidazole cream - 1% QD (553) **Comparator 2** Metronidazole gel vehicle - QD (189)
Outcomes	Assessments (5): baseline, week 2, 4, 7 and 10 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Per cent reduction from baseline in inflammatory lesion counts at week 10✴

	2. Per cent of subjects rated as success (clear or almost clear in dichotomised Investigator's Global Severity Score)✴ **Secondary outcomes** 1. To show non-inferiority of metronidazole gel 1% to metronidazole cream 1% in the treatment of rosacea 2. To show superiority over its gel vehicle 3. Assess safety and tolerability of the treatments✴ 4. Inflammatory lesions count✴ 5. Investigator's Global Severity Score (score 0 = clear to 4 = severe)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 10): "Supported by Galderma R&D Inc."
Declaration of interest	Page 10; Dr Beutner and Mr Calvarese are employees of Dow Pharmaceutical Sciences. Dr Graeber is an employee of Galderma R&D Inc
Notes	One of our primary outcomes is addressed (adverse events) Poster presentation, after e-mail contact extensive information has been provided by authors See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 10): "This was a multicenter, randomized, investigator-blind, active and vehicle-controlled, parallel comparison." After e-mail contact with investigators we received additional information which enabled us to change the grading for this criterion from 'Unclear' to 'Yes' Quote: "Prior to the start of the study, a randomization list was supplied by the Sponsor. Drug supplies for the entire trial were numbered sequentially. The drug supplies for Metronidazole Gel 1%, Noritate Cream 1%, and Vehicle Gel were packaged according to the randomization list in blocks of 7 using a ratio of 3:3:1. Study drug supplies were distributed to each of the investigational sites in complete blocks in order to maintain the randomization ratio within an investigational site. A unique drug kit number was associated with each drug supply kit, and this corresponded to the subject number. These

		numbers were assigned sequentially as subjects entering the study at each investigational site." Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence was not described in sufficient detail in the report E-mail contact with the investigator confirmed "the randomization schedule remained blinded from those involved in the clinical conduct of the study until the database lock memo was issued" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 10): "...investigator blind." E-mail contact with the investigator confirmed "the study drugs were different in appearance. To protect the blinding, a study staff designee, other than the Investigator making evaluations, dispensed and collected study drug from subjects. Additionally, both the person in charge of study drug dispensation and the subject were instructed not to discuss the study treatment with the Investigator or other evaluator(s)". Participants were not blinded Comment: We judged this as at unclear risk of bias
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 10): "...investigator blind." Comment: As the investigators were the outcome assessors the report was unclear how they were blinded E-mail contact with the investigator confirmed "the study drugs were different in appearance. To protect the blinding, a study staff designee, other than the Investigator making evaluations, dispensed and collected study drug from subjects. Additionally, both the person in charge of study drug dispensation and the subject were instructed not to discuss the study treatment with the Investigator or other evaluator(s)" Blinding of the outcomes assessors, key personnel, was ensured, and it was unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Number of participants unclear, dropouts not reported

		E-mail contact with the investigator confirmed "57 (10.2%) discontinued in metronidazole gel group, 72 (13.0%) in metronidazole cream and 27 (14.3%) in vehicle gel group". Reasons for dropouts stated and ITT analysis LOCF Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, but unclear if there was a 'wash-out' period, unclear if groups were treated equally E-mail contact with the investigator confirmed "no financial arrangements have been made with any of the investigators. Each listed investigator was required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor and none disclosed any such interests" Comment: We judged this as at a low risk of bias

Bhargava 2016

Methods	RCT, prospective, placebo-controlled, double-blind Date of study January 2013 to June 2014 Setting Three referral eye centres, northern part India
Participants	**Randomised:** 130 participants (mean age 48 years (range 21 to 70), 52 male, 78 female) **Inclusion criteria** • Participants with rosacea as diagnosed by dermatologist based on the guidelines proposed by National Rosacea Society Expert Committee (Wilkin 2002) • Participants with rosacea referred from dermatology clinic having dry eye symptoms or complaining of ocular irritation (Dry Eye Scoring System, DESS) **Ocular involvement:** Yes **Exclusion criteria** • Corneal or episcleral/scleral involvement • Allergic conjunctivitis • Contact lens wear • Herpetic eye disease

	• Diabetes • Other skin diseases • Inability to swallow soft gel capsules • On regular course of aspirin or anti-coagulants (cyclo-oxygenase-2 inhibitors) • Allergic to fluorescein • Systemic (tetracyclines and corticosteroids) or topical medications (other than artificial tear supplements) that could affect tear film or meibomian gland function (beta-blockers, benzodiazepines, and anti-histamines) were discontinued 3 weeks prior to start of study **Dropouts and withdrawals** • 14/130 (10.8%); omega 3 fatty acids (O3FA) group (14), placebo group (0) • Lost to follow-up; O3FA group (6), placebo group (0) • Adverse events; O3FA group (8), placebo group (0) **Baseline data mean (SD)** Mildly symptomatic (n); O3FA group (12), placebo group (15) Moderately symptomatic (n); O3FA group (45), placebo group (36) Severely symptomatic (n); O3FA group (8), placebo group (14) Symptom score (DESS); O3FA group 9.1 (2.4), placebo group 8.6 (2.6) Meibom gland score; O3FA group 1.6 (1), placebo group 1.5 (1.3) Tear break-up time (TBUT); O3FA group 9.6 (1.7), placebo group 9.2 (2.3) Schirmer score; O3FA group 13.6 (5), placebo group 13.1 (5.2)
Interventions	Six months **Intervention** Omega-3 fatty acids (O3FA) (180 mg eicosapentaenoic acid (EPA) and 120 mg docosahexaenoic acid (DHA) in one capsule) - BID (65) **Comparator** Placebo - one capsule - BID (65) All participants were prescribed 0.5% carboxymethylcellulose eyedrops four times a day. However, patients were instructed to not to use tear supplements, at least 2 h prior to tear film testing

Outcomes	Assessments (4): baseline, month 1, 3 and 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Decrease from baseline in subjective dry eye symptoms scoring (DESS) (questionnaire, score 0-6 = mild, score 6.1-12 moderate, 12.1 to 18 severe)✶ **Secondary outcomes** 1. Change in meibomian gland score (lower = improvement)✶ 2. Change in Schirmer test value (increase = improvement)✶ 3. Change in tear break-up time (TBUT)(increased time = improvement)✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 7): "The authors report no conflicts of interest"
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 80 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "The allocation codes were generated by a disk operating system-based software in the department of community ophthalmology. Patients were randomly allocated to one of the two groups by a parallel assignment." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 2): "The codes were sealed in blue-colored envelopes that were opened by health care personnel not involved in patient care." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. This was probably done

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 1 and 2): "double-masked" and "The two types of capsules and packs were similar to each other" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	14/130 (10.8%) all from O3FA group. Unbalanced number of drop-outs with all drop-outs included in analyses (last observation carried forward) Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Bitar 1990

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Department of Dermatology, Hotel-Dieu Hospital; University of Montreal, Montréal, Québec, Canada
Participants	**Randomised:** 100 adult participants (mean age 50.3 years (SD 1.6) in treatment group, 50.8 years (1.9) in control group, 41 male, 59 female) **Inclusion criteria** • Participants with acne rosacea **Ocular involvement:** Unclear

	Exclusion criteria • Alcohol or drug abuse • Keratoconjunctivitis • Conditions requiring anticoagulants or active antabuse treatment • Pregnant, nursing female • Participants requiring antibiotics, or vasodilators **Dropouts and withdrawals** • 18/100 (18%); metronidazole group (8), control group (10) • Lack of effect; metronidazole group (2), control group (3) • Intercurrent illness; metronidazole group (2), control group (1) • Dosage violation; metronidazole group (1), control group (0) • Administrative reasons; metronidazole group (1), control group (4) • Lost to follow-up; metronidazole group (2), control group (1) • Adverse event; metronidazole group (0), control group (1) **Baseline data mean (SEM)** Number of papules; metronidazole group 8.1 (0.7), control group 8.9 (0.7) Number of pustules; metronidazole group 3.2 (0.4), control group 4.3 (0.6)
Interventions	Two months **Intervention** Metronidazole cream 1% - BID (50) **Comparator** Placebo cream - BID (50)
Outcomes	Assessments (3): baseline, month 1 and 2 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Improvement in clinical evaluation by physician (presence or absence facial erythrosis, of rosacea at different sites, N of papules and pustules, erythema, and telangiectasia)✶

	2. Improvement of global impression > 4 weeks (ECDEU assessment manual, rating 1 to 7, higher is worse)✴ **Secondary outcomes** 1. Adverse effects✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 248): "This study was supported by Rhône-Poulenc Pharma Inc, Montréal, Canada"
Declaration of interest	None declared
Notes	We only included the first 4 weeks (quality of the study declined after 4 weeks) One of our primary outcomes was addressed (adverse events) See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 243): "50 patients were randomly assigned to treatment with metronidazole 1% cream, while the other 50 patients received placebo cream." "Metronidazole 1% cream and placebo cream were randomly distributed." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 242): "...double-blind." Quote (page 243): "Tubes were identical in appearance and creams were of same colour and consistency." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Low risk	Quote (page 242-3): "...double-blind." "Tubes were identical in appearance and creams were of same colour and consistency." Outcomes were investigator- and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	18/100 (18%); metronidazole group (8), control group (10) in second month, similar reasons reported and balanced across both groups. ITT analysis only first month Comment: No dropouts in first month and we only included data for the first month, therefore considered as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration was adequate, and participants on antibiotics or vasodilators were excluded. Compliance was assessed Quote (page 243): Concomitant medications which were "considered to be vital to the general health of the patients were permitted and noted", i.e. nonsteroidal anti-inflammatory and antihypertensive agents. The dropout rate was high in the second month in both groups, and in the absence of an ITT analysis only data from the first month was entered into the RevMan analysis Comment: We considered this as at low risk of bias

Bjerke 1989

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, Department of Dermatology, Haukeland Hospital, Bergen; Rikshopitalet, Oslo; Florø Hospital, Florø of Ullevål Hospital Oslo, Regionsykehuset, Trondheim, Norway
Participants	**Randomised:** 97 participants (mean age 47 years (range 18 to 77), 44 male, 53 female) **Inclusion criteria**

	• Participants with facial rosacea with at least 10 papules or pustules or both, erythema, and telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Pregnancy, lactation • Age < 18 years • Allergy to component study drugs • Any treatment with antibiotics, or other rosacea treatments in last 4 weeks **Dropouts and withdrawals** • 4/97 (4.1%); metronidazole group (1), placebo group (3) • Cured; metronidazole group (1), placebo group (0) • Insufficient effect; metronidazole group (0), placebo group (3) **Baseline data mean (SD)** No details reported
Interventions	Two months **Intervention** Metronidazole cream - 1% BID (50) **Comparator** Placebo cream - BID (47)
Outcomes	Assessments (3): baseline, week 4 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Self-assessed changes in rosacea severity (improved, unchanged, worse)✴ 2. Physician's global evaluation (improved, unchanged, worse)✴ 3. Lesion count reduction✴ 4. Reduction of papules✴ 5. Reduction of pustules✴ 6. Reduction in erythema (0 = normal skin, 5 = blue red skin)✴ 7. Reduction of telangiectasia (0 = none, 3 = many)✴

	Secondary outcomes 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Page 187, one of the investigators is employed by Dumex, the manufacturer of metronidazole. No conflict of interest declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 188): "The trial was a randomized...." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 188): "The trial was double-blind." Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 188): "The trial was double-blind." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	4/97 (4.1%), ITT analysis. Reasons for withdrawals reported Comment: We considered this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those

		mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Wash-out period before study started unclear, no other local or oral treatment was allowed, study duration adequate, no sponsoring mentioned, however, study details are incomplete Comment: Insufficient information to assess whether important risk of bias exists

Bjerke 1999

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, Dermatology Department, Haukeland Hospital, of Ullevål, and National Hosital (Rikshospitalet), Oslo, Norway
Participants	**Randomised:** 116 participants (mean age 48.4 years in treatment group, 50.3 years in control group, 57 male, 59 female) **Inclusion criteria** • 18 years of age • Participants with grade 2 rosacea (Mills and Kligman classification) with at least 10 inflammatory lesions (papules and pustules), persistent erythema and telangiectasia No ocular involvement **Exclusion criteria** • Mild form of rosacea, or severe form complicated by rhinophyma • Marked ophthalmological complications • Steroid rosacea • Diseases and medications which obscured the course and evaluation of rosacea • Hypersensitivity to ingredients of study medication **Dropouts and withdrawals** • 8/116 (6.9%); azelaic acid group (5), placebo group (1) unclear from which group (2) • Side effects; azelaic acid group (5), placebo group (1)

	• Protocol violation or only attended at baseline; unclear from which group (2) **Baseline data mean** Number of inflammatory lesions; azelaic acid group 30.8, placebo group 31.7
Interventions	Three months **Intervention** Azelaic acid cream 20% - BID (76) **Comparator** Vehicle - BID (38)
Outcomes	Assessments (4): baseline, month 1, 2 and 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Self-assessed changes in rosacea severity (complete remission, marked improvement, moderate improvement, no improvement or deterioration)✴ 2. Decrease in N of lesions✴ 3. Physician's global impression of improvement (complete remission, marked improvement, moderate improvement, no improvement or deterioration)✴ 4. Decrease in erythema and telangiectasia (0 = none, 6 = severe)✴ **Secondary outcomes** 1. Tolerability of treatment 2. Cosmetic characteristics ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	One of the investigators was employed by Schering AG Berlin, Germany, the manufacturer of the azelaic acid cream. However, none declared
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 456): "The assignment of study medication was random." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 456): "double-blind, parallel group comparison between azelaic acid 20% cream and its vehicle." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 456): "..double-blind.." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	8/116 (6.9%); azelaic acid group (5), placebo group (1), unclear from which group (2) Quote (page 456): "All available patients (completed and withdrawals) were included in a confirmatory Intention-to-treat analysis of treatment differences with the results achieved at their last observation carried forward (LOCF)." Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate. Unclear if there was a wash-out period before study, unclear if groups were treated equally, no sponsoring mentioned Comment: Insufficient information to assess whether important risk of bias exists

Bleicher 1987

Methods	RCT, prospective, placebo-controlled, double-blind, within-patient comparison Date of study Unreported Setting Two centres, Department of Dermatology, Harvard Medical School; Department of Dermatology, Massachusetts General Hospital, Boston, US
Participants	**Randomised:** 40 adult participants (mean age 48.7 years, 16 male, 24 female) **Inclusion criteria** • Participants with moderate to severe rosacea and at least moderate erythema No ocular involvement **Exclusion criteria** • Pregnant or nursing female • Participants receiving anticoagulants • Antibiotics or corticosteroids, or both • History of paraben allergy or metronidazole hypersensitivity • Participants with unilateral or mild rosacea **Dropouts and withdrawals** • 2/40 (5%) • Flare-up (1) • Flare-up unilateral (1) **Baseline data mean** Number of lesions counts; 30.8
Interventions	Nine weeks **Intervention** Metronidazole 0.75% gel - BID **Comparator** Placebo (vehicle) - BID
Outcomes	Assessments (5): baseline, week 3, 6, 9 and 12 **Outcomes of the trial** (as reported) **Primary outcomes**

	1. Self-assessed changes in rosacea severity✶ 2. Physician's global evaluation✶ 3. Decrease in lesion counts✶ 4. Erythema, and telangiectasia (0 = absent, 3 = severe)✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 614): "Study was funded, in part, by Curatek Pharmaceuticals, Elk Grove Village, Ill. The metronidazole gel and vehicle placebo used were also provided by Curatek Pharmaceuticals. Statistical analysis was performed by an independent statistical consultant."
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 610): "Patients were randomly assigned to receive either 0.75% metronidazole in a water based gel or the gel-base alone to each half of the face." "Randomization by Curatek Pharmaceuticals, Elk grove Village, Ill." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 610): "Randomization by Curatek Pharmaceuticals, Elk grove Village, Ill." Comment: Appears to be a form of central randomisation, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 609 and 610): "double-blind" and "Identical appearing tubes, colour coded and labelled right and left containing active treatment or placebo." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Low risk	Quote (page 609-10): "...double-blind." and "Identical appearing tubes, colour coded and labelled right and left containing active treatment or placebo." Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Quote (page 611 and 612): "Two patients did not complete the study. One discontinued after 2 days due to a flare-up in rosacea related to withdrawal from his systemic antibiotic therapy. Data on this patient were not included in the results. A second patient withdrew at five weeks because of a severe unilateral flare-up on the placebo-treated side." Comment: Second patient was included in the analysis. We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate. Wash-out period before study at least 3 weeks. Other treatments that might affect rosacea were required to be discontinued The study appears to be free of other forms of bias

Blom 1984

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Department of Dermatology, regional Hospital Örebro, Sweden
Participants	**Randomised:** 40 (age and gender unreported) **Inclusion criteria** • Participants with classical rosacea of different severity **Ocular involvement:** Unclear **Exclusion criteria**

	• Any treatment whether systemic or topical within preceding month **Dropouts and withdrawals** • 3/40 (7.5%); 3, probably in lymecycline group, no reasons mentioned **Baseline data mean** Total number of lesions; sulfur group 213, lymecycline group 143
Interventions	Four weeks **Intervention** Sulphur 10% cream topically - QD + placebo capsules - BID (20) **Comparator** Lymecycline 150 mg - BID + vehicle cream - QD (20) Unreported how many participants were randomised into each group
Outcomes	Assessments (2): baseline and week 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Total number of papules and pustules within a defined area measured with a flexible frame - internal measurement 3.5 cm x 2.5 cm was counted✴ 2. Grade of erythema (none, slight, moderate, severe)✴ 3. Clinical progress, participants and clinicians assessments (complete remission, much better, slightly better, unchanged, worse)✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 359): "This work was supported by Essex Läkemedel AB"
Declaration of interest	None declared
Notes	Participants who failed to respond or got worse were switched to the alternative treatment, unclear who and how many. Lack

	of usable data and inability to trace the investigators (see Table 6) One of our primary outcomes was addressed (participant-assessed changes in rosacea severity)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 358): "Patients were allocated to either regimen 1 or 2 according to a randomization code" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 358): "double-blind study" Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 358): "double-blind study" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	3/40 dropouts, probably in lymecycline group, no reasons mentioned. Per-protocol analysis Comment: Low number of dropouts and although per protocol analysis judged as at a low risk of bias
Selective reporting (reporting bias)	High risk	Only number of papules and pustules is addressed and not the other primary efficacy outcome measures Comment: We judged this as at a high risk of bias
Other bias	High risk	Participants who failed to respond or got worse were switched to the alternative treatment,

		unclear who and how many Comment: We judged this as at a high risk of bias

Braithwaite 2015

Methods	RCT, prospective, placebo-controlled, investigator-blinded Date of study Unreported Setting Hospital-based research facility and four community-based research and/ or primary care sites, New Zealand
Participants	**Randomised:** 138 participants (mean age 58 years (range 18 to 90), 69 male, 68 female, 1 gender unreported) **Inclusion criteria** • ≥ 16 years with physicians diagnosis of facial rosacea • Investigator Global Assessment of Rosacea severity (IGA-RSS) of facial rosacea ≥ 2 **Ocular involvement:** Unclear **Exclusion criteria** • Current requirement for systemic corticosteroids, or systemic corticosteroid treatment in the 4 weeks prior to visit 1 • Current requirement for oral or topical antibiotic therapy for rosacea • Current requirement for topical corticosteroid treatment for rosacea • Known or suspected allergy to honey or cetomacrogol control cream • Any other condition which, at the investigators discretion, it was believed may present a safety risk or impact the feasibility of the study or the study results **Dropouts and withdrawals** • 23/138 (16.6%); Honevo group (8), cetomacrogol group (15) • Withdrawn (randomised incorrectly); Honevo group (1), cetomacrogol group (0) • Worsening rosacea; Honevo group (3), cetomacrogol group (8) • Use of prohibited medication; Honevo group (2), cetomacrogol group (2) • Discontinued for other reasons unrelated to the study; Honevo group (2), cetomacrogol group (3)

	• Did not want to be on control medication; Honevo group (0), cetomacrogol group (1) • Study inconvenience; Honevo group (0), cetomacrogol group (1) **Baseline data mean (SD)** IGA-RSS; Honevo group 3 (0.9), cetomacrogol group 3 (0.9) Visual analogue scale (VAS); Honevo group 36.8 (21.2), cetomacrogol group 32.0 (19.1)
Interventions	Eight weeks **Intervention** Kanuka honey plus 10% glycerine (Honevo) for 30-60 min - BID (69) **Comparator** Cetomacrogol cream for 30-60 min - BID (69)
Outcomes	Assessments (3): baseline, week 2 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. The proportion of subjects who have a 2 or greater improvement in Investigator-rated 7 point Rosacea Severity Score (RSS)(IGA-RSS)(0 = clear, 6 = severe)✴ **Secondary outcomes** 1. Subject-rated global rosacea improvement using a Visual Analogue Score (VAS)((0 mm 'mildest possible' symptoms and 100 mm 'worst possible' symptoms)✴ 2. Change from baseline in IGA-RSS✴ 3. Dermatology Quality of Life Index (DLQI)✴ 4. Adverse events✴ 5. Daily self-reported use (applications per day) 6. Weekly self-reported global rosacea severity (VAS scale)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 7): "This study was funded by HoneyLab. HoneyLab provided the Honevo (medical-grade kanuka honey and 10% glycerine) for the study"
Declaration of interest	Quote (page 7): "Competing interests: None declared"
Notes	All our primary outcomes were addressed

	See comparison 51 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "randomised" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "It was generated using a random number sequencer by our study statistician"
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: "Once the randomisation sequence was developed for each site by the statistician, it was sent electronically to an individual who was not otherwise associated with the study. Individual randomisation slips were generated by that person and placed within sequentially numbered opaque sealed envelopes which were then delivered to each site. Each envelope was accessed by study staff and opened at the point of randomisation. Study staff were unaware of the randomisation sequence" Comment: Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 2): "with assessor blinding" Participants were not blinded Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "Outcome assessors of the IGA-RSS were blinded in that they had nothing to do with the participants during the enrolment period or for any consequent visits and were thus unaware of the treatment arm to which the participant had been allocated. The blinded assessor entered the room during visits solely for the purposes of undertaking the IGA-RSS on the participants. The assessments were undertaken in silence to ensure that there was no communication about treatment arms."

		Comment: The report provided sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator as well as participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: As the patients were not blinded this remains unclear risk
Incomplete outcome data (attrition bias)	Unclear risk	23/138 (16.6%); Honevo group (8), cetomacrogol group (15). Unbalanced number of drop-outs. ITT analysis with drop-outs considered as non-responders. Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on www.anzctr.org.au (ACTRN12614000004662). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Breneman 1998

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, setting not specified other than in Cincinnati, Ohio, US
Participants	**Randomised:** 156 participants (mean age 48.5 years (SD 12.6) in treatment group and 46.9 years (SD 11.9) in control group, 51 male, 105 female) **Inclusion criteria** • Participants with stage II rosacea as defined by the Plewig and Kligman classification system (persistent erythema, numerous telangiectases, papules, and pustules) **Ocular involvement:** Unclear **Exclusion criteria**

	• Use of topical anti-acne, retinoid, or corticosteroid preparations • Systemic antibiotics or corticosteroids **Dropouts and withdrawals** • 17/156 (10.8%); metronidazole group (15), placebo group (2) • Prohibited medication or non-compliant; metronidazole group (12), placebo group (2) • Lost to follow-up; metronidazole group (3), placebo group (2) **Baseline data mean (SD)** Number of papules; metronidazole group 13, placebo group 15 Number of pustules; metronidazole group 2, placebo group 3 Baseline rosacea severity score; metronidazole group 2.10 (0.24), placebo group 2.16 (0.33)
Interventions	10 weeks **Intervention** Metronidazole 1% cream - QD (104) **Comparator** Placebo (vehicle) - QD (52)
Outcomes	Assessments (5): baseline, week 2, 4, 7 and 10 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change from baseline in inflammatory lesion count✴ 2. Current overall rosacea severity score (0 = none, 3 = severe)✴ 3. Physician's global evaluation score of very good improvement (0 = 0% to 24% improvement, 6 = 100%)✴ 4. Erythema, telangiectasia, burning, and scaling (0 = none, 3 = severe)✴ **Secondary outcomes** 1. Cosmetic acceptability 2. Degree of absorption 3. Skin feel after use of treatment

	✶Denotes outcomes pre-specified for this review
Funding source	Unclear, reprint requests "Dermik Laboratories Inc,", the manufacturer of metronidazole, but no source of funding reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 44): "This was a double-blind, randomized, parallel group clinical trial..." "Patients were randomly assigned..." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 44): "This was a double-blind, randomized, parallel group clinical trial comparing the efficacy of metronidazole 1% cream to vehicle." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 44) : "..double-blind.." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	17/156 (10.8%); metronidazole group (15), placebo group (2). Reasons reported. Per-protocol analysis

		Comment: Double the number (104) patients were enrolled in the active treatment group compared to 52 in the vehicle group. The percentage of excluded patients in the treatment group was higher than in the vehicle group. Because far more people in this group took prohibited medication that could have influenced in a positive way the outcomes on rosacea, the review authors consider that this does not pose any threat to the validity of the results in this study Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Adequate wash-out period before the study. Adequate study duration. No medication allowed that might influence outcome Comment: The study appears to be free of other forms of bias

Breneman 2004

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, University Dermatology Consultants, Cincinnati; The Savin Centre, New Haven; Department of Dermatology, University of Pennsylvania School of Medicine, US
Participants	**Randomised:** 53 participants (mean age 43.1 years (SD 11.7) in treatment group and 45.7 years (12.9) in control group, 8 male and 18 female in treatment group, 9 male and 17 female in control group) **Inclusion criteria** • Participants with stage II rosacea as defined by the Plewig and Kligman classification system (persistent erythema, numerous telangiectases, papules, and pustules) No ocular involvement **Exclusion criteria** • Any significant disease or other facial disease • Moderate or severe rhinophyma • Dense-like telangiectasia • Plaque-like oedema

	• Ocular rosacea • Treatment with topical or systemic antibiotics, retinoids, systemic steroids, or topical steroids within 4 weeks of initiation • History of regional enteritis • Colitis • Pregnant and nursing female • Known hypersensitivity to study ingredients **Dropouts and withdrawals** • 5/53 (9.4%); treatment group (3), vehicle group (2) • Adverse events; treatment group (2), vehicle group (1) • Withdrew consent; treatment group (1), vehicle group (0) • Lack of efficacy; treatment group (0), vehicle group (1) **Baseline data mean (SD)** Number of papules and pustules; treatment group 17.7 (9.7), vehicle group 19.3 (11.4)
Interventions	Twelve weeks **Intervention** Benzoyl peroxide 5% and clindamycin 1% gel - QD (27) **Comparator** Placebo (vehicle) - QD (26)
Outcomes	Assessments (5): baseline, week 3, 6, 9 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Percentage change in N of papules and pustules from baseline to end of study✴ 2. Change from baseline in severity of erythema, telangiectasia, flushing, burning or stinging (0 = none, 3 = severe)✴ 3. Overall rosacea severity assessment (0 = clear, 5 = very severe), and physician's (0 = clear, 5 = very severe) and patient's global assessment (1 = much better, 4 = worse)✴ **Secondary outcomes** 1. Adverse events✴

	Leyden 2004 - same study, different outcome measures. Overall global improvement as rated by 3 independent investigators using photographs ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 381): "This study was supported by Dermik Laboratories, a division of Aventis Pharmaceuticals Inc, Berwyn, PA", Dermik Laboratories is the manufacturer of BenzaClin®
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) Some SDs are lacking, and most data are skewed. This also applies to Leyden 2004 See comparison 26 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 382): "Patients were randomly assigned in a 1:1 ratio..... Randomization was performed according to a computer generated random code." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 382): "Treatments were identified by a code number, which was assigned in chronological order at each site." Comment: Form of central allocation, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 382): "BP/C gel and vehicle only gel were supplied in identical jars and were indistinguishable in color, texture, and smell. Both were packaged in identical patient kits with indistinguishable labelling." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias

Incomplete outcome data (attrition bias)	Low risk	17/156 (10.8%); metronidazole group (15), placebo group (2). ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	No information about sponsorship or support was reported. Wash-out period before study unreported, nor if other medications were recorded or allowed that might influence the outcomes Comment: Insufficient information to assess whether important risk of bias exists

Bribeche 2015

Methods	RCT, prospective, placebo-controlled, single-blinded Date of study November 2012 to August 2013 Setting Dermatology Clinic of Zaporozhye, University Hospital, Zaporozhye, Ukraine
Participants	**Randomised:** 65 participants (age 25 to 67 years, 32 male, 33 female) **Inclusion criteria** • Age ≥ 18 years and a diagnosis of mild to moderate rosacea • A score of 2 to 3 on the IGA Scale (0 to 4 scale: 0 = clear, no signs or symptoms present; 1 = minimal, one or two papules; 2 = mild, some (3 to 10) papules and pustules; 3 = moderate, moderate (11 to 19) number of papules and pustules; 4 = severe, numerous (≥ 20) papules, pustules and nodules) • A score of 2 to 3 on the CEA Scale (0 to 4 scale: 0 = none, no redness present; 1 = mild, slight pinkness; 2 = moderate, definite redness; 3 = significant, marked erythema; 4 = severe, fiery redness) **Ocular involvement:** Unclear **Exclusion criteria** • Topical treatment for rosacea < 2 weeks prior to study entry • Systemic treatment < 4 weeks prior to study entry

	• Lactating women • Use of any rosacea treatment (over the counter or prescription) during the course of the study • Use of systemic or topical corticosteroids, 4 weeks prior to study entry and during the study • Use or anticipation of laser or intense pulsed light treatments < 3 months prior to study entry or during the trial • Concomitant administration of cytochrome P450 inducers • Use of tetracycline family antibiotics at any dose • Use of any acne or rosacea treatments, including spironolactone, during the study **Dropouts and withdrawals** • 2/65 (3%); 1 in each group • Erysipleas requiring antibiotics; praziquantel (1) • Appendicitis requiring appendectomy and antibiotics; vehicle (1) **Baseline data (N or mean (range))** IGA score minimal; praziquantel (4), vehicle (1) IGA score mild; praziquantel (11), vehicle (9) IGA score moderate; praziquantel (28), vehicle (12) CEAS score mild; praziquantel (5), vehicle (3) CEAS score moderate; praziquantel (12), vehicle (8) CEAS score significant; praziquantel (26), vehicle (11) DLQI; praziquantel 15.8 (4 to 23), vehicle 14.6 (5 to 21)
Interventions	12 weeks with 4 weeks follow-up **Intervention** Praziquantel 3% ointment - BID (43) **Comparator** Vehicle ointment - BID (22)
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment Scale (IGAS) (0 to 4)✴ 2. Clinical Erythema Assessment Scale (CEAS) (0 to 4)✴ **Secondary outcomes**

	1. The Dermatology Life Quality Index (DLQI)✴ 2. Adverse events✴ 3. Antimicrobial potential potency of praziquantel (MIC) ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1 Epub): "Funding: None"
Declaration of interest	Quote (page 1 Epub): "Conflicts of interest: None"
Notes	Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 43 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2 Epub): "were randomly assigned" and "using a computer-generated randomization schedule" Comment: Probably done
Allocation concealment (selection bias)	High risk	Quote (page 2 Epub): "The assignment was performed in a single-blinded manner (for safety reasons" The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Not sure if allocation concealment and blinding are confused. There was insufficient information to permit a clear judgement After e-mail communication it became clear that two investigators had access to the list Comment: We judged this as at a high risk of bias
Blinding of participants and personnel (performance bias)	High risk	Quote (page 2 Epub): "The assignment was performed in a single-blinded manner (for safety reasons)", in which the subjects were blinded to the treatment affectation" Comment: Investigators not blinded. The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	Quote (page 2 Epub): "The assignment was performed in a single-blinded manner (for safety reasons)," in which the subjects were

		blinded to the treatment affectation" After e-mail-communication: "praziquantel ointment and the placebo had the same colour (white), and ointment were given to participants in identical boxes for both groups" Comment: Outcomes were participant and investigator assessed. As the investigators were not blinded the outcome measurement of IGA and CEA are likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	2/65 (3%), ITT analysis. Reasons for withdrawals reported Comment: We considered this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period prior to study entry adequate, no other treatments allowed, no sponsoring Comment: The study appears to be free of other forms of bias

Buendia-Bordera 2013

Methods	RCT, prospective, placebo-controlled, within-patient comparison Date of study Unreported Setting Instituto de Fotomedicina, Centro Medico Teknon, Barcelona, Spain
Participants	**Randomised:** 31 participants (age and gender unreported) **Inclusion criteria** • Subjects with photo type I to IV presenting a rosacea subtype I condition on both sides **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** Not reported **Baseline data (mean)** Nothing reported

Interventions	One treatment, follow-up 30 days **Intervention** PDL treatment (9 to 12 J/cm^2, 7 mm spot) + post-laser serum **Comparator** PDL treatment (9 to 12 J/cm^2, 7 mm spot) + placebo
Outcomes	Assessments (5): baseline, day 1, 9, 21 and 30 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Immediate soothing effect (thermography imaging) 2. Evaluate skin condition and stratum corneum thickness (IVCM captures and Trans Epidermal Water Loss (TEWL)) 3. Erythema (spectroscopy and photographs)✴ 4. Oedema and dermal density (ultrasound imaging) **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Nothing reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed Abstract, few data presented. Unable to contact principal investigator, no exact data are provided (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 43): "applied on a randomized side of the face" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been

		foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding reported Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding reported Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	No information on dropouts and withdrawals Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Carmichael 1993

Methods	RCT, prospective, placebo-controlled, double-blind, within-patient comparison Date of study Unreported Setting Department of Dermatology, University Wales College of Medicine, Cardiff, UK
Participants	**Randomised:** 33 participants (mean age 56.9 years (range 38 to 70) for 15 males and mean 52.8 years (range 31 to 82) for 18 females) **Inclusion criteria** • Participants with typical rosacea with persistent symmetrical erythema affecting either cheek together with at least 10 inflammatory papules or pustules **Ocular involvement:** Unclear **Exclusion criteria** • If topical medications such as corticosteroids, antibiotics, retinoids or other drugs that could affect the course of the disease had not been stopped 2 weeks prior to study • If systemic medications such as corticosteroids, antibiotics, retinoids or other drugs that could influence

	the disease had not been stopped 4 weeks prior to study **Dropouts and withdrawals:** None **Baseline data mean (SEM)** Number of papules; azelaic acid site 13.0 (1.5), vehicle site 13.3 (1.6) Number of pustules; azelaic acid site 1.2 (0.4), vehicle site 1.6 (0.5)
Interventions	13 weeks **Intervention** Azelaic acid cream 20% - BID **Comparator** Placebo (vehicle) - BID
Outcomes	Assessments (5): baseline, week 3, 6, 9 and 13 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Subjective severity score of changes in rosacea severity (VAS) by physicians✴ 2. Decrease in papule count, pustule count✴ 3. Decrease in erythema, and telangiectasia (VAS 10-point and "electronic meter (Innovaderm, Cardiff) to convert the analogue score to a digital reading")✴ 4. Physician's overall rating of complete remission or marked improvement (poor, moderate, good, excellent)✴ **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared. Two investigators were employed by Schering AG, Berlin, Germany, the manufacturer of azelaic acid cream
Notes	One of our primary outcomes was addressed (adverse events) Subjective severity scale and overall rating by physicians is not consistent and data on inflammatory lesions were skewed See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page S19): "Allocation of the preparations to the facial side was randomized." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Low risk	Quote (page S19): "Comparison between 20% azelaic acid and its identical-appearing vehicle." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	There were no dropouts (page S21). ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out period adequate before start, study duration adequate. No topical or systemic

		medications that could influence outcomes were allowed Comment: The study appears to be free of other forms of bias

Chang 2012

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Two centres, Massachusetts General Hospital, Boston and Stanford Hospital and Clinic, Redwood City, US
Participants	**Randomised:** 83 participants (mean age 52.2 years, 23 male, 57 female and 3 gender unreported) **Inclusion criteria** • ≥ 18 years of age • Papulopustular rosacea with 4 to 50 facial inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • Acne conglobata • Acne fulminans • Secondary acne (chloracne, drug induced acne etc) • Severe acne requiring systemic treatment • History of regional enteritis or inflammatory bowel disease • Use of topical rosacea treatments two weeks prior to study entry • Use of systemic antibiotics four weeks prior to study entry • Use of systemic retinoids three months prior to study entry • Laser or light based therapies two months prior to study entry • Concomitant use of medications that are reported to exacerbate rosacea • Other dermatologic conditions that require use of interfering topical or systemic therapy or that might interfere with study assessments such as, but not limited to, atopic dermatitis, perioral dermatitis or acne vulgaris • Pregnant or planning pregnancy • Use of any investigational drugs within past four weeks

	• Known hypersensitivity or previous allergic reaction to clindamycin or retinoids **Dropouts and withdrawals** • 8/83 (9.6%); clindamycin + tretinoin group (4), placebo group (4), however just 3/83 excluded from analysis • Lost to follow-up; clindamycin + tretinoin group (2), placebo group (3) • Irritant contact dermatitis; clindamycin + tretinoin group (1), placebo group (1) • Worsening rosacea; clindamycin + tretinoin group (1), placebo group (0) **Baseline data mean (SD)** Number of inflammatory lesions; clindamycin + tretinoin group 14.3 (9.5), placebo group 18.7 (14.1)
Interventions	12 weeks **Intervention** Clindamycin phosphate 1.2% + tretinoin 0.025% gel - QD (43) **Comparator** Placebo gel - QD (40)
Outcomes	Assessments (4): baseline, week 2, 6 and 12 **Outcomes of the trial** (as reported) **Primary outcomes:** 1. Absolute change in inflammatory lesion count✶ 2. Percentage decrease in papule and pustule count between the groups✶ **Secondary outcomes:** 1. Improvement in clinical features as flushing, erythema, papules, pustules, telangiectasia, burning, stinging, plaques, dry appearance, oedema, ocular symptoms, peripheral location and phymatous changes (Wilkin 2004)✶ 2. Improvement in Physician's Global Assessment regarding subtype✶ 3. Improvement in subjects' self assessment (RosaQoL, Nicholson 2007)✶ 4. Tolerabity (scaling, dryness and erythema)

	5. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (338): "This study was funded by a grant from Medicis"
Declaration of interest	Quote (338):"The authors have no conflict of interest to disclose"
Notes	Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 28 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 334): "Qualifying subjects were randomized via a computerized random number generator" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 334): "The research staff member who randomized the study population was not involved in any study assessments." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 334): "CT gel and placebo gel were indistinguishable on visual inspection with respect to color, consistency and odor" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator- and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	3/83 were not included in the analyses. Per-protocol analysis Comment: Low number of participants excluded from analysis and although per-protocol analysis judged as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT00823901). In the protocol

		reduction of transient erythema was the single secondary outcome and was specified in Methods section of the report but embedded in improvement of clinical features of rosacea. The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally The study appeared to be free of other forms of bias

Dahl 1998

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre (6 centres) in US We only included second phase (first phase was open and not controlled)
Participants	**Randomised:** 88 participants (range 20 to 74 years of age, mean age 48.6 years in treatment group versus 43.7 years in control group, 32 male, 56 female) **Inclusion criteria** • Participants with moderate to severe rosacea, at least 6 inflammatory lesions, moderate erythema, and telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 33/88 (37.5%); metronidazole group (14) and vehicle group (19) • Relapse; metronidazole group (9) and vehicle group (18) • Lost to follow-up, protocol violation, personal reasons; metronidazole group (5) and vehicle group (1) **Baseline data mean (SD)** Number of inflammatory lesions; metronidazole group 0.9 (2.2) and vehicle group 0.5 (1.0)
Interventions	Six months

	Intervention Metronidazole 0.75% gel - BID (44) **Comparator** Placebo (vehicle) - BID (44)
Outcomes	Assessments (7): baseline, week 4, 8, 12, 16, 20 and 24 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Relapse (appearance of papules and pustules)✴ **Secondary outcomes** 1. Erythema (0 = no redness, 3 = severe erythema)✴ 2. Telangiectasia (0 = absent, 3 = many vessels)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 683): "The study was funded by a grant from Galderma Laboratories Inc, Fort Worth, Tex."
Declaration of interest	Quote (page 683): "Dr Herndon is a paid consultant for Galderma Laboratories Inc. Drs Tuley and Czernielewski and Mr Baker are employees of Galderma laboratories Inc."
Notes	None of our primary outcomes were addressed. We only included the double-blind randomised second phase See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 680): "...were randomized into 2 treatment groups." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation

		sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 680): "...double-blind." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 680): "..double-blind.." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	33/88 (37.5%); metronidazole group (14) and vehicle group (19). 9/44 in metronidazole group relapsed, versus 18/44 in vehicle group. No subjects discontinued because of adverse events Quote (page 680): "An intention-to-treat analysis was conducted for relapse rates, lesion counts and erythema. For subjects who experienced relapse or discontinued for other reasons, lesions counts and erythema were carried forward as data for all subsequent visits to prevent drop-out bias" Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Adequate study duration, sponsorship and declaration of interest stated. No wash-out period (first phase was active treatment), unclear if groups were treated equally aside from intervention Comment: Insufficient information to assess whether an important risk of bias exists

Dahl 2001

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Department of Dermatology, Mayo Medical School, Scottsdale; Department of Dermatology, Baylor College of Medicine, Houston; Department of Dermatology, University of Missouri, Kansas City School of Medicine, US

Participants	**Randomised:** 72 participants (mean age 45 years (range 22 to 78) in 0.75% cream group versus 47 years (range 28 to 75) in metronidazole 1% group, 10 male and 26 female in metronidazole 0.75% group versus 11 male and 25 female in metronidazole 1% group) **Inclusion criteria** • Participants with moderate to severe rosacea. Each subject had 8 to 50 inflammatory lesions (papules, pustules). Erythema was scored on a scale of 0 to 3 at each of the 5 facial regions (forehead, right and left cheeks, chin, and nose). All subjects entered the study with total erythema scores of at least 7.0 from 5 regions or with erythema scores of 2.0 or higher from at least 2 of the 5 regions **Ocular involvement:** Unclear **Exclusion criteria** • < 18 years of age • Underlying conditions or diseases that might interfere with evaluations • If they required systemic or topical treatments • Known not to respond to metronidazole in any dose were also excluded **Dropouts and withdrawals** • 11/72 (15.3%); metronidazole 0.75% group (4), metronidazole 1% group (7) • Lack of efficacy; metronidazole 0.75% group (2), metronidazole 1% group (5) • Adverse events; metronidazole 0.75% group (1), metronidazole 1% group (1) • Subjects request; metronidazole 0.75% group (1), metronidazole 1% group (0) • Protocol violation; metronidazole 0.75% group (0), metronidazole 1% group (1) **Baseline data mean** Number of inflammatory lesions; metronidazole 0.75% group 19, metronidazole 1% group 25
Interventions	12 weeks **Intervention** Metronidazole 0.75% cream - QD (36) **Comparator**

	Metronidazole 1% cream - QD (36)
Outcomes	Assessments (5): baseline, week 3, 6, 9 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Median percentage change inflammatory lesion counts (pustules and papules) from baseline to endpoint✴ 2. Percentage change in total erythema severity score from baseline to endpoint (0 to 3.0 at each of the five facial regions (forehead, right and left cheeks, chin, and nose)✴ 3. Physician's assessment of global severity based on intensity of erythema and the number of facial lesions at endpoint (0 = clear to almost clear, 5 = very severe)✴ **Secondary outcomes** 1. Median percentage change in inflammatory lesion count from baseline to week 3, 6, 9 and 12 visits✴ 2. Percentage of change in total erythema score from baseline to week 3, 6, 9 and 12 visits✴ 3. Physician's evaluation of global severity at week 3, 6, 9 and 12✴ 4. Dryness scores at week 3, 6, 9 and 12 5. Dropout due to treatment failures ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 738): "Supported by Galderma Laboratories, Inc."
Declaration of interest	Quote (page 738): "Dr Tuley and Mr Baker are employees of Galderma Laboratories. Drs Dahl, Jarratt, and Kaplan all received financial compensation from Galderma Laboratories, Inc for performing this study"
Notes	None of our primary outcomes were addressed See comparison 8 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 725): "Patients were randomly assigned to receive 0.75% metronidazole cream or 1.0% metronidazole cream."

		E-mail contact with the investigator confirmed "subjects were randomised to 1 of the 2 treatment groups at a ratio of 1:1. The randomisation process was done in blocks of 4, stratified by investigators. The randomisation was carried out using SAS PROC PLAN." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	High risk	Quote (page 724): "A double-blind format was not used because the study drugs were label-blinded commercial products contained in tubes of different sizes and shapes." Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	Quote (page 724) : "A double-blind format was not used because the study drugs were label-blinded commercial products contained in tubes of different sizes and shapes." Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	11/72 (15.3%); metronidazole 0.75% group (4), metronidazole 1% group (7). ITT analysis, based on LOCF However, "Intention to treat population ranged from 30 to 35 subjects in 0.75% metronidazole group and from 29 to 34 in 1.0% metronidazole group." Page 725 Comment: ITT population did not appear to include all randomised participants. Unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Wash-out period adequate, study duration adequate, groups treated equally. Sponsoring by Galderma Laboratories, Inc. 2 authors are employees of Galderma

		Quote (page 723): "The authors received financial compensation from Galderma Laboratories, Inc for performing this study." Comment: The study was not double-blind combined with the financial support may pose a potential risk of bias

Dayan 2017

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting DeNova Research, Chigago, IL, US
Participants	**Randomised:** 9 participants (aged 26-61 years, gender unreported) **Inclusion criteria** • Participants with erythematotelangiectatic or papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria:** • Pregnancy **Dropouts and withdrawals** • 1/9 (11.1%); incobotulinumtoxinA group (1) and placebo group (0) **Baseline data mean (SD)** Nothing reported
Interventions	Once, follow-up 16 weeks **Intervention** IncobotulinumtoxinA injections across cheeks up to 20 units - once (5) **Comparator** Saline injections - across cheeks up to 20 units - once (4)
Outcomes	Assessments (5): baseline, week 1, 4, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes**

	1. Change in rosacea (live rosacea assessment for each side of the face using the Rosacea Clinical Scorecard for clinical assessment)(0 = absent, 3 = severe)✶ 2. Adverse events✶ **Secondary outcomes** 1. Change in self-esteem (self-esteem change will be determined by patient self-evaluation using the Heatherton & Polivy State Self-Esteem (HPSS) scale)✶ 2. Patient satisfaction (1 = highly satisfied, 4 = unsatisfied)✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 554): "This study was supported by a grant from Merz North America to SHD"
Declaration of interest	Quote (page 554): "The authors have no financial disclosures"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 53 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 550): "Subjects were randomly divided into 2 groups as follows: a randomization schedule linked sequential Treatment Assignment Numbers (TANs) to treatment codes (Group 1 or Group 2). As subjects enrolled in the study, they were assigned the lowest available TAN, which subsequently randomly assigned them to either Group 1 or group 2" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 550: " Both the study investigator and subjects were blind to the initial treatment received" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 549): "..double-blind.." Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Number of drop-out 1/9 (11.1%); incobotulinumtoxinA group (1) and placebo group (0). Per-protocol analysis. Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	High risk	The protocol for the study was available on clinicaltrials.gov (NCT01614743). The investigators did not report on safety ("rate of adverse events" one of the prespecified outcomes), nor provided baseline data for the groups and follow up data for placebo group were lacking at prespecified follow up period during first 16 weeks Comment: We judged this as at a high risk of bias
Other bias	Unclear risk	Study duration adequate, no washout described, unclear whether other treatments were allowed, groups treated equally. However, authors report "there was a large statistically significant difference in scores at baseline in self esteem scores" Comment: We judged this as at an unclear risk of bias

Del Rosso 2007a

Methods	RCT, prospective, placebo-controlled, double-blind Date of study June 2004 to April 2005 Setting Multicentre, 14 sites in US
Participants	**Randomised:** 251 participants (age 46.8 (SD 13.2) in treatment group and 47.6 (SD 11.5) in placebo group, 91% (SD 71.7) female in treatment group, and 95% (SD 76.6) female in placebo group) **Inclusion criteria**

	• Healthy participants of at least 18 years of age with moderate to severe rosacea, which was defined as the presence of 10 to 40 papules and pustules and 2 or fewer nodules. Patients were also required to have telangiectasia and moderate to severe erythema as determined with the use of the Clinician's Erythema Assessment (CEA) scale No ocular involvement **Exclusion criteria** • Initiation or change in hormonal method of contraception within 4 months of baseline or during study • Use of topical acne treatments or topical or systemic antibiotics within 4 weeks of baseline • Use of an investigational drug within 90 days of baseline • Known hypersensitivity to tetracyclines, use of clinically significant concomitant drug therapy • Use of systemic anti-inflammatory drug or corticosteroids in the 4 weeks before baseline or during the study • Use of vasodilators or alpha-adrenergic receptor-blocking agents 6 weeks before baseline or during study • Ocular rosacea and or blepharitis, meibomianitis requiring treatment by an ophthalmologist **Dropouts and withdrawals** • 47/251 (18.7%); doxycycline group (26), placebo group (21) • Adverse events; doxycycline group (10), placebo group (4) • Illness not drug-related; doxycycline group (1), placebo group (1) • Uncooperative; doxycycline group (5), placebo group (4) • Lost to follow-up; doxycycline group (4), placebo group (2) • Protocol violation; doxycycline group (2), placebo group (2) • Treatment failure; doxycycline group (2), placebo group (2) • Other; doxycycline group (2), placebo group (6) **Baseline data mean (SD)**

	Lesion counts (papules, pustules, nodules); doxycycline group 19.5 (8.8), placebo group 20.3 (10.4) Clinical Erythema Assessment (CEA); doxycycline group 9.7 (3.0), placebo group 9.5 (2.7)
Interventions	16 weeks **Intervention** Doxycycline 40 mg capsule - QD (127) **Comparator** Placebo capsule - QD (124)
Outcomes	Assessments (5): baseline, week 3, 6, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean change from baseline in total inflammatory lesion count (papules, pustules, nodules) at week 16✶ **Secondary outcomes** 1. Mean change from baseline in CEA scale (0 = no redness present, 4 = severe redness. Total CEA scores are derived by summing scores over five facial areas and ranged from 0 to 20)✶ 2. Mean change in Investigator's Global Assessment scale (IGA) (0 = no signs or symptoms present, 4 = 20 or more papules, pustules, nodules (severe). In addition, static dichotomised IGA score (yes or no) defined as participants who achieved a score of 0 (clear) or 1 (near clear))✶ 3. Safety was evaluated by recoding adverse events, concomitant medication use, and vital signs and routine laboratory tests✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 791): "Supported by CollaGenex Pharmaceuticals, Inc."
Declaration of interest	All authors have received grants from Collagenex or worked as consultants for Collagenex (page 791)
Notes	One of our primary outcomes was addressed (adverse events) Some SD were missing and these were calculated by the review authors See comparison 57 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 794): "For each study site, a master randomisation list in blocks of 4 was prepared by the sponsor for all study sites. With the use of a computer-generated randomisation scheme, patients were assigned in equal proportions (1:1) to receive drug or placebo." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 794): "Master randomisation list in blocks of 4 was prepared by the sponsor for all study sites." Comment: A form of central randomisation was used. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 794): "Investigators, study site personnel, and patients were blinded with respect to the identity of the study medication being taken. All the employees of the sponsor and its affiliates who were involved in data monitoring, data entry, or data analysis were blinded as well." "Study drug and placebo capsules were identical in size, shape, and colour." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 794): "Investigators, study site personnel, and patients were blinded with respect to the identity of the study medication being taken. All the employees of the sponsor and its affiliates who were involved in data monitoring, data entry, or data analysis were blinded as well." "Study drug and placebo capsules were identical in size, shape, and colour." Blinding of the outcomes assessors, key personnel, was ensured, and it was unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Incomplete outcome data were adequately addressed, reasons for withdrawal reported, no differences between the 2 groups. ITT analysis Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported

		Comment: We judged this as at a low risk of bias
Other bias	Low risk	Adequate wash-out period before the study, adequate study duration, clinically significant concomitant drug therapy was forbidden Study supported by Collagenex Pharmaceuticals. All authors have received grants from Collagenex or worked as consultants for Collagenex Comment: As the study appeared to be triple-blinded and there was no selective reporting we do not consider that the sponsorship and support represented any additional bias

Del Rosso 2007b

Methods	RCT, prospective, placebo-controlled, double-blind Date of study June 2004 to April 2005 Setting Multicentre, 14 sites in US
Participants	**Randomised:** 286 participants (age 46.3 (SD 12.7) in treatment group and 47.6 in placebo group, 94% (SD 66.2) female in treatment group, and 95% (SD 66.0) female in placebo group) **Inclusion criteria** • Healthy participants of at least 18 years of age with moderate to severe rosacea, which was defined as the presence of 10 to 40 papules and pustules and 2 or fewer nodules. Patients were also required to have telangiectasia and moderate to severe erythema as determined with the use of the Clinician's Erythema Assessment (CEA) scale No ocular involvement **Exclusion criteria** • Initiation or change in hormonal method of contraception within 4 months of baseline or during study • Use of topical acne treatments or topical or systemic antibiotics within 4 weeks of baseline • Use of an investigational drug within 90 days of baseline • Known hypersensitivity to tetracyclines, use of clinically significant concomitant drug therapy • Use of systemic anti-inflammatory drug or corticosteroids in the 4 weeks before baseline or during the study

	• Use of vasodilators or alpha-adrenergic receptor-blocking agents 6 weeks before baseline or during study • Ocular rosacea and or blepharitis, meibomianitis requiring treatment by an ophthalmologist **Dropouts and withdrawals** • 53/286 (18.5%); doxycycline group (27), placebo group (26) • Adverse event-related; doxycycline group (9), placebo group (7) • Illness not drug-related; doxycycline group (1), placebo group (0) • Uncooperative; doxycycline group (2), placebo group (1) • Lost to follow-up; doxycycline group (5), placebo group (5) • Protocol violation; doxycycline group (4), placebo group (5) • Treatment failure; doxycycline group (1), placebo group (4) • Other; doxycycline group (5), placebo group (4) **Baseline data mean (SD)** Lesion count; doxycycline group 20.5 (11.7), placebo group 21.23 (12.5) Clinical Erythema Assessment; doxycycline group 9.5 (2.9), placebo group 9.1 (2.5)
Interventions	16 weeks **Intervention** Doxycycline 40 mg capsule - QD (142) **Comparator** Placebo capsule - QD (144)
Outcomes	Assessments (5): baseline, week 3, 6, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean change from baseline in total inflammatory lesion count (papules, pustules, nodules) at week 16✴ **Secondary outcomes**

	1. Mean change from baseline in Clinician's Erythema Assessment (CEA) scale (0 = no redness present, 4 = severe redness. Total CEA scores are derived by summing scores over 5 facial areas and ranged from 0 to 20)✴ 2. Mean change in Investigator's Global Assessment scale (IGA) (0 = no signs or symptoms present, 4 = 20 or more papules, pustules, nodules (severe). In addition static dichotomised IGA score (yes or no) defined as: participants who achieved a score of 0 (clear) or 1 (near clear)✴ 3. Safety was evaluated by recording adverse events, concomitant medication use, and vital signs and routine laboratory tests✴ 4. Four week post-treatment evaluation: mean change from baseline in total inflammatory lesion count, mean change in CEA and IGA scores from week 16 to 20✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 791): "Supported by CollaGenex Pharmaceuticals, Inc."
Declaration of interest	All authors have received grants from Collagenex or worked as consultants for Collagenex (page 791)
Notes	One of our primary outcomes was addressed (adverse events) Some SD were missing and these were calculated by the review authors See comparison 57 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 794): "For each study site, a master randomisation list in blocks of 4 was prepared by the sponsor for all study sites. With the use of a computer-generated randomisation scheme, patients were assigned in equal proportions (1:1) to receive drug or placebo." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 794): "Master randomisation list in blocks of 4 was prepared by the sponsor for all study site." Comment: A form of central randomisation was used. Probably done

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 794): "Investigators, study site personnel, and patients were blinded with respect to identity of the study medication being taken. All the employees of the sponsor and its affiliates who were involved in data monitoring, data entry, or data analysis were blinded as well." "Study drug and placebo capsules were identical in size, shape, and colour." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 794): "Investigators, study site personnel, and patients were blinded with respect to identity of the study medication being taken. All the employees of the sponsor and its affiliates who were involved in data monitoring, data entry, or data analysis were blinded as well." "Study drug and placebo capsules were identical in size, shape, and colour." Blinding of the outcomes assessors, key personnel, was ensured, and it was unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Incomplete outcome data were adequately addressed, reasons for withdrawal reported, no differences between the 2 groups. ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Adequate wash-out period before the study, adequate study duration, clinically significant concomitant drug therapy was forbidden Study supported by Collagenex Pharmaceuticals. All authors have received grants from Collagenex or worked as consultants for Collagenex Comment: As the study appeared to be triple-blinded and there was no selective reporting we do not consider that the sponsorship and support represented any additional bias

Del Rosso 2008

Methods	RCT, prospective, active-controlled, double-blind

	Date of study Unreported Setting Department of Dermatology, Valley Hospital Medical Center, Las Vegas; Department of Dermatology, Advanced Skin Research Center, Omaha, University of Washington, Washington, US
Participants	**Randomised:** 91 participants (age 44.3 years in 40 mg group and 45.2 in 100 mg group, 29 females and 15 males in 40 mg group and 35 females and 12 males in 100 mg group) **Inclusion criteria** • Healthy participants of at least 18 years of age with moderate to severe rosacea, which was defined as the presence of 10 to 40 papules and pustules and two or fewer nodules, a score of 2 to 5 on the Investigator's Global Assessment (IGA) scale, a total erythema score of 5 to 20, with at least one of the facial areas having a specific score of ≥ 2 on the Clinician's Erythema Assessment (CEA) scale, and presence of telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Changes in hormonal contraception within 4 months of baseline • Use of rosacea treatments within 2 weeks of baseline • Hypersensitivity to treatment drugs • Clinically significant concomitant drugs **Dropouts and withdrawals** • 24/91 (26.3%); 40 mg doxycycline group (14) and 100 mg doxycycline group (10) • Adverse events; 40 mg doxycycline group (5) and 100 mg doxycycline group (4) • Protocol violation; 40 mg doxycycline group (3) and 100 mg doxycycline group (1) • Lost to follow-up; 40 mg doxycycline group (4) and 100 mg doxycycline group (0) • Patient withdrew consent; 40 mg doxycycline group (2) and 100 mg doxycycline group (1) **Baseline data mean (SD)** Nothing reported
Interventions	16 weeks **Intervention**

	Doxycycline 40 mg QD + metronidazole gel 1% - QD (44) **Comparator** Doxycycline 100 mg QD + metronidazole gel 1% - QD (47)
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean change from baseline in total inflammatory lesion count (papules, pustules, nodules) at week 16✴ **Secondary outcomes** 1. Change in Investigator's Global Assessment scale (IGA), (0 = skin completely clear of inflammatory lesions, 5 ≥ 25 papules and pustules, nodules must be present (severe))✴ 2. Change in Clinician's Erythema Assessment (CEA) from baseline (0 = no redness present, 4 = severe redness)✴ 3. Change in total lesion counts at each time point✴ 4. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 576): "The study was supported through educational grants from Collagenex Corporation"
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (adverse events) All SD are missing and these were calculated by the review authors See comparison 65 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 574): "Subjects were randomized to receive daily administration of drugs." Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 574): "Both the doxycycline 100 mg capsules and the 40 mg capsules were over encapsulated to ensure the capsules were indistinguishable during administration and to maintain a double-blind study." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 574): "Both the doxycycline 100 mg capsules and the 40 mg capsules were over encapsulated to ensure the capsules were indistinguishable during administration and to maintain a double-blind study." Blinding of the outcomes assessors, key personnel, and participants was ensured, and it was unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	Incomplete outcome data were adequately addressed, reasons for withdrawal reported, no differences between the 2 groups. ITT analysis Comment: High but balanced dropout rate and although combined with ITT analysis (LOCF) judged as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Adequate wash-out period before study started, adequate study duration, clinically significant concomitant drug therapy was not permitted Comment: The study appears to be free of other forms of bias

Del Rosso 2010

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study February to July 2009 Setting Multicentre, US
Participants	**Randomised:** 207 participants (mean age 49 years, 71 male, 136 female) **Inclusion criteria** • Mild to moderate papulopustular rosacea with 10 to 50 inflammatory lesions, persistent erythema with or without telangiectasia and with Physician's Global Assessment score ≥ 4 • ≥ 18 years of age • Wash-out period before start of study • Pre-menopausal women should be on reliable contraception No ocular involvement **Exclusion criteria** • Involvement in another clinical trial less than four weeks prior to study entry • Pregnant and lactating women • Known non-responders to azelaic acid or metronidazole • Participants with subtype I, III or IV rosacea • Corticosteroid induced rosacea • Dermatoses that interfered with rosacea diagnosis or evaluation • Concurrent use of systemic or topical steroids, systemic or topical retinoids, topical imidazole antimycotics, chronic NSAIDs, or drugs causing acneiform eruptions • Oral isotretinoin less than 6 months prior to study entry • Topical retinoids less than 2 weeks prior to study entry • Topical antibiotics, imidazole antimycotics, azelaic acid formulations, corticosteroids in the face less than 2 weeks prior to study entry • Systemic corticosteroids less than 4 weeks prior to study entry • Hypersensitivity to any component of the trial drugs **Dropouts and withdrawals** • 13/207 (6.3%); azelaic acid group (6), metronidazole group (7)

	• Adverse events; azelaic acid group (1), metronidazole group (1) • Remaining causes for discontinuations not reported **Baseline data (mean)** Number of inflammatory lesions; azelaic acid group 20.6, metronidazole group 21.9
Interventions	12 weeks **Intervention** Azelaic acid gel 15% - BID and doxycycline 40 mg - QD (106) **Comparator** Metronidazole 1% gel - QD and doxycycline 40 mg - QD (101) Patients were instructed how to clean their face and what to use to clean their face and what moisturizer to use. No other soaps, cleansers and moisturizers were allowed
Outcomes	Assessments (6): baseline, week 2, 4, 6, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in inflammatory lesion count from baseline✴ **Secondary outcomes** 1. Investigator's Global Assessment (IGA) for rosacea status (papules, pustules, erythema and telangiectasia from 0 = clear to 6 = severe)✴ 2. Therapeutic success (IGA score of 0 or 1)✴ 3. Patient response rate (IGA score of 0, 1 or 2)✴ 4. Investigator's overall rating of improvement (1 = excellent improvement, 5 = deterioration)✴ 5. Participant's rating of improvement (1 = excellent, 5 = worse)✴ 6. Adverse events✴ 7. Participant's assessment of tolerability and cosmetic acceptability (1 = very good, 4 = poor, 5 = no opinion) ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 612): "This study was supported by Intendis"
Declaration of interest	Quote (page 612): "Dr Del Rosso is a consultant to and serves as a speaker for ...Galderma...Intendis...Dr Bruce has served as an investigator (grants) for Actavis.....Dr Jaratt has

	served as consultant for Stiefel...He has received honoraria from ...Galderma, ...He has been principal investigator for...Galderma..Intendis...Dr Menter is a consultant, speaker, and is on the advisory board for Abbott....He is a consultant and speaker for Eli Lilly and Stiefel. He is an investigator for .....He has received grants and honoraria from ....etc "He received honoraria from Galderma...."
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 66 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 608-9): "were randomized at a ratio of 1:1.." and "randomly assigned" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "Randomization was done centrally by the generation of a randomization list using the randomization program RANCODE (version 3.6). Randomization used blocks." Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: "..each newly enrolled patient was allocated to study medication with the lowest randomization number available in that particular site at the subjects baseline visit." Comment: Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 608): "investigator-blinded" Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "Six drug tubes (tubes with a blinded label to cover the trademarks) and 3 bottles were packaged by a CMO in individual numbered kit boxes. ...The patient was advised

		not to discuss the treatment schedule with the investigator." Comment: Blinding of investigators effective, however participants were not blinded but unlikely to represent a threat to performance bias
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 608): "investigator-blinded". Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: Blinding of investigators effective, but in view of the different treatment regime once versus twice daily, blinding of participants was not ensured and therefore we judged this as at unclear risk of bias
Incomplete outcome data (attrition bias)	Low risk	13/207 (6.3%); azelaic acid group (6), metronidazole group (7), reasons in part reported. Per-protocol analysis Comment: Low number of dropouts and although per-protocol analysis judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov NCT00855595, and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, clinically significant concomitant drug therapy was not permitted, groups treated equally Comment: The study appears to be free of other forms of bias

Di Nardo 2016

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, US
Participants	**Randomised:** 170 participants (mean age 50 years, 49 male, 121 female) **Inclusion criteria** • Adults 18-70 years

	• Papulopustular rosacea with 5 to 50 inflammatory lesions **Ocular involvement**: Unclear **Exclusion criteria** • Concomitant medications that might interfere with clinical assessments **Dropouts and withdrawals:** Not reported **Baseline data median** Inflammatory lesion count: doxycycline group 9, placebo group 11
Interventions	12 weeks **Intervention** Doxycycline 40 mg (modified release) - QD (84) **Comparator** Placebo capsules - QD (86)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change from baseline in inflammatory lesion counts✴ **Secondary outcomes** 1. Change from baseline in biochemical markers of rosacea from tape stripping and/or skin biopsy 2. Investigator's Global Assessment (IGA) scores ((0 = clear, 1 = near clear, 2 = mild, 3 = moderate, and 4 = severe)✴ 3. Change from baseline in Clinician's Erythema Assessment (CEA) scores ((0 = none, 1 = mild, 2 = moderate, 3 = significant and 4 = severe)✴ 4. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1086): "Funding for clinical research study provided by Galderma Laboratories LP."
Declaration of interest	Quote (page 1086): "Dr Holmes, Preston, and Winkelman were employees of Galderma Laboratories LP when this work was conducted. Drs Di Nardo, Huang, and Gallo, and Ms Muto have no conflicts of interest to declare"

Notes	One of our primary outcomes was addressed (adverse events) See comparison 57 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1087): "Patients were randomly assigned" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1086): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 1086): "..double-blind.." Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No drop-out reported which is quite unlikely after 12 weeks. However, on website clinical trials.gov it is reported that 10/170 dropped out (5.9%); doxycycline group 7, placebo group 3. ITT analysis Comment: Low number of dropouts, judged as at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available on clinicaltrials.gov (NCT01308619), however, clinicians erythema assessment was no longer mentioned as outcome in the paper, but results were posted at clinicaltrials.gov

		Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study not reported (however, was reported and adequate in protocol), clinically significant concomitant drug therapy was not permitted, groups treated equally Comment: We judged this at a low risk of bias

Draelos 2005b

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Department of Dermatology, Wake Forest University School of Medicine, Winston-Salem, North Carolina, US
Participants	**Randomised:** 30 participants (ages between 20 and 65, gender unreported, both sexes) **Inclusion criteria** • Participants with mild to moderate facial rosacea, defined as perceivable redness and less than 15 inflammatory papules. Fitzpatrick skin type I to III. Minimal ordinal entry score of 5 and maximal score of 14. Ordinal scale from 0 to 4 rated by dermatologist for erythema, desquamation, uneven skin tone, dermatitis, and overall severity of disease **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 2/30 (6.7%), 1 in each group (personal reasons) **Baseline data mean (SD)** Nothing reported
Interventions	Four weeks **Intervention** Lotion vehicle + 1% 4-ethoxybenzaldehyde - BID (20) **Comparator** Lotion vehicle - BID (10)

Outcomes	Assessments (2): baseline and week 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Ordinal assessment erythema, desquamation, dermatitis, uneven skin tone, overall disease severity (0 to 4 for each item)✴ 2. Subjects were asked to assess their facial condition in terms of stinging, burning, itching, redness, peeling, roughness and overall impression **Secondary outcomes** 1. Facial photography 2. Product tolerability 3. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 881): "This study was funded by an educational grant from Cutanix Corporation"
Declaration of interest	Quote (page 881): "Zoe Draelos, MD, has indicated no significant interest with commercial supporters, Bryan Fuller, PhD, is the inventor of the active, which was licensed through the Oklahoma Health Sciences Center to Cutanix"
Notes	One of our primary outcomes was addressed (adverse events) SDs are missing from the report See comparison 41 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 882): "The 30 subjects were randomized at a 2:1 ratio." Comment: Unclear E-mail contact with the investigator confirmed a random number generator was used Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear

		assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 882): "All products were dispensed in identical bottles with identical labelling. Neither the dermatologist investigator nor the subjects knew the contents of the bottle." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 882): "All products were dispensed in identical bottles with identical labelling. Neither the dermatologist investigator nor the subjects knew the contents of the bottle." Blinding of the outcomes assessors, key personnel, and participants was ensured, and it was unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Reasons for the 2 withdrawals were reported, but unclear in which group. After clarification with the author this was confirmed as 1 in each group. Per-protocol analysis Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	High risk	Percentage improvement in dermatitis was not addressed, no exact data were reported for the self-assessments carried out by the participants Comment: We judged this as at a high risk of bias
Other bias	Unclear risk	One of the investigators is the inventor of the formula, which may represent a potential conflict of interests. No baseline balance descriptives. Treatment duration adequate, no wash-out prior to study described Comment: We judged this as at unclear risk of bias

Draelos 2006

Methods	RCT, prospective, "placebo"-controlled, investigator-blinded Date of study Unreported Setting

	Department of Dermatology; Wake Forest University School of Medicine, Winston-Salem, North Carolina, US
Participants	**Randomised:** 67 participants (age between 19 to 66, gender unreported) **Inclusion criteria** • Participants with a prior history of regular use of skin care products including cleansers and moisturizers and with moderate rosacea, defined as the presence of a minimum of 5 but not more than 50 inflammatory papules and pustules, accompanied by persistent erythema and telangiectasia. An overall score greater than 2 on the rosacea investigator's global severity rating scale was required to qualify for study entry **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • Five participants were lost to follow-up, unclear how many participants from which group. This remains unclear after e-mail contact with the author: "the dropouts were for personal reasons, not related to product. They were random between the groups" **Baseline data mean (SD)** Lesion counts; group non-standardised care 10, group PHA skin care 7 (estimated from a graph)
Interventions	12 weeks **Intervention** Azelaic acid 15% gel + habitual self-selected skin cleanser and moisturizer - BID (33) **Comparator** Azelaic acid 15% gel BID + standardised PHA (polyhydroxy acid) containing cleanser, and anti-aging moisturizer (29) Unclear to which groups the other five participants were allocated
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes**

	1. N of inflammatory papules and pustules✶ 2. Global assessment of rosacea and erythema, dryness and telangiectasia by investigator. Severity of erythema, dryness and telangiectasia rated 7-point ordinal scale from 0 to 3 (0 = none, 0.5 = minimal, 1 = mild, 1.5 = mildly moderate, 2 = moderate, 2.5 = moderately severe, 3 = severe)✶ 3. Participants were asked to assess severity of subjective untoward symptoms such as stinging, burning, itching, tightness and tingling on a 5-point ordinal scale (0 = none, 1 = minimal, 2 = mild, 3 = moderate, 4 = severe)✶ 4. Constant lighting was used for all assessments and 3-point digital colour photography was used to capture rosacea improvement **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Two investigators were employed by NeoStrata Company, Inc., Princeton, NJ, however, no conflict of interest declared
Notes	None of our primary outcomes were addressed The combination of incomplete and selective reporting of outcome data did not permit entry of any data into a meta-analysis. It was unclear how many participants were randomised to each intervention and because very limited outcomes data were reported no reliable conclusions could be drawn (Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 23): "The investigation was designed as a 12-week investigator blinded, randomized study of parallel groups." Comment: Unclear E-mail contact with the investigator confirmed "a randomisation schedule with a random number generator was developed" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen

		in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 23): "...investigator-blinded." Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 23): "...investigator-blinded." Comment: Both the participant and the investigator were outcomes assessors and the report was unclear what measures were used, if any, to blind study personnel from knowledge of which intervention a participant received Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	High risk	Five participants were lost to follow-up for "personal reasons", and it was unclear how many occurred in each group, at which stage of the study, and whether data were available for any of the other assessment time points. Per-protocol analysis. After e-mail contact with the author: "the dropouts were for personal reasons, not related to product. They were random between the groups" Comment: We judged this as at a high risk of bias
Selective reporting (reporting bias)	High risk	Not all predefined outcomes were addressed or reported clearly, i.e. Investigator's Global Assessment of rosacea, observations of tingling and tightness by participants. No precise data were reported, data had to be estimated from figures Comment: We judged this as at a high risk of bias
Other bias	High risk	Wash-out period adequate, study duration adequate. No baseline descriptives Study sponsorship was not reported, but 2 authors were from Neostrata Company the manufacturer of the PHA cleanser and moisturizer. Unclear how many participants started in each group. Possible imbalance in the baseline scores of lesion count in the 2 groups.

		The actual comparison was non-standardised skin care versus PHA moisturizer Comment: We judged this as at a high risk of bias

Draelos 2009

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Unspecified, US
Participants	**Randomised:** 146 women, age not reported **Inclusion criteria** • Adult women with rosacea or ethnic sensitive skin (90/56) **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • Not reported **Baseline data mean** Nothing reported
Interventions	Six weeks (first 2 weeks wash-out period) **Intervention** Facial foundation with niacinamide and N-acetylglucosamine, cleanser and moisturizer **Comparator** Marketed foundation with cleanser and moisturizer Unclear how many were randomised to each group
Outcomes	Assessments (2): baseline, week 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Evaluation by Investigator (facial photography)✴ 2. Self-evaluation questionnaire **Secondary outcomes**

	1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared but four investigators are employed by The Proctor and Gamble Company, Cincinnati, OH, US
Notes	Poster abstract, limited data None of our primary outcomes was addressed, no response from PI to fill in gaps (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page AB82): "subjects were randomized to" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page AB82): "double-blind" Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page AB82): "double-blind". Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	No information on drop-outs and withdrawals Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided

		Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Draelos 2013a

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre (20) in US
Participants	**Randomised:** 401 participants (mean age 48.5 years (range 19 to 83 years), 103 male, 298 female) **Inclusion criteria** • ≥ 19 years with papulopustular rosacea with Investigator's Global Assessment score of moderate to severe, 12 to 50 inflammatory lesions as well as persistent erythema with or without telangiectasia No ocular involvement **Exclusion criteria** • Unresponsiveness to azelaic acid • Presence of dermatoses that might interfere with rosacea diagnosis or evaluation, or both • Presence of ocular or phymatous rosacea • Laser surgery on the face for treatment of telangiectasia or other conditions < 6 weeks prior to study entry • Use of any topical prescription or non-prescription medications to treat rosacea within 6 weeks of or during the study • Systemic use of any prescription or non-prescription medications to treat rosacea (i.e. retinoids within 6 months of or during the study; tetracycline (e.g. doxycycline, minocycline) within 2 months of or during the study; corticosteroids, erythromycin or azithromycin within 4 weeks of or during the study) • Expected initiation or change in dose in the last 90 days of treatment with beta-blockers, vasodilators, vasoconstrictors, nonsteroidal anti-inflammatory drugs, hormone therapy, or other drugs known to cause acneiform eruptions **Dropouts and withdrawals**

	• 41/401 (10.2%); azelaic acid group (21), vehicle group (20) • Withdrawal of consent; azelaic acid group (5), vehicle group (6) • Protocol deviation; azelaic acid group (2), vehicle group (2) • Adverse event; azelaic acid group (4), vehicle group (1) • Lost to follow-up; azelaic acid group (5), vehicle group (7) • Lack of efficacy; azelaic acid group (0), vehicle group (0) • Other; azelaic acid group (1), vehicle group (1) • Unknown or missing; azelaic acid group (4), vehicle group (3) **Baseline data N (%)** Moderate rosacea; azelaic acid group 172 (86.9), vehicle group 189 (93.1) Severe rosacea; azelaic acid group 26 (13.1), vehicle group 14 (6.9)
Interventions	12 weeks **Intervention** Azelaic acid foam 15% - BID (198) **Comparator** Vehicle foam - BID (203)
Outcomes	Assessments (5); baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Therapeutic success rate (success defined as at least a 2-point improvement from baseline, with resulting IGA scores of clear or minimal) or failure (defined as IGA scores of mild, moderate, or severe)✴ 2. Nominal change in inflammatory lesion count from baseline to end-of-treatment✴ **Secondary outcomes** 1. Per cent change in inflammatory lesion count✴ 2. Treatment response rate (dichotomizing the IGA as responders (clear, minimal, or mild IGA) and non-responders (moderate or severe IGA)✴

	3. Subjective reports on QOL (RosaQoL, Nicholson 2007)✴ 4. Subjective reports on treatment response (excellent, good, fair, no improvement, or worse)✴ 5. Cosmetic acceptability (very good, good, satisfactory, poor, or no opinion) 6. Tolerability (excellent, good, acceptable despite minor irritation, less acceptable due to continuous irritation, not acceptable, or no opinion) 7. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	None declared. Quote (page 315): "Editorial support through inVentiv Medical Communications, New York, New York, was provided by Bayer HealthCare Pharmaceuticals"
Declaration of interest	Quote (page 306): "Dr. Draelos is a researcher for Bayer HealthCare Pharmaceuticals. Dr. Elewski has conducted clinical research for Bayer HealthCare Pharmaceuticals and Galderma Laboratories, LP. Mr. Staedtler and Dr. Havlickova are employees of Bayer HealthCare Pharmaceuticals"
Notes	All our primary outcomes are addressed See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 308): "The computer-generated randomization procedure used blocks. Whole randomization blocks were allocated to the study centers, ensuring that the comparison groups maintained the planned allocation ratio for the treatment groups overall and within each center" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Form of central allocation Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 307): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "The blind was maintained by dispensing the vehicle and the vehicle plus the active in identical containers"

		Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 307): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: "The blind was maintained by dispensing the vehicle and the vehicle plus the active in identical containers" Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	41/401 (10.2%); azelaic acid group (21), vehicle group (20), reasons reported. ITT analysis (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available on clinicaltrials.gov (NCT01025635). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported. However, exact data on QoL scores were missing which is a primary outcome in our review Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally The study appeared to be free of other forms of bias

Draelos 2013b

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Dermatology clinic and the routine setting of a woman's home, US
Participants	**Randomised:** 40 women (age unreported) **Inclusion criteria** • Mild to moderate atopic dermatitis, eczema, acne or rosacea

	• Women between 18 and 65 years **Ocular involvement:** Unclear **Exclusion criteria** • Occurrence of skin disease other than AD, eczema, rosacea or acne • Other medical conditions that might interfere with skin evaluations • Occurrence of a disease that might pose a risk to participating panellists • Occurrence of clinically significant unstable medical disorder • Use of topical therapy or medication other than hydrocortisone 1% cream or triamcinolone cream 0.1% < 96 hours before study entry • Pregnancy or intention to become pregnant, active lactation • Participation in other clinical trial < 4 weeks prior to study entry • Use of indoor tanning booth • Unwilling or unable to comply with study protocol **Dropouts and withdrawals:** None **Baseline data mean** Nothing reported
Interventions	Three weeks **Intervention** Gentle foaming cleanser containing hydrophobically modified polymers - QD (20) **Comparator** Commercial gentle liquid non-foaming facial cleanser - QD (20)
Outcomes	Assessments (3); baseline, week 1 and 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator assessed presence or absence of facial irritation (stinging, erythema, burning, worsening of eczema, atopic dermatitis, acne or rosacea on a 5-point Likert scale) **Secondary outcomes**

	1. Investigator-led assessment of dirt removal and removal of cosmetics and sebum 2. Facial skin softness, smoothness, irritation, erythema, and desquamation✴ 3. Presence of comedones 4. Global disease severity✴ 5. Participant's assessment of skin and performance of cleanser (5-point Likert scale) 6. Tolerability ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared. Three investigators are employed by Johnson & Johnson Consumer Companies, Inc, Skillman, NU, US
Notes	None of our primary outcomes were addressed There are no separate data on women with rosacea (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 314-6): "randomized".."were divided equally into two groups" and "Study participants were stratified and balanced for demographics and presence and severity of acne, eczema, rosacea and atopic dermatitis" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "Subjects were randomized in two balanced populations based on a computer generated randomization sequence" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: No further additional information to change our judgement
Blinding of participants and	Low risk	Quote (page 314-5): "double-blind"

personnel (performance bias)		Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "..identically appearing products packaged identically" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 314-5): "double-blind". Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: "..identically appearing products packaged identically" Comment: Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	There were no losses to follow up Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, clinically significant concomitant drug therapy was not permitted, groups treated equally Comment: The study appears to be free of other forms of bias

Draelos 2015

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study Unreported Setting Multicentre (48), US
Participants	**Randomised**: 961 participants (mean age 51.5 years, 259 male, 702 female)

	Inclusion criteria • ≥ 18 years with moderate to severe papulopustular rosacea as by Investigator's Global Assessment presenting with 12-50 inflammatory lesions and persistent erythema with or without telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Presence of dermatoses that could interfere with rosacea diagnosis or evaluation • Facial laser surgery • Topical use of any medication to treat rosacea within 6 weeks before randomisation • Systemic use of any medications to treat rosacea • Known unresponsiveness to AzA treatment • Alcohol or drug use • Parallel participation in other clinical studies **Dropouts and withdrawals** • 143/961 (14.9%); azelaic acid group (64), vehicle group (79) • Adverse events; azelaic acid group (6), vehicle group (12) • Participant withdrawal; azelaic acid group (24), vehicle group (36) • Lost to follow-up; azelaic acid group (28), vehicle group (23) • Protocol deviation; azelaic acid group (4), vehicle group (5) • Other reason; azelaic acid group (2), vehicle group (3) **Baseline data mean (SD)** Investigator's Global Assessment score (IGA) moderate (n); azelaic acid group 419, vehicle group 415 IGA severe (n); azelaic acid group 65, vehicle group 62 Inflammatory lesions (n); azelaic acid group 21.7 (9.1), vehicle group 21.2 (8.7) Erythema rating mild (n); azelaic acid group 43, vehicle group 39 Erythema rating moderate (n); azelaic acid group 365, vehicle group 369 Erythema rating severe (n); azelaic acid group 76, vehicle group 69 Dermatology Quality of Life Index (DLQI); azelaic acid group 5.4 (4.8), vehicle group 5.4 (4.9)

Interventions	12 weeks **Intervention** Azelaic acid 15% foam - BID (484) **Comparator** Vehicle foam - BID (477)
Outcomes	Assessments (5); baseline, week 4, 8, 12 and after 4 week follow-up **Outcomes of the trial** (as reported) **Primary outcomes** 1. Efficacy of azelaic acid foam 15% (evaluation by therapeutic success rate according to Investigator's Global Assessment)(clear, minimal, mild, moderate, severe)✶ 2. Efficacy of azelaic acid foam 15% (evaluation by change in inflammatory lesion count)✶ **Secondary outcomes** 1. Evaluation of all adverse events✶ 2. Collection of subject's global assessments on treatment response and tolerability as well as subject's opinion on cosmetic parameters (5 point Likert scale from excellent to worse)✶ 3. Evaluation by using different Quality of Life questionnaires (DLQI, RosaQoL, EQ-5D-5L)✶ 4. Change from baseline in erythema intensity score (clear, almost clear, mild, moderate, severe)✶ 5. Change from baseline in telangiectasia rating (none, mild, moderate, severe)✶ ✶Denotes outcomes pre-specified for this review
Funding source	Not reported but it states Bayer on clinicaltrials.gov
Declaration of interest	Quote (page 54): "Dr. Draelos received a research grant from Bayer HealthCare Pharmaceuticals Inc. Dr. Elewski is an advisory board member, consultant, and investigator for Bayer HealthCare Pharmaceuticals Inc, and she is an investigator for Galderma Laboratories, LP. Dr. Harper is a consultant, researcher, and speaker for Bayer HealthCare Pharmaceuticals Inc. Mr. Sand, Mr. Staedtler, and Drs. Nkulikiyinka and Shakery are employees of Bayer Pharma AG. Mr. Staedtler also holds a patent for the vehicle formulation."

Notes	All our primary outcomes were addressed Some of the outcomes are addressed in the copublications under Draelos 2015 See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 56 and appendix): "961 were randomized to treatment" and "the randomization list generated by a computer program using blocks. Complete blocks of study medication were distributed to the centers" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (Appendix): "Complete blocks of study medication were distributed to the centers" Comment: A form of central randomisation was used. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 55 and Appendix): "double-blind" and "The investigational product was filled in identical containers" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 55 and appendix): "double-blind" and "The investigational product was filled in identical containers". Outcomes were investigator as well participant-assessed Comment: Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	143/961 (14.9%); azelaic acid group (64), vehicle group (79). Per-protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01555463). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias

Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Study supported by Bayer. All authors have received grants from Bayer or worked as consultants, investigators or speakers for Bayer of were employees Comment: As the study appeared to be triple-blinded and there was no selective reporting we do not consider that the sponsorship and support represented any additional bias Comment: The study appeared to be free of other forms of bias

Dreno 1998

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unspecified Setting Multicentre, several centres in France
Participants	**Randomised:** 100 participants (age and gender unreported) **Inclusion criteria** • Participants with moderate to severe rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 21/100 (21%), cream group (6) and gel group (15), reasons unreported, an additional 12 were not included in the efficacy analysis: cream group (6), gel group (6) **Baseline data mean (SD)** Nothing reported
Interventions	12 weeks **Intervention** Metronidazole 0.75% cream - BID (47) **Comparator** Metronidazole 0.75% gel - BID (53)
Outcomes	Assessments (4): baseline, week 4, 8 and 12

	Outcomes of the trial (as reported) **Primary outcomes** 1. Decrease in inflammatory lesions at week 12 and Investigator's Global Assessment✶ **Secondary outcomes** 1. Erythema, telangiectasia✶ 2. Safety assessments, adverse events✶ 3. Participant's preference ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared. One investigator was employed by Galderma, manufacturer of at least one of the investigated drugs
Notes	One of our primary outcomes was addressed (adverse events) See comparison 9 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (S272): "This multicenter, controlled, randomized, investigator-masked study..." Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page S272): "...investigator-masked study." Not clear what measures were used to blind study participants and personnel from knowledge of which intervention a participant received Outcomes assessments: Principally by the investigators

		Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page S272): "...investigator-masked study." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	High risk	Quote (S272): "100 patients enrolled and analysed for ITT..." (21 withdrew/12 losses to follow up). Per-protocol analysis at week 12 - 67/100 Comment: Losses were accounted for but the data analysis as reported appeared to be per-protocol with exclusion of outcome data for 33/100 participants. We judged this as at a high risk of bias
Selective reporting (reporting bias)	High risk	One pre-specified outcome was inadequately addressed and reported: Investigator's Global Assessment of improvement Comment: We judged this as at a high risk of bias
Other bias	Unclear risk	Wash-out period not stated, study duration adequate, unclear if groups were treated equally. Poster abstract Comment: Insufficient information to permit a clear judgement

Elewski 2003

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Multicentre, 13 centres in US
Participants	**Randomised:** 251 participants (mean age 49 years in treatment group versus 46 years in control group, 32 male and 92 female versus 34 male and 93 female) **Inclusion criteria** • ≥ 18 years of age • Participants with papulopustular rosacea (10-50 inflamed papules and/or pustules), persistent erythema, and telangiectasia

	Ocular involvement: Participants with marked involvement were excluded **Exclusion criteria** • Mild rosacea, severe rosacea • Rosacea fulminans • Marked ocular rosacea • Steroid rosacea • Dermatoses that might interfere with evaluations • Known hypersensitivity to study treatments • Lactating and pregnant female **Dropouts and withdrawals** • 22/251 (8.8%); azelaic group (14), metronidazole group (8) • Adverse events; azelaic group (5), metronidazole group (0) • Lack of efficacy; azelaic group (1), metronidazole group (2) • Deviated from protocol; azelaic group (3), metronidazole group (2) • Withdrew consent; azelaic group (3), metronidazole group (3) • Other reasons; azelaic group (2), metronidazole group (3) **Baseline data mean** Lesion counts; azelaic group 18, metronidazole group 19
Interventions	15 weeks **Intervention** Azelaic acid 15% gel - BID (124) **Comparator** Metronidazole 0.75% gel - BID (127)
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 15 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in inflammatory lesion count✴ **Secondary outcomes** 1. Percentage change in inflammatory lesion count✴

	2. Change in severity for erythema and telangiectasia (0=none, 3 = severe)✴ 3. Investigator's Global Assessment (0 = clear, 6 = severe)✴ 4. Investigator's overall improvement (1 = complete remission, 6 = deterioration)✴ 5. Participant's overall improvement ratings (1 = excellent, 5 = worsening)✴ 6. Participant's opinion of cosmetic acceptability 7. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 1444): "The authors received financial compensation from Berlex Laboratories Inc, Montville, NJ, for serving as principal investigators for this study"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 16 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1145): "Computer-generated block wise randomisation method was used to ensure balance between the groups..." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1445): "Assignment occurred by the physician in ascending order with newly accepted patient receiving study medication with the lowest randomisation number available in the center." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1445): "To preserve blinding, study medication was dispensed and collected only by a study nurse or assistant not involved with selection and assessment of patients." Comment: The report was also unclear what measures were used to blind study participants from knowledge of which intervention they received or any information relating to whether the intended blinding was effective

		Comment: Insufficient information to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 1445): "To preserve blinding, study medication was dispensed and collected only by a study nurse or assistant not involved with selection and assessment of patients." Comment: Assignment to intervention was by the investigators who were also the outcomes assessors. No satisfactory evidence of blinding. Outcomes were investigator and participant assessed Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	Intention-to-treat analysis. All participants were accounted for Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Wash-out period and study duration adequate, not permitted to receive any concurrent therapy. Authors received financial compensation from Berlex Laboratories, Inc, Montville, NJ, for serving as principal investigators for this study Comment: Insufficient information to assess whether important risk of bias exists

Ertl 1994

Methods	RCT, prospective, placebo-controlled (both groups have same topical treatment but different systemic treatments), double-blind, cross-over Date of study March to May 1991 Setting Department of Dermatology University of Arizona, and University of Pennsylvania School of Medicine, US
Participants	**Randomised:** 22 participants (mean age 59 years (range 34 to 77 years), 12 male, 10 female) **Inclusion criteria** • Participants with severe or recalcitrant rosacea

	• Severe rosacea was defined clinically as disease activity with significant erythema with multiple papules and pustules • Recalcitrant rosacea was defined as disease activity incompletely controlled by prior therapies **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 2/22 (9%); group with placebo capsules + 0.025% tretinoin cream • Stopping medication (1) • Bruising after venipuncture (1) **Baseline data mean** Individual participant data are provided for lesion counts, comparable
Interventions	16 weeks to cross-over but oral isotretinoin withheld **Intervention** Isotretinoin 10 mg + tretinoin 0.025% cream - QD (6) **Comparator 1** Placebo capsules + tretinoin 0.025% cream - QD (8) **Comparator 2** Isotretinoin 10 mg + placebo cream - QD (8)
Outcomes	Assessments (2): baseline and week 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Changes in clinical erythema (four-point VAS scale) 2. Number of inflammatory papules and pustules 3. Adverse events (four-point VAS scale)✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported

Declaration of interest	None declared
Notes	After 16 weeks cross-over but oral isotretinoin withheld; second phase unbalanced comparison. We only included first phase One of our primary outcomes was addressed (adverse events) Data unreliable, its re-analysis using the individual participant data confirmed its flawed analysis by the investigators (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 320): "three separate treatment groups were randomly assigned" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 320) : "Subjects were given coded bottles containing either isotretinoin or placebo capsules. The creams were dispensed in tubes containing either 0.025% tretinoin cream or the vehicle" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	2/22 lost to follow-up; data presented as individual participant data Comment: We judged this as at a low risk of bias

Selective reporting (reporting bias)	High risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported. Data unreliable, its re-analysis using the individual participant data confirmed its flawed analysis by the investigators Comment: We judged this as at a high risk of bias
Other bias	Low risk	Wash-out phase before study started adequate, study duration adequate, groups treated equally, in first 16 weeks, no sponsoring Comment: The study appeared to be free of other forms of bias

Espagne 1993

Methods	RCT, prospective, placebo-controlled, double-blind Date of study April to October 1990 Setting Multicentre (18), France
Participants	**Randomised:** 51 participants (age and gender unreported) **Inclusion criteria** • ≥ 18 years of age • Participants with rosacea for at least 3 months, defined by presence of at least 3 papules or pustules, or both; and erythema or telangiectasia, or both **Ocular involvement:** Unclear **Exclusion criteria** • Rhinophymas • Peri-oral dermatitis or isolated pustules on the chin, acne • Female at fertile age without contraception **Dropouts and withdrawals** • 6/51 (11.7%); metronidazole group (2), placebo group (4) • Inefficacy; metronidazole group (0), placebo group (3) • Intolerance; metronidazole group (0), placebo group (1) • Lost to follow-up; metronidazole group (2), placebo group (0) **Baseline data mean (SD)** Inflammatory lesions; metronidazole group 10.7 (7.9), placebo group 15.4 (12.5)

Interventions	Six weeks **Intervention** Metronidazole 0.75% gel - BID (26) **Comparator** Placebo gel (vehicle) - BID (25)
Outcomes	Assessments (3): baseline week 3 and 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. The relative variation of number of papules and pustules between day 0 and day 42✶ 2. The absolute reduction of this number estimated on the absolute difference in time of the mean numbers✶ 3. The percentage of reduction in the means of papules and pustules as a function of time 4. The percentage of patients having presented a reduction of at least 50% of their initial number of papules and pustules✶ **Secondary outcomes** 1. The extent of erythema (0 = zero; 1 = mild; 2 = moderate; 3 = severe)✶ 2. Global assessment by the patient and the doctor (aggravated, stable, improved, cured)✶ 3. Local tolerance was assessed on the sensations of burning, pruritus, cutaneous dryness, counted as present or absent ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Two investigators were employees of Schering Plough
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) Allocation to intervention was based on up to 4 participants in each of 18 clinics but not all clinics enrolled 4 participants. The report did not provide any reassurance that the allocation sequence was adequately generated (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	High risk	Quote (page 129): "la randomisation a porté sur des groups de 4, chaque médicin constituent un centre et devant inclure 4 malades" Comment: Allocation to intervention was based on up to 4 participants in each of 18 clinics but not all clinics enrolled 4 participants. The report did not provide any reassurance that the allocation sequence was adequately generated and there was lack of evidence that any form of central randomisation had been employed for the 18 clinics involved in this study
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 130): "Les emballages, les tubes, la coloration des gels étaient strictement comparables et indiscernables par les malades ou les expérimateureurs" (packaging, tubes, colour of gels were indistinguishable for participants and investigators). Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	6/51 (11.7%); metronidazole group (2), placebo group (4), ITT (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started adequate, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

EUCTR2006-001999-20-HU

Methods	RCT, prospective, active and placebo-controlled, single-blinded Date of study June 2006 to June 2007 Setting Multicentre, across Europe
Participants	**Randomised:** 296 participants (mean age 51.9 years, 95 male, 201 female **Inclusion criteria** • Male or female ≥18 years with papulopustular rosacea and at least 15 inflammatory facial lesions, with at least mild erythema **Ocular involvement:** Unclear **Exclusion criteria** • Peri-oral dermatitis • Other forms of demodicidosis • Facial keratosis pilaris • Actual or history of seborrhoeic dermatitis **Dropouts and withdrawals** • 23/296 (7.8%); CD5024 0.1% QD group (2), CD5024 0.3% QD group (2), CD5024 1% QD group (3), CD5024 1% BID group (5), metronidazole 0.75% BID group (4), vehicle QD group (7) • Adverse events; CD5024 0.1% QD group (1), CD5024 0.3% QD group (2), CD5024 1% QD group (1), CD5024 1% BID group (2), metronidazole 0.75% BID group (2), vehicle QD group (0) • Subject's request; CD5024 0.1% QD group (0), CD5024 0.3% QD group (0), CD5024 1% QD group (1), CD5024 1% BID group (1), metronidazole 0.75% BID group (2), vehicle QD group (50) • Protocol violation; CD5024 0.1% QD group (1), CD5024 0.3% QD group (0), CD5024 1% QD group (0), CD5024 1% BID group (1), metronidazole 0.75% BID group (0), vehicle QD group (1) • Lack of efficacy; CD5024 0.1% QD group (0), CD5024 0.3% QD group (0), CD5024 1% QD group (1), CD5024 1% BID group (0), metronidazole 0.75% BID group (0), vehicle QD group (0) • Other reasons; CD5024 0.1% QD group (0), CD5024 0.3% QD group (0), CD5024 1% QD group (0),

	CD5024 1% BID group (1), metronidazole 0.75% BID group (0), vehicle QD group (0) **Baseline data mean (SD)** Inflammatory lesions; CD5024 0.1% QD group 31.1 (15.0), CD5024 0.3% QD group 35.1 (20.5), CD5024 1% QD group 35.8 (18.2), CD5024 1% BID group 37.3 (39.0), metronidazole 0.75% BID group 37.4 (23.9), vehicle QD group 35.8 (19.9)
Interventions	12 weeks **Intervention** CD5024 0.1% cream - QD (51) **Comparator 1** CD5024 0.3% cream - QD (47) **Comparator 2** CD5024 1% cream - QD (52) **Comparator 3** CD5024 1% cream - BID (48) **Comparator 4** Metronidazole 0.75% cream - BID (48) **Comparator 5** Vehicle cream -QD (50)
Outcomes	Assessments (2): baseline and week 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Percent changes in inflammatory lesions **Secondary outcomes** 1. Change from baseline in Investigator's Global assessment (IGA, IGA 1 composite score of erythema and inflammatory lesions, IGA 2 inflammatory lesions only)✴ 2. Success rate at week 12 (IGA 1 and IGA 2 clear or almost clear)✴

	3. Change from baseline in erythema and telangiectasia scores✴ 4. Adverse events✴ 5. Quality of life with DLQI and EQ5D✴ 6. Participant satisfaction (questionnaire) ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Dose finding study for CD5024 (ivermectin), website accessed 13-3-2018 Data presented although not published in full. Conclusion 1% cream (ivermectin) once or twice daily was significantly superior to its vehicle for percentage change of inflammatory lesion counts as well as for the success rate after 12 weeks of treatment confirming a dose relationship. The drug was well tolerated Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 14 and 20 Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomised" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "single-blind" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed

		Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "single-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	23/296 (7.8%), reasons reported and balanced between groups. ITT analysis and per-protocol analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

EUCTR2006-003707-40-DE

Methods	RCT, prospective, placebo-controlled, investigator-blinded Date of study December 2006 to June 2007 Setting Multicentre (6), Germany and France
Participants	**Randomised:** 50 participants (mean age 47 years, 8 male, 42 female) **Inclusion criteria** • Male or female 18-65 years with erythematotelangiectatic rosacea characterised by persistent erythema, an erythema severity score graded at least 3 on a 5-point scale and no history of inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria**

	• The subject has a particular form of rosacea (papulopustular rosacea, rhinophyma, severe forms (rosacea conglobata or fulminans), corticosteroids-induced rosacea or isolated pustulosis of the chin), with facial erythrosis of any type (known carcinoid syndrome, dysthyroidism, mastocytosis, serotonin syndrome…) or with peri-oral dermatitis. • Underlying disease, surgical or medical condition, which could interfere with evaluations of the rosacea condition itself (e.g. lupus erythematosus, atopic dermatitis, eczema, acne vulgaris, and psoriasis or could put the subject at risk (uncontrolled chronic or serious diseases which would normally prevent participation in any clinical trial, such as a cancer, AIDS, renal or hepatic impairment) • Facial skin condition which would interfere with study assessments such as an abnormal pigmentation or skin type IV, V and VI on the Fitzpatrick scale or a beard or other facial hair • Abnormal ECG • Past migraine history • Use of antimotility drug (loperamide) • Past digestive surgical history **Dropouts and withdrawals** • 2/50 (4%); CD06713 group (2), placebo group (0) • Discontinued medication; CD06713 group (1), placebo group (0) • Adverse event; CD06713 group (1), placebo group (0) **Baseline data median** Erythema score; CD06713 group 6.13 placebo group 6.46
Interventions	Four weeks **Intervention** CD06713 8 mg - BID (24) **Comparator** Placebo/day - BID (26)
Outcomes	Assessments (4): baseline, day 1, 8, 15 and 29 (and follow up at day 50) **Outcomes of the trial** (as reported) **Primary outcomes**

	1. The change from baseline in combined erythema score (total sum erythema score of the right and left cheek) **Secondary outcomes** 1. Worst erythema severity score across both cheeks 2. Change from baseline in erythema score categorized as improved, same, or worsened✶ 3. Change from baseline in telangiectases severity score✶ 4. Inflammatory lesions (papule/pustule) count✶ 5. Change from baseline in the mean chromametric parameter a* 6. Change from baseline in the mean chromametric parameter b* 7. Change from baseline in the mean chromametric parameter L* 8. Subject's Global Assessment of Improvement✶ 9. Flushes count 10. Erythema relapse rate (follow-up period)✶ 11. Erythema rebound rate ✶Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 13-3-2018 CD06713 is ondansetron Data presented although not published in full. No statistically significant differences between ondansetron and placebo (efficacy and safety)\ One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 81 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomised" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been

		foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "investigator-blinded" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received. Participants were not blinded Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "investigator-blinded" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	2/50 (4%); CD06713 group (2), placebo group (0). ITT and per-protocol analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

EUCTR2009-013111-35-DE

Methods	RCT, prospective, active- and placebo-controlled, double-blind Date of study January to June 2010 Setting Multicentre, Germany

Participants	**Randomised:** 74 participants (mean age 47 years, 10 male, 64 female) **Inclusion criteria** • Male or female 18-65 years with erythematotelangiectatic rosacea characterised by persistent erythema, an erythema severity score graded at least 3 on a 5-point scale and no history of inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • The subject has a particular form of rosacea (papulopustular rosacea, rhinophyma, severe forms (rosacea conglobata or fulminans), corticosteroids-induced rosacea or isolated pustulosis of the chin), with facial erythrosis of any type (known carcinoid syndrome, dysthyroidism, mastocytosis, serotonin syndrome…) or with peri-oral dermatitis. • Underlying disease, surgical or medical condition, which could interfere with evaluations of the rosacea condition itself (e.g. lupus erythematosus, atopic dermatitis, eczema, acne vulgaris, and psoriasis or could put the subject at risk (uncontrolled chronic or serious diseases which would normally prevent participation in any clinical trial, such as a cancer, AIDS, renal or hepatic impairment) • Past history of gastric or duodenal ulcer, gastroesophageal reflux disease (GERD), oesophagitis or pathological hypersecretory conditions or a Zollinger-Ellison syndrome or recurrent gastralgias **Dropouts and withdrawals** • 10/74 (13.5%); CD08514 10 mg BID group (4), CD08514 40 mg BID group (2), half placebo tablet BID (2). two placebo tablets BID (2) • Discontinued medication; CD08514 10 mg BID group (1), CD08514 40 mg BID group (2), half placebo tablet BID (0). two placebo tablets BID (1) • Other reasons; CD08514 10 mg BID group (3), CD08514 40 mg BID group (0), half placebo tablet BID (2). two placebo tablets BID (1) **Baseline data mean** Erythema score; for all groups estimated from figure at 6.6
Interventions	Eight weeks **Intervention**

	CD08514 10 mg - BID (23) **Comparator 1** CD08514 40 mg - BID (24) Comparator 2 Placebo half tablet - BID (14) Comparator 3 Placebo tablet - BID (13)
Outcomes	Assessments (11): baseline, day 1, 2, 5, 12, 19, 26, 33, 40, 47, 54 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change from baseline in cheek-combined erythema severity score (total sum score of the two cheeks)✶ **Secondary outcomes** 1. To evaluate the safety profile of CD08514 40 mg and 10 mg BID✶ ✶Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 15-3-2018, sent mail to Galderma NL in 2014, CD08514 is famotidine CD08514 10 mg and 40 mg BID (famotidine) orally over 8 weeks did not demonstrate superior efficacy to placebo in subjects with moderate to severe erythemato-telangiectatic rosacea although PK (pharmacokinetic) assessments showed that the CD08514 was detectable in the plasma and in the skin. There were no safety concerns One of our primary outcomes was addressed (adverse events) See comparison 82 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	10/74 (13.5%); CD08514 10 mg BID group (4), CD08514 40 mg BID group (2), half placebo tablet BID (2). two placebo tablets BID (2). ITT and per-protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally

		Comment: This study appears to be free of other forms of bias

EUCTR2010-018319-13-DE

Methods	RCT, prospective, placebo-controlled, double-blind Date of study September 2010 to May 2011 Setting Multicentre (24) in France, Germany, Czech Republic, Hungary, Finland and Slovakia
Participants	**Randomised:** 210 participants (mean age 55.4 years, 66 male, 144 female) **Inclusion criteria** • Male or female 18 years or older with papulopustular rosacea (at least 15 inflammatory lesions, and have Investigator's Global Assessment (IGA) score of 3 (moderate) or 4 (severe) on a 5-point scale) **Ocular involvement**: Probably but not on systemic treatment **Exclusion criteria** • Particular forms of rosacea that could be confounded with papulopustular rosacea • Ocular rosacea requiring systemic or an interfering treatment • Underlying diseases putting them at risk, or subjects with clinically significant neutrophil cell count abnormalities **Dropouts and withdrawals** • 24/210 (11.4%); CD5024 1% group (9), vehicle group (15), reasons unreported **Baseline data mean (SD)** IGA 3 - Moderate (n); CD5024 1% group (84), vehicle group (85) IGA 4- Severe (n): CD5024 1% group (20), vehicle group (21) Papules;CD5024 1% group 26.4 (14.0), vehicle group 30.0 (24.9) Pustules; CD5024 1% group 8.9 (9.5), vehicle group 10.0 (9.9)
Interventions	12 weeks **Intervention** CD5024 1% cream - QD (104) **Comparator**

	Vehicle - QD (106)
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Potential effect of CD5024 on the induction of neutropenia 2. Improvement in Investigator Global Assessment from baseline✴ 3. Absolute change in inflammatory lesion count from baseline✴ **Secondary outcomes** 1. To evaluate the general safety 2. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 16-3-2018, CD5024 1% cream is ivermectin One of our primary outcomes was addressed (adverse events) See comparison 15 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear

		assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	24/210 (11.4%); CD5024 1% group (9), vehicle group (15), reasons unreported. ITT and per-protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

EUCTR2011-002057-65-DE

Methods	RCT, prospective, placebo-controlled, investigator-blinded, within-patient comparison Date of study October to December 2011 Setting proDERM GmbH, Hamburg, Germany
Participants	**Randomised:** 23 participants (mean age 50.3 years, 2 male, 18 female, 3 gender unreported) **Inclusion criteria**

	• Male or female 18 years or older with moderate to severe erythematotelangiectatic rosacea (persistent erythema, an erythema severity score of at least 3 on a 5 point scale on each cheek (similar on both), possible presence of telangiectasia, flushing/blushing, edema **Ocular involvement:** Probably, but not on systemic treatment **Exclusion criteria** • Inflammatory lesions (papules and/or pustules) in the 3 months before the screening • > 3 inflammatory lesions at start run in phase **Dropouts and withdrawals** 3/23 (13%); did not fulfil the inclusion criteria “Erythema Severity Score 3” after the run-in phase anymore. **Baseline data mean (SD)** Erythema severity score on the cheek; Solaraze side 3.3 (0.4), placebo side 3.3 (0.4) Telangiectasia score (Dermascore); Solaraze side 4.4 (1.0), placebo side 4.4 (1.0) Flushing/blushing episodes per week; Solaraze side 9.8 (6.8), placebo side 9.8 (6.8)
Interventions	Four weeks **Intervention** CD08100/02 3% gel - QD **Comparator** Placebo gel - QD
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change from baseline in cheek erythema severity score for each cheek on day 26✴ 2. Improvement in Investigator Global Assessment✴ 3. Absolute change in inflammatory lesion count from baseline✴ **Secondary outcomes** 1. Change from baseline in the telangiectasia score using Dermascore for each side of the face at each evaluation visit✴

	2. Edema score for each side of the face at each evaluation visit 3. Number of flushing/blushing episodes per week 4. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 13-3-2018, CD08100/02 3% gel is diclofenac sodium gel 3% (Solaraze). Conclusion: No efficacy of Solaraze® in erythematotelangiectatic rosacea was shown during the study, in comparison with placebo after 4 weeks of daily applications One of our primary outcomes was addressed (adverse events) See comparison 55 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "investigator-blinded" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website) "investigator-blinded" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	3/23 (13%); did not fulfil the inclusion criteria “Erythema Severity Score 3” after the run-in phase anymore. Per-protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, sides treated equally Comment: This study appears to be free of other forms of bias

EUCTR2011-002058-30-DE

Methods	RCT, prospective, active- and placebo-controlled, investigator blinded, within-patient comparison Date of study December 2011 to March 2012 Setting Multicentre (7), Germany
Participants	**Randomised:** 58 participants (mean age and gender unreported) **Inclusion criteria** • Male or female 18 years or older with moderate to severe papulopustular rosacea (at least 15 inflammatory facial lesions (papules and / or pustules) **Ocular involvement**: Unclear **Exclusion criteria** • Lesions located on the central part of the face (nose, chin and middle forehead) **Dropouts and withdrawals:** None **Baseline data mean (SD)** Nothing reported
Interventions	Six weeks **Intervention**

	CD08100/02 3% gel - QD five days per week **Comparator 1** Placebo gel - QD five days per week **Comparator 2** Metronidazole 0.75% gel - QD five days per week
Outcomes	Assessments (2): baseline, week 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Inflammatory lesions (count of papules and pustules including cheeks and left and right side of forehead, but not nose, chin or middle forehead)✴ 2. Erythema (severity score)✴ 3. Telangiectasia (severity score)✴ 4. Edema (severity score) 5. Flushing / blushing (frequency, severity and duration): reporting on a daily basis by the subject and recording by the investigator every week 6. Functional signs (scores of itching, dryness sensation, and stinging / burning) **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 16-3-2018. Only generic comments are provided no exact data. See Table 6. Quote "Once daily treatment with CD08100/02 3% gel respectively with Metronidazole 1% gel of one hemiface in comparison with the other hemiface treated with placebo gel showed a statistically significant effect on total inflammatory lesions after 6 weeks of treatment and percentage change from Baseline, but only in the CD08100/02 3% gel treatment arm." One of our primary outcomes was addressed (adverse events)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomised" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "investigator-blinded" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website) "investigator-blinded" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported. Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	High risk	No actual data are provided only generic comments about efficacy Comment: We judged this as at a high risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, sides treated equally Comment: This study appears to be free of other forms of bias

EUCTR2012-001044-22-SE

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study September 2012 to October 2013 Setting Multicentre (8), France, Russia and Sweden
Participants	**Randomised:** 112 participants (mean age 44 years, 31 male, 81 female) **Inclusion criteria** • Male or female 18 years or older with moderate to severe facial erythema of rosacea **Ocular involvement**: Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** • 9/112 (8.0%); CD07805/47 0.5% gel group (7), placebo gel group (2) • Protocol deviation; CD07805/47 0.5% gel group (1), placebo gel group (1) • Adverse event; CD07805/47 0.5% gel group (6), placebo gel group (1) **Baseline data mean (SD)** Nothing reported
Interventions	29 days **Intervention** CD7805/47 0.5% gel - QD (57) **Comparator** Placebo gel - QD (55)
Outcomes	Assessments (6): baseline, day 1 at 30 min and day 29 at hours 3, 5, 7 and 9 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Clinician Erythema Assessment (CEA)✴ 2. Patient Self Assessment (PSA)✴ **Secondary outcomes**

	1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 22-4-2018, sent mail to Galderma NL in 2014. CD7805/47 0.5% is brimonidine tartrate 0.5% Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 3 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomised" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the

		study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	9/112 (8.0%); CD07805/47 0.5% gel group (7), placebo gel group (2), reasons reported. ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

EUCTR2013-005083-26-DE

Methods	RCT, prospective, placebo-controlled, double-blind, cross-over and within-patient for a part Date of study April to June 2014 Setting Single-centre, Germany
Participants	**Randomised:** 34 participants (mean age 50.2 years, 31 male, 2 female, 1 gender unreported) **Inclusion criteria** • Male or female 18 years or older with mild to moderate erythematotelangiectatic rosacea (ETR) or mild to moderate papulopustular rosacea (PPR) **Ocular involvement**: Unclear **Exclusion criteria** • Not reported **Dropouts and withdrawals:** • 1/34 (2.9%); did not perform any efficacy assessment **Baseline data mean (SD)** Nothing reported
Interventions	Period 1 (1 week, cross-over in first and 3rd session and within-participant 2nd session); Period 2 (4 weeks, cross-over

	after 2 weeks) **Intervention** CD7805/47 0.5% gel - QD **Comparator** Placebo gel (vehicle) - QD
Outcomes	Assessments (3): baseline, week 2 and 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Number of flushes **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	Nothing reported
Notes	Website accessed 16-3-2018, CD7805/47 0.5% is brimonidine tartrate 0.5%, data reporting very limited and confusing (see Table 6) One of our primary outcomes was addressed (adverse events)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received Outcomes were investigator as well participant-assessed Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	1/34 (2.9%); did not perform any efficacy assessment Comment: We judged this at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full and the data presenting was fairy confusing Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

Fabi 2011

Methods	RCT, prospective, controlled, within-patient comparison Date of study Unreported Setting Laser clinic, San Diego, US
Participants	**Randomised:** 20 participants (mean age 46.5 years, 2 male, 9 female, 9 gender unreported) **Inclusion criteria** • Mild to moderate rosacea **Ocular involvement:** Unclear **Exclusion criteria**

	• None reported **Dropouts and withdrawals** • 9/20 (45%); reasons unreported **Baseline data mean** Nothing reported
Interventions	Six weeks **Intervention** Intense pulsed light therapy + azelaic acid 15 % gel - BID **Comparator** Intense pulsed light therapy
Outcomes	Assessments (3); baseline, week 2 and 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator Global Assessment (telangiectasias, papules, pustules and nodules, six-point Likert scale)✴ 2. Participant-assessed improvement; five category (overall skin appearance, amount of acne bumps, skin dryness, amount of moisturizer needed, and overall assessment of skin) questionnaire✴ 3. Standardised photography **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	Poster abstract, limited data, unable to contact investigators One of our primary outcomes was addressed (participant assessed changes in rosacea severity). No exact data were provided (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 969): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding reported Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding reported. Outcomes were investigator as well participant-assessed Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	High risk	9/20 (45%); reasons unreported. Per-protocol analysis Comment: High dropout rate assessed as at a high risk of bias
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Faghihi 2015

Methods	RCT, prospective, active-controlled, double-blind Date of study April to December 2013 Setting Department of Dermatology, Skin Diseases and Leishmaniasis Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
Participants	**Randomised:** 56 participants (>18 years, mean age 35 years, 15 male, 41 female) **Inclusion criteria** • At least five lesions of papulopustular rosacea

	Ocular involvement: Unclear **Exclusion criteria** • Topical corticosteroids in the last 14 days • Topical retinoids in the last 30 days • Systemic retinoids in the last 180 days • Other systemic medications effective on inflammation in the last 30 days • Physical therapies effective on rosacea in the last 30 days • Associated lesions such as cysts, comedones, scars in favour of acne vulgaris, hematologic diseases, G6PD deficiency, hypersensitivity to dapsone and sulfa medications, pregnancy and breast feeding were excluded too **Dropouts and withdrawals** • 6/58 (10.3%); dapsone group (3), metronidazole group (3) • Not using medication regularly; dapsone group (1), metronidazole group (2) • Drug intolerance; dapsone group (2), metronidazole group (1) **Baseline data mean (SD)** Number of inflammatory lesions; dapsone group 15 (7.4), metronidazole group 17.6 (7.7) IGA score; dapsone group 3.9 (0.9), metronidazole group 4.2 (1.2) VAS score; dapsone group 6.6 (1.8), metronidazole group 6.9 (2.0)
Interventions	12 weeks **Intervention** Dapsone 5% gel - BID (28) **Comparator** Metronidazole 0.75% gel - BID (28) Both treatment groups received doxycycline 100 mg/day
Outcomes	Assessments (4); baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Number of inflammatory lesions✴

	2. Investigator Global Assessment (IGA) score (0-6, higher is worse)✶ **Secondary outcomes** 1. VAS of severity of disorder (patient-assessed)✶ 2. Frequency of signs and symptoms 3. Adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 605): "All authors declare no conflicts of interest, financial or otherwise"
Notes	Dr. Gita Faghihi G_faghihi@med.mui.ac.ir or Dr. Parastoo Khosravani p_khosravani@resident.mui.ac.ir Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 71 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 603): "Simple randomization method was used" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 603): Both gels were similar in shape, odor, size and color and manufactured by one pharmaceutical company (Pars Darou, Iran)" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken

		Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	6/58 (10.3%); dapsone group (3), metronidazole group (3), reasons reported. ITT analysis. Comment: Low and balanced number of drop-outs combined with ITT analysis considered as at a low risk of bias
Selective reporting (reporting bias)	High risk	The protocol for the study was available on apps.who.int/trialsearch/ (IRCT2014010516079N1). The protocol prespecified primary outcome density of demodex mites was not addressed, also the prespecified outcome 'side effects' was not addressed Comment: We judged this as at high risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Methods	RCT, prospective 'placebo'-controlled (both treatment arms had same topical treatment; one arm systemic active treatment versus placebo), double-blind Date of study Unreported Setting Multicentre - unclear which ones but at least Department of Dermatology, University of Louisville, Louisville, US
Participants	**Randomised**: 72 participants (mean age 47.8 years, 16 male, 56 female) **Inclusion criteria** • ≥ 18 years of age • Participants with rosacea, defined as 8 to 40 total lesions (papules and pustules), ≤ 2 nodules, presence of moderate to severe erythema and presence of telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Topical rosacea or acne treatments • Use of systemic corticosteroids • Use of vasodilators **Dropouts and withdrawals** • 8/72 (11.1%); doxycycline group (6) and placebo group (2)

	• Adverse events; doxycycline group (3) and placebo group (1) • 1 participant withdrew consent, 2 were lost to follow up, and 1 dropped out due to protocol violation, but unclear from which group **Baseline data mean** Number of lesions; doxycycline group 21.3 and placebo group 18.7 Basal erythema score; doxycycline group 8.6 and placebo group 9.2
Interventions	16 weeks **Intervention** Doxycycline 40 mg QD + metronidazole gel 1% BID (36) **Comparator** Placebo capsules + metronidazole gel 1% - BID (36) After 12 weeks, metronidazole gel stopped, but oral medication or placebo continued until week 16
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean change in total inflammatory lesion count from baseline to endpoint✴ **Secondary outcomes** 1. Investigator's Global Assessment (IGA) score from baseline to endpoint (0 = clear, 5 = very severe)✴ 2. Mean percentage change in total lesions from baseline✴ 3. Change in Clinician's Erythema Assessment score from baseline to weeks 4, 8, 12 and 16 (0 = none, 4 = severe)✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed We only included data from the first 12 weeks of the study See comparison 67 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 642): "This was a randomized, multi-center, outpatient, double-blind placebo-controlled trial." E-mail contact with the investigator confirmed randomisation was carried out using a computer-generated table provided by the sponsor Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence was not reported E-mail contact with the investigator confirmed "pharmacy-controlled central allocation and neither investigators or study staff were involved in the generation of the sequence" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 642): "This was a randomized...double-blind..." Comment: The report did not describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. Insufficient information to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 642): "This was a randomized...double-blind..." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	8/72 (11.1%); doxycycline group (6) and placebo group (2). Per-protocol analysis Comment: Low number of dropouts, and although slightly unbalanced, judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate. Wash-out phase before study not reported, groups treated equally Comment: We judged this as at low risk of bias

Fowler 2012a

Methods	RCT, prospective, active and placebo-controlled, double-blind Date of study Unreported Setting Multicentre (5) in US
Participants	**Randomised:** 122 participants (mean age 45.7 years (SD 12.1), 30 male, 92 female) **Inclusion criteria** • ≥ 18 years with with moderate to severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self Assessment (PSA) **Ocular involvement:** Unclear **Exclusion criteria** • Three or more facial inflammatory lesions of rosacea **Dropouts and withdrawals:** None **Baseline data N (%)** CEA moderate; BT 0.07% 22 (78.6), BT 0.18% 23 (74.2), BT 0.5% 23 (74.2), vehicle 25 (78.1) CEA severe; BT 0.07% 6 (21.4), BT 0.18% 8 (25.8), BT 0.5% 8 (25.8), vehicle 7 (21.9) PSA mild; BT 0.07% 1 (3.6), BT 0.18% 1 (3.2), BT 0.5% 0 (0), vehicle 2 (6.3) PSA moderate; BT 0.07% 12 (42.9), BT 0.18% 24 (77.4), BT 0.5% 26 (83.9), vehicle 26 (81.3) PSA severe; BT 0.07% 15 (53.6), BT 0.18% 6 (19.4), BT 0.5% 5 (16.1), vehicle 4 (12.5)
Interventions	One application, follow-up 12 hours **Intervention** Brimonidine tartrate 0.07% gel single application (28) **Comparator 1** Brimonidine tartrate 0.18% gel single application (31) **Comparator 2** Brimonidine tartrate 0.5% gel single application (31) **Comparator 3** Vehicle gel single application (32)

Outcomes	Assessments (14): baseline, 30 min, 1 hour and then each hour until 12 hours **Outcomes of the trial** (as reported) **Primary outcomes** 1. Clinician's Erythema Assessment (CEA) (The Chroma Meter (Konic Minolta CR-400; Konic Minolta Sensing Americas, Inc, Ramsey. NJ, USA) a* parameter (red green scale), score 0 to 4, clear to severe)✴ 2. Patient's Self Assessment (PSA) of erythema (score 0 to 4, clear to severe)✴ 3. Inflammatory lesion counts and severity of telangiectasia (score 0 to 4, clear to severe)✴ **Secondary outcomes** 1. Adverse events, vital signs, intraocular pressure✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 633): "The two studies were funded by Galderma R&D"
Declaration of interest	Quote (page 633): "The investigators received grants for conducting the studies. YL and ML are employees of Galderma R&D"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 1 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 634): "Subjects were randomized in a 1:1:1:1 ratio to receive" and "randomization lists were generated prior to study initiation by an independent statistician using SAS hoc Plan procedure (SAS Institute, Cary, NC, U.S.A.)." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 634): "The randomization lists were then sent to the clinical supply group, and only the personnel directly involved with labelling and packaging had access." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 634): "The integrity of the blinding was ensured by packaging the topical gels in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication." The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up. ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT00989014). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	This is a phase II study, duration for this design adequate, groups treated equally. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Fowler 2012b

Methods	RCT, prospective, active- and placebo-controlled, double-blind Date of study Unreported Setting Multicentre (17) in US
Participants	**Randomised:** 269 participants (mean age 44.3 years, 52 male, 217 female) **Inclusion criteria** • ≥ 18 years with with moderate to severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self Assessment (PSA)

	Ocular involvement: Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 9/269 (3.3%); BT 0.18% QD (2), BT 0.18% BID (2), BT 0.5% (2), vehicle QD (2), vehicle BID (1) • Adverse event; BT 0.18% QD (0), BT 0.18% BID (1), BT 0.5% (0), vehicle QD (0), vehicle BID (0) • Subject request; BT 0.18% QD (2), BT 0.18% BID (0), BT 0.5% (0), vehicle QD (2), vehicle BID (0) • Protocol violation; BT 0.18% QD (0), BT 0.18% BID (0), BT 0.5% (2), vehicle QD (0), vehicle BID (1) • Other; BT 0.18% QD (0), BT 0.18% BID (1), BT 0.5% (0), vehicle QD (0), vehicle BID (0) **Baseline data N (%)** CEA moderate; BT 0.18% QD 44 (81.5), BT 0.18% BID 42 (77.8), BT 0.5% 47 (88.7), vehicle QD 48 (87.3), vehicle BID 44 (83) CEA severe; BT 0.18% QD 10 (18.5), BT 0.18% BID 12 (22.2), BT 0.5% 6 (11.3), vehicle QD 7 (12.7), vehicle BID 9 (17) PSA moderate; BT 0.18% QD 45 (83.3), BT 0.18% BID 45 (83.3), BT 0.5% 44 (83), vehicle QD 46 (83.6), vehicle BID 45 (84.9) PSA severe; BT 0.18% QD 9 (16.7), BT 0.18% BID 9 (16.7), BT 0.5% 9 (17), vehicle QD 9 (16.4), vehicle BID 8 (5.1)
Interventions	Four weeks, and four weeks follow-up **Intervention** Brimonidine tartrate 0.18% gel - QD (54) **Comparator 1** Brimonidine tartrate 0.18% gel - BID (54) **Comparator 2** Brimonidine tartrate 0.5% gel - QD (53) **Comparator 3** Vehicle gel - QD (55) **Comparator 4**

	Vehicle gel - BID (53)
Outcomes	Assessments (23): baseline (5x), day 1 (5x), 15 (5x), 29 (5x), week 5, 6 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. 2 grade improvement on Clinician Erythema Assessment (CEA) and Patient Self Assessment (PSA)✴ 2. Inflammatory lesion counts and severity of telangiectasia (score 0 to 4, clear to severe)✴ 3. Investigator's Global Assessment (IGA) of the lesions (score 0 to 4, clear to severe)✴ **Secondary outcomes** 1. Adverse events, vital signs, intraocular pressure✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 633): "The two studies were funded by Galderma R&D"
Declaration of interest	Quote (page 633): "The investigators received grants for conducting the studies. YL and ML are employees of Galderma R&D"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 2 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 634): "Subjects were randomized in a 1:1:1:1:1 ratio to the groups" and "randomization lists were generated prior to study initiation by an independent statistician using SAS hoc Plan procedure (SAS Institute, Cary, NC, U.S.A.)." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 634): "The randomization lists were then sent to the clinical supply group, and only the personnel directly involved with labelling and packaging had access." Comment: The report provides sufficient detail and reassurance that participants and

		investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 634): "The integrity of the blinding was ensured by packaging the topical gels in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication." The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	9/269 (3.3%); BT 0.18% QD (2), BT 0.18% BID (2), BT 0.5% (2), vehicle QD (2), vehicle BID (1), reasons reported. ITT analysis (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01174030). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	This is a phase II study, duration for this design adequate, groups treated equally. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Fowler 2013a

Methods	RCT, prospective, placebo-controlled, double-blind Date of study May 2011 to September 2011 Setting Multicentre in US and Canada
Participants	**Randomised:** 260 participants (mean age 48.8 years, 54 male, 206 female) **Inclusion criteria**

	• ≥ 18 years with with moderate to severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self Assessment (PSA) **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 6/260 (2.3%); brimonidine tartrate 0.5% gel group (2), vehicle gel group (4) • Adverse event; brimonidine tartrate 0.5% gel group (2), vehicle gel group (1) • Subject request; brimonidine tartrate 0.5% gel group (0), vehicle gel group (1) • Protocol violation; brimonidine tartrate 0.5% gel group (0), vehicle gel group (1) • Lost to follow-up; brimonidine tartrate 0.5% gel group (0), vehicle gel group (1) **Baseline data N (%)** CEA moderate; brimonidine tartrate 0.5% gel group 111 (86), vehicle gel group 113 (86.3) CEA severe; brimonidine tartrate 0.5% gel group 18 (14), vehicle gel group 18 (13.7) PSA mild; brimonidine tartrate 0.5% gel group 0 (0), vehicle gel group 1 (0.8) PSA moderate; brimonidine tartrate 0.5% gel group 107 (82.9), vehicle gel group 114 (87) PSA severe; brimonidine tartrate 0.5% gel group 22 (17.1), vehicle gel group 16 (12.2)
Interventions	Four weeks with four weeks follow up **Intervention** Brimonidine tartrate 0.5% gel - QD (129) **Comparator** Vehicle gel - QD (131) A wash-out period was mandatory for subjects receiving prescription medications for inflammatory conditions, rosacea, or acne (for most treatments 4 weeks, isotretinoin 6 months)
Outcomes	Assessments (6): baseline, day 1, 15, 29, week 6 and 8 **Outcomes of the trial** (as reported)

	Primary outcomes 1. 2 grade improvement on both CEA and PSA over 12 hours✴ 2. 1 grade improvement on both CEA and PSA over 12 hours✴ 3. Inflammatory lesion counts and severity of telangiectasia (score 0 to 4, clear to severe)✴ 4. Investigator's Global Assessment (IGA) of the lesions (score 0 to 4, clear to severe)✴ **Secondary outcomes** 1. 1-grade improvement from baseline on both CEA and PSA at 30 minutes on day 1✴ 2. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 656): "The two studies were funded by Galderma R&D"
Declaration of interest	Quote (page 656): "The investigators received grants for conducting the studies. Ms. Rudisill and Dr. Leoni are employees of Galderma R&D."
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 3 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 651): "Subjects were randomized in a 1:1 ratio to the groups of BT gel 0.5% and vehicle gel" and "Randomization lists were generated prior to study initiation by an independent statistician using SAS Proc Plan procedure" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 651): "The randomization lists were then sent to the clinical supply group, and only the personnel directly involved with labeling and packaging had access" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 651): "The integrity of the blinding was ensured by packaging the topical gels in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication." The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	6/260 (2.3%); brimonidine tartrate 0.5% gel group (2), vehicle gel group (4). ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01355458). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, groups treated equally. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Fowler 2013b

Methods	RCT, prospective, placebo-controlled, double-blind Date of study May 2011 to November 2011 Setting Multicentre in US and Canada
Participants	**Randomised:** 293 participants (mean age 47.5 years, 80 male, 213 female) **Inclusion criteria** • ≥ 18 years with with moderate to severe erythema according to both Clinician's Erythema Assessment (CEA) and Patient's Self Assessment (PSA)

	Ocular involvement: Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 10/293 (3.4%); brimonidine tartrate 0.5% gel group (7), vehicle gel group (3) • Adverse event; brimonidine tartrate 0.5% gel group (1), vehicle gel group (1) • Subject request; brimonidine tartrate 0.5% gel group (2), vehicle gel group (0) • Protocol violation; brimonidine tartrate 0.5% gel group (3), vehicle gel group (2) • Lost to follow-up; brimonidine tartrate 0.5% gel group (2), vehicle gel group (0) **Baseline data N (%)** CEA moderate; brimonidine tartrate 0.5% gel group 108 (73), vehicle gel group 115 (79.3) CEA severe; brimonidine tartrate 0.5% gel group 40 (27), vehicle gel group 30 (20.7) PSA mild; brimonidine tartrate 0.5% gel group 0 (0), vehicle gel group 2 (6.3) PSA moderate; brimonidine tartrate 0.5% gel group 129 (87.2), vehicle gel group 122 (84.1) PSA severe; brimonidine tartrate 0.5% gel group 19 (12.8), vehicle gel group 23 (15.9)
Interventions	Four weeks with four weeks follow-up **Intervention** Brimonidine tartrate 0.5% gel - QD (148) **Comparator** Vehicle gel - QD (145) A wash-out period was mandatory for subjects receiving prescription medications for inflammatory conditions, rosacea, or acne (for most treatments 4 weeks, isotretinoin 6 months)
Outcomes	Assessments (6): baseline, day 1, 15, 29, week 6 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. 2 grade improvement on both CEA and PSA over 12 hours✴

	2. 1 grade improvement on both CEA and PSA over 12 hours✴ 3. Inflammatory lesion counts and severity of telangiectasia (score 0 to 4, clear to severe)✴ 4. Investigator's Global Assessment (IGA) of the lesions (score 0 to 4, clear to severe)✴ **Secondary outcomes** 1. 1 grade improvement from baseline on both CEA and PSA at 30 minutes on day 1✴ 2. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 656): "The two studies were funded by Galderma R&D"
Declaration of interest	Quote (page 656): "The investigators received grants for conducting the studies. Ms. Rudisill and Dr. Leoni are employees of Galderma R&D."
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 3 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 651): "Subjects were randomized in a 1:1 ratio to the groups of BT gel 0.5% and vehicle gel" and "Randomization lists were generated prior to study initiation by an independent statistician using SAS Proc Plan procedure" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 651): "The randomization lists were then sent to the clinical supply group, and only the personnel directly involved with labeling and packaging had access" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 651): "The integrity of the blinding was ensured by packaging the topical gels in identical tubes and requiring a third party other than the investigator/evaluator to dispense the medication."

		Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	10/293 (3.4%); brimonidine tartrate 0.5% gel group (7), vehicle gel group (3). Reasons not reported. ITT analysis. Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01355471). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, groups treated equally. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Gollnick 2010

Methods	RCT, prospective, active- and placebo-control, double-blind Date of study Unreported Setting Multicentre (35) in Germany
Participants	**Randomised:** 573 participants (mean age 53.3 years (SD 14.0), 259 male, 290 female, 24 gender unreported) **Inclusion criteria** • Rosacea subtype II and III (at least 8 inflammatory lesions and a Physician's Global Assessment score of at least 4 (on a score 0 to 8) and the disease had to be present at least for three months prior to study entry) • For women of childbearing age an additional prerequisite was a negative pregnancy test within the first three days of the present menstrual cycle that they had used hormonal contraception during the last cycle

	before the start of the study and that they were willing to continue this and use a barrier method during the entire study duration until at least 35 days after the last treatment **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 72/573 (12.6%); isotretinoin 0.1 mg/kg (10/111), isotretinoin 0.3 mg/kg (18/147), isotretinoin 0.5 mg/kg (16/116), doxycycline (20/152), placebo (8/47) • Treatment duration < 27 days and 1 had a chronic disease affecting absorption and metabolization of the drug 24/573; isotretinoin 0.1 mg/kg (2/111), isotretinoin 0.3 mg/kg (5/147), isotretinoin 0.5 mg/kg (7/116), doxycycline (9/152), placebo (1/47) • Major protocol violation 48/573; isotretinoin 0.1 mg/kg (8/111), isotretinoin 0.3 mg/kg (13/147), isotretinoin 0.5 mg/kg (9/116), doxycycline (11/152), placebo (7/47) **Baseline data median** Number of inflammatory lesions; isotretinoin 0.1 group 17, isotretinoin 0.3 group 18, isotretinoin 0.5 group 16, doxy 18, placebo 19 Physician's Global Assessment; all groups 5
Interventions	12 weeks **Intervention** Isotretinoin 0.1 mg/kg daily (111) **Comparator 1** Isotretinoin 0.3 mg/kg daily (147) **Comparator 2** Isotretinoin 0.5 mg/kg daily (116) **Comparator 3** Doxycycline 100 mg for 14 days and then 50 mg daily (152) **Comparator 4**

	Placebo daily (47)
Outcomes	Assessments (5): baseline, week 2, 4, 6, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in pustules and papules or noduli at end of study✴ **Secondary outcomes** 1. Reduction in number of pustules and papules or noduli at each control visit✴ 2. Changes in severity grades of the individual signs and symptoms of rosacea (erythema, oedema, telangiectases, seborrhoea and rhinophyma (no, mild, moderate, severe)✴ 3. Total improvement physician assessed (complete remission, marked, moderate or slight improvement, no change, worsening)✴ 4. Total improvement participant assessed (excellent, good or moderate improvement, no change, worsening)✴ 5. Safety (laboratory values, tolerance, adverse events)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 514): "The study was supported by Almirall Hermal GmbH"
Declaration of interest	Quote (page 514): "Professor Gollnick received lecturer fees for the subject rosacea from various firms: Almirall Hermal GmbH, Galderma, Schering/Intendis"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 74 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 506): "were allocated to 5 different treatment groups in a randomized and blinded manner" and "For random assignment to the different treatment groups patients were stratified according to weight (50–70, 71–90, 91–110 and 111–130 kg). After a request by fax through the treating physician a

		central stratified randomization and mailing of the medication occurred." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Form of central allocation, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 506): "The study medications were blinded according to § 10 of the German Drug Law (Arzneimittelgesetz, AMG) and provided by Almirall Hermal GmbH, Reinbek, Germany. Isotretinoin was employed as capsules with 10 mg isotretinoin and doxycycline as tablets with 50 mg doxycycline each. Due to the double dummy study design each patients had to take both isotretinoin/placebo capsules or doxycycline/placebo tablets." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	72/573 (12.6%); Isotretinoin 0.1 mg/kg (10/111), Isotretinoin 0.3 mg/kg (18/147), Isotretinoin 0.5 mg/kg (16/116), doxycycline (20/152), placebo (8/47). reasons reported, Per-protocol analysis Comment: Low and balanced number of dropouts and although per-protocol analysis judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on https://www.clinicaltrialsregister.eu/ctr-search/search as EudraCT-Nr 2006-002410-35. The pre-specified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, groups treated equally. However, cohorts, and flow diagram are rather unclear. Study supported by Almirall Hermal GmbH and the Principal Investigator received fees Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Grosshans 1997

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Clinique Dermatologique des Hospiteaux Universitaires de Strasbourg, France
Participants	**Randomised:** 34 participants (mean age 44 years (SD 13) in treatment group versus 49 years (14) in control group, 6 male, 28 female) **Inclusion criteria** • Participants with papulopustular rosacea with erythema, telangiectasia, and flushing **Ocular involvement:** Unclear **Exclusion criteria** • Keratitis • Steroid rosacea • Participants with orthostatic hypotension or on antihypertensive drugs • Pregnant and nursing females • Serious renal and hepatic failure • Participants treated for depression **Dropouts and withdrawals** • 1/34 (14.7%); rilmenidine group (2) and placebo group (3) • Reasons for dropouts in rilmenidine group; dysarthria (1), "bad observation" (1) • Reasons for dropouts in placebo group; nausea (1), taking prohibited medication (1), urinary tract infection (1) **Baseline data mean (SD)** Nothing reported
Interventions	Four months **Intervention** Rilmenidine 1 mg - QD (15) **Comparator** Placebo tablets (19)
Outcomes	Assessments (3): baseline, week 6 and 12 **Outcomes of the trial** (as reported)

	Primary outcomes 1. N of participants with a decrease of at least 50% in lesion count✶ 2. Decrease in lesion count and erythema✶ 3. Physician's global investigation✶ **Secondary outcomes** 1. Variation in number of flushes 2. Self-assessed changes in rosacea severity✶ 3. Variation redness of the face ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) Males tend to have more severe rosacea and all the males were in the control group See comparison 78 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 688): "Il' s' aggisait d'un essai randomisé en double insu." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 687): "....en double insu." [translated as 'double-blind'] Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of

		which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 687): "....en double insu." [translated as 'double-blind'] Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	5/34 (14.7%); rilmenidine group (2) and placebo group (3). ITT analysis. All participants appear to have been accounted for (pages 688, 689) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out period long enough before the study, no concomitant therapy for rosacea was allowed, additional medication recorded, sponsorship or support not reported Comment: We judged this as at a low risk of bias

Guillet 1999

Methods	RCT, prospective, active-controlled, investigator-masked Date of study Unreported Setting Multicentre, 9 centres in Europe (France, Ireland, Spain, and Belgium)
Participants	**Randomised:** 114 participants (age 22 to 82 years, gender unreported) **Inclusion criteria** • Participants with moderate to severe rosacea, defined as at least presence of 6 inflammatory lesions on the face, moderate erythema, and presence of telangiectasia **Ocular involvement:** Unclear **Exclusion criteria**

	• None reported **Dropouts/Withdrawals:** Unclear **Baseline data mean (SD)** Nothing reported
Interventions	12 weeks **Intervention** Metronidazole 0.75% gel (57) **Comparator** Metronidazole 0.75% lotion - application frequency unclear (57)
Outcomes	Assessments (2): baseline, week 12, and maybe more **Outcomes of the trial** (as reported) **Primary outcomes** 1. Compare efficacy and safety between 2 formulations✶ 2. Reduction in inflammatory lesion count✶ 3. Physician's global evaluation✶ **Secondary outcomes** 1. Tolerance 2. Cosmetic acceptability ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	A poster of an old study, much information is either poorly reported or missing, e.g. number of dropouts None of our primary outcomes were addressed (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page S145): "The randomised, investigator-blinded study lasted twelve weeks." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page S145): "...investigator masked." The report did not clarify what measures were used to blind study participants and personnel from knowledge of which intervention a participant received Comment: Insufficient information to make a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page S145): "...investigator masked." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Comment: Inadequate reporting of rates of attrition and exclusions to permit clear judgement of (e.g. number randomised not stated, no reasons for missing data provided)
Selective reporting (reporting bias)	Unclear risk	Methods section not specific about which outcomes were being sought Quote (page S145): "To compare the efficacy and safety as well as the cosmetic acceptability?" Comment: Insufficient information to permit a clear judgement
Other bias	Unclear risk	Study duration adequate, wash-out phase before study started adequate, groups treated equally, no information about sponsorship or support. Inadequate detail about the baseline characteristics of the participants, the interventions delivered, and methods of standardisation of outcomes assessment across the 9 international centres Comment: Insufficient information to assess whether important risk of bias exists

Han 2014

Methods	RCT, prospective, active-controlled, open, within-patient comparison Date of study Unreported Setting Department of Dermatology, Keimyung University School of Medicine, Korea

Participants	**Randomised:** 25 participants (mean age 45.5 years, 9 male, 16 female) **Inclusion criteria** • Participants with erythematotelangiectatic rosacea, facial flushing, telangiectasia, nevus flammeus, hypertrophic scar **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts/Withdrawals:** Unclear **Baseline data mean (SD)** Nothing reported
Interventions	1- 24 weeks **Intervention** Pulsed Dye laser 1 to 6 treatments **Comparator** Diode laser (IRIS 532 nm) 1 to 6 treatments
Outcomes	Assessments (2): baseline, end of treatment **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean change in mexameter scores 2. 7-point telangiectasia grading system 3. Investigator's and patients' clinical assessments✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	A poster abstract, no reporting of data One of our primary outcomes was addressed (participant-assessed changes in rosacea severity). No separate data for rosacea (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 105): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding. Outcomes were investigator- and participant assessed Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	No details provided Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Heitz 2014

Methods	RCT, prospective, active-controlled Date of study Unreported Setting Nouvel hopital civil de Strasbourg, France
Participants	**Randomised:** 95 participants (age and gender unreported) **Inclusion criteria** • Moderate to severe Meibomian gland dysfunction with or without rosacea

	Ocular involvement: Yes **Exclusion criteria:** • None reported **Dropouts/Withdrawals:** Unclear, 7% non compliant in both groups **Baseline data mean (SD)** Nothing reported
Interventions	Three months **Intervention** Azithromycin 500 mg three times a week tapered (49) **Comparator** Doxycycline 100 mg -QD (46)
Outcomes	Assessments (2): baseline and 3 months **Outcomes of the trial** (as reported) **Primary outcomes** 1. Palpebral signs and dermatologic signs of rosacea✶ **Secondary outcomes** 1. Quality of life✶ 2. Tear Break Up Time 3. Corneal staining 4. Tolerance 5. Compliance ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 1481): "Support None"
Declaration of interest	Quote (page 1481): "Commercial Relationships Antoine Heitz, None; Sauer Arnaud, None; Carine Merklen, None; Bernard Cribier, None; Claude Speeg-Schatz, None; Tristan Bourcier, None"
Notes	One of our primary outcomes was addressed (quality of life). A poster abstract, no reporting of precise data (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 1481): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding. Outcomes were investigator- and participant assessed Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	No details provided, 7% in both groups were not compliant Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided, no exact data Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Huang 2012

Methods	RCT, prospective, active-controlled Date of study Unreported Setting Department of Dermatology, the People's Hospital, Zhengzhou, China
Participants	**Randomised:** 60 participants (range 21 to 52 years, mean age 31.63 years (SD 9.16), 36 male, 24 female) **Inclusion criteria** • Rosacea with skin burning, itching, pain or swelling • Erythema, telangiectasia, papules and pustules

	Ocular involvement: Unclear **Exclusion criteria** • Seborrhoeic dermatitis • Steroid dependent dermatosis • Allergy to tacrolimus • Glucocorticosteroids or tetracyclines < 1 week prior to study entry • Severe heart, liver or kidney disease **Dropouts/Withdrawals:** None **Baseline data mean** Nothing reported
Interventions	Three months **Intervention** Tacrolimus ointment - BID (30) **Comparator** Tacrolimus ointment - BID + 2 treatments with pulsed dye laser (30)
Outcomes	Assessments (3): baseline, week 4 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Pruritus (0 = none, 3 = severe) 2. Erythema, telangiectasia, papules, pustules (0 = none, 3 = severe)✴ 3. Involved area (mild, moderate, severe) 4. Effective rate (sum of scores before treatment - sum of scores after treatment)/sum of scores before treatment; cure (effective rate ≥ 90%), very effective (effective rate 60% to 89%), effective (effective rate 20% to 59%), not effective (effective rate < 20%)✴ **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	Translated from Chinese, see Acknowledgements. One of primary outcomes was assessed (adverse events)

	See comparison 89 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 308): "divided randomly into two groups" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding reported and no sham laser treatment Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding reported and no sham laser treatment. Investigator and participant assessed outcomes Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up reported Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, wash-out period before study started too short Comment: Insufficient information to assess whether important risk of bias exists

Huang 2014

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported

	Setting Multicentre US
Participants	**Randomised:** 170 participants (age and gender unreported) **Inclusion criteria** • 18 to 70 years with papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** Not reported **Baseline data mean** Nothing reported
Interventions	12 weeks **Intervention** Doxycycline 40 mg - QD **Comparator** Placebo - QD Unclear how many were randomised to each group
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Efficacy (Investigator's Global Assessment)✴ 2. Lesion count✴ 3. Safety (adverse events)✴ 4. Biomarker levels, such as MMP9, KLK5, cathelicidin, and total proteases (skin tape strips and 2 mm skin biopsies) **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page AB9): "Funded by Galderma Laboratories LP"
Declaration of interest	None declared. Several investigators are employed by Galderma Laboratories LP
Notes	One of our primary outcomes was addressed (adverse events) Limited data from poster abstract (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page AB9): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page AB9): "double-blind" Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page AB9): "double-blind" Comment: Outcomes were investigator and participant assessed. Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Poster abstract, with limited information Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided. Pubished as protocol NCT01308619 in clinicaltrials.gov Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Jackson 2013

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Two centres in US

Participants	**Randomised:** 60 participants (age and gender unreported) **Inclusion criteria** • ≥ 18 years with rosacea (10 to 40 papules and pustules, ≤ 2 nodules) • Investigator's Global Assessment score 2 to 4 • Score ≥ 2 on Clinical Erythema Assessment scale • Females of childbearing potential must use 2 methods of birth control throughout study • Negative pregnancy test and non-lactating **Ocular involvement:** Unclear **Exclusion criteria** • Start OAC within 3 months prior to study entry, discontinuation during study or change of OAC during study • Systemic antibiotics < 4 weeks prior to study entry • Systemic investigational drug < 4 weeks or topical investigational drug < 2 weeks prior to study entry • Pregnant women, or women of childbearing potential that don't use adequate birth control • Known hypersensitivity for tetracyclines • Concomitant drug therapy that could interfere with assessments • Use of any rosacea treatment • Topical steroids in the face < 4 weeks prior to study entry • Gastric bypass surgery or are considered achlorhydric • Diseases with known photosensitivity • Use of known photosensitising drugs • Use of tanning bed **Dropouts and withdrawals** • 5/60 (8.3%); all in minocycline + azelaic acid group (upset stomach and urticaria (2), bilateral oophorectomy with dermoid cyst removal (1), gastric erosion after lap band surgery (1), a severe respiratory infection, and cholecystitis (1) **Baseline data mean (SD)** Total lesion count: minocycline 15 (7), minocycline + azelaic acid 15 (5) IGA: minocycline 3 (1), minocycline + azelaic acid 3 (1) CEA: minocycline 9 (2), minocycline + azelaic acid 9 (3)
Interventions	12 weeks with four week follow up **Intervention**

	Minocycline 45 mg - QD (30) **Comparator** Minocycline 45 mg + azelaic acid 15% - QD (30)
Outcomes	Assessments (5): baseline, week 4, 8, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (0 = clear, 5 = very severe)✴ 2. Clinical Erythema Assessment (0 = none, 4 = severe fiery redness)✴ 3. Lesion count✴ 4. Adverse events✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 298): "Funding for the study was provided by Medicis"
Declaration of interest	Quote (page 298): "Dr Jackson has served as a speaker, consultant, and investigator for Medicis"
Notes	One of our primary outcomes was addressed (adverse events) See comparison 69 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 294/295): "Treatment was randomly allocated in blocks of 2. Blocks were centrally assigned to investigators as needed and based on enrollment" "The randomization process assigned equal numbers of patients to each treatment group." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 294): "Treatment was randomly allocated in blocks of 2. Blocks were centrally assigned to investigators as needed and based on enrollment"

		Comment: Form of central allocation, probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 295): "Blinded study medication was identified using the patient randomization number" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 295): "Blinded study medication was identified using the patient randomization number" Comment: Outcomes were investigator and participant assessed Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	5/60 (8.3%); all in minocycline + azelaic acid group, reasons reported Comment: Low number of dropouts and ITT analysis (LOCF) judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out before the study started adequate, no concomitant therapy for rosacea was allowed Comment: We judged this as at low risk of bias

Jaque 2012

Methods	RCT, prospective, placebo-controlled, double-blind Date of study September to December 2011 Setting Dermatology Department of Pontificia Catholic University, Santiago, Chile
Participants	**Randomised:** 67 participants (mean age 39 years, 9 male, 58 female) **Inclusion criteria** • 18 years with erythematotelangiectatic rosacea (persistent centrofacial erythema and flushing >10 min) **Ocular involvement:** Unclear **Exclusion criteria**

	• Pregnant and lactating women • > 5 inflammatory lesions and/or > 1 nodule • Topical or oral treatment for rosacea or acne in the previous 12 weeks before enrolment • Laser treatment in the previous six months before enrolment • Use of systemic corticosteroids in the previous 12 months • Use of beta blockers in the previous 12 months **Dropouts and withdrawals** • 6/67 (9.0%); timolol group (3), placebo group (3) • Lost to follow-up; timolol group (2), placebo group (3) • Discontinued treatment; timolol group (1), placebo group (0) **Baseline data mean** Erythema; timolol group 17.77, placebo group 17.85
Interventions	12 weeks **Intervention** Topical timolol 1% in oil free base - QD (34) **Comparator** Placebo - oil free base - QD (33) Both groups received a cleanser, hydrating cream and sunscreen
Outcomes	Assessments (3): baseline, week 6 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in erythema (Minolta CR 200)✴ **Secondary outcomes** 1. Improvement in clinical signs✴ 2. Change in size of telangiectasia 3. Quality of life (DLQI)✴ 4. Subject's own assessment (VAS)✴ 5. Treatment adherence 6. Adverse events✴ ✴Denotes outcomes pre-specified for this review

Funding source	None reported
Declaration of interest	Quote (page 421-22): "Los preparados magistrales y los limpiadores, hidratantes y protectores solares fueron donados por el laboratorio Dispolab y el timolol y crema base oil free por Recetario Magistral de Farmacia Ahumada, ambas entidades no participan de la investigación" (the medication, cleansers and hydrating creams were provided by two different labs/pharmacies not participating in the study)
Notes	All our primary outcomes were addressed See comparison 52 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 420): "Se utilizó una tabla de randomización del sistema Excel 2010 que asignó los pacientes a dos grupos según orden de llegada al estudio" (excel random number generator) Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 420): "El enrolamiento estuvo a cargo de un investigador ciego a tratamiento. La asignación de los pacientes a la intervención fue hecha por la enfermera del Departamento de Dermatología siguiendo los códigos de la secuencia y de los frascos" (assignment by a nurse pf the dermatology department blind to treatment folllowing the numbers on the bottles) Comment: Form of central allocation. The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 420): "Tanto el timolol en base oil free como el placebo (base oil free) fueron idénticos en tamaño (30 g), textura, color y olor. Fueron entregados en un mismo pote con una etiqueta que tenía escrito el número del participante (del 1 al 60) sin especificar a qué tratamiento correspondía" (both treatments in similar boxes, similar texture, colour and smell" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	6/67 (9.0%); timolol group (3), placebo group (3) Comment: Low and balanced number of drop-outs. We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out before the study started adequate, no concomitant therapy for rosacea was allowed Comment: We judged this as at low risk of bias

Jorizzo 1998

Methods	RCT, prospective, placebo-controlled and active-controlled (4 treatment arms), double-blind Date of study Unreported Setting Multicentre, Department of Dermatology, Bowman Gray School of Medicine, Wake Forest University, Winston Salem; Department of Dermatology, Mount Sinai Medical School, New York, US
Participants	**Randomised:** 277 participants (age and gender unreported) **Inclusion criteria** • Participants with with a minimum stage II rosacea score as defined by the Plewig and Kligman classification system (i.e. persistent erythema, numerous papules, pustules, and telangiectases) **Ocular involvement:** Unclear **Exclusion criteria** • No topical anti-acne, retinoid, or corticosteroid drugs were allowed within 2 weeks of study entry; nor any systemic antibiotics, anti-acne medication, or corticosteroids within 4 weeks of study entry **Dropouts and withdrawals:** Unclear **Baseline data mean (SD)** Nothing reported
Interventions	10 weeks

	Intervention Metronidazole 1% - QD **Comparator 1** Metronidazole 1% - BID **Comparator 2** Placebo (vehicle) - QD **Comparator 3** Placebo - BID Unclear how many participants started in each group
Outcomes	Assessments (5): baseline, week 2, 4, 7 and 10 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Decrease in N of lesions✴ 2. Assessment of erythema (0 = none, 3 = severe)✴ 3. Physician's global evaluation (0 = none, 3 = severe)✴ **Secondary outcomes** 1. Safety✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 502): "Supported by Dermik Laboratories, Inc., 500 Arcola Rd, Collegeville, PA 19426."
Declaration of interest	Quote (page 502): "Dr Tobey formerly was formerly Vice President of Research and Development, Dermik Laboratories, Inc."
Notes	One of our primary outcomes was addressed (adverse events) Unclear how many participants started in each group (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 502) : ".... randomized, double-blind, multicenter trial." Comment: Insufficient detail was reported about the method used to generate the allocation

		sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 502): "Patients were blinded as to treatment, and evaluators were blinded as to treatment and application regimen." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 502): "Patients were blinded as to treatment, and evaluators were blinded as to treatment and application regimen." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No dropouts reported. ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	High risk	Unclear how many participants were in each intervention group. Withdrawals were unreported Comment: We judged this as at a high risk of bias
Other bias	Unclear risk	Study duration adequate, wash-out period prior to study entry adequate. Study was supported by Dermik Laboratories, Inc, 500 Arcola Rd, Collegeville, PA 19426. One co-investigator was formerly vice-president of research and development, Dermik Laboratories Comment: Realistic and potential risk of bias

Karsai 2008

Methods	RCT, prospective, active-controlled, double-blind, within-patient comparison Date of study Participants were recruited from September to November 2006 Setting Laserklinik Karlsruhe, Karlsruhe, Germany

Participants	**Randomised:** 20 participants (mean age 62 years (SD 12.3, range 37 to 81 years), 14 male, 6 female) **Inclusion criteria** • Participants with nasal alar telangiectasia with similar vessel densities on both sides, vessel size < 0.6 mm **Ocular involvement:** Unclear **Exclusion criteria:** • Hypersensitivity to light • Medication that is known to increase sensitivity to sunlight • Medication that alters wound healing process • Seizure disorders triggered by light, pregnancy • Gold therapy • Suspicious pigmented lesions • Unprotected sun exposure within 4 weeks of treatment **Dropouts and withdrawals:** None **Baseline data mean (SD)** Nothing reported
Interventions	One treatment **Intervention** 959 nm pulsed dye laser (PDL) + 1064 Nd:YAG laser (sequential application) **Comparator 1** 959 nm PDL **Comparator 2** 1064 Nd:YAG If no effect, treatment was repeated up to 3 times in same session Evaluation after 4 weeks
Outcomes	Assessments (2): baseline and week 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Improvement assessed by review of standardised photographs by three investigators blinded with respect to treatment modality (Grade 1 = clearance of less than 10% of vessels, grade 2 = clearance of 10% to 50% of the vessels, grade 3 = clearance of 51% to 90% of the

	vessels, and grade 4 = clearance of > 90% of the vessels)✴ **Secondary outcomes** 1. Participants were asked about symptoms or side effects✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 702): "The authors have indicated no significant interest with commercial supporters"
Notes	One of our primary outcomes was addressed (adverse events) See comparison 84 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 703): "Patients were randomized to receive one of four treatment regimens." "Twenty patients were studied using the sequence delivery of PDL and NdYAG wavelets combined on one side of their nose This could be right or left side. The other side received either PDL, or NdYAG." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 704): "blinded assessment of photographs taken before and after final evaluation". Investigators were blinded with respect to treatment modality, it is unclear if participants knew what treatment they were receiving on each side of the nose. Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	There were no dropouts reported. Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias.
Other bias	High risk	The investigator used a Chi^2 statistic on cell values less than 5, invalidating the analysis Also, reports "possible confounding with ages that was not accounted for" Comment: We judged this as at a high risk of bias

Kendall 2014

Methods	RCT, prospective, active-controlled, double-blind, cross-over Date of study Unreported Setting Multicentre US
Participants	**Randomised:** 70 participants (age and gender unreported) **Inclusion criteria** • Moderate to severe erythema of rosacea • Wash-out period, unclear how long **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** 2/70 (2.9%) in brimonidine group; adverse event (1) and protocol deviation (1) **Baseline data mean** Nothing reported
Interventions	15 days **Intervention** Brimonidine tartrate 0.5% gel - QD (35) **Comparator**

	Azelaic acid 15% gel - BID (35) Wash-out period (unspecified) and cross-over
Outcomes	Assessments (2): baseline and day 15 **Outcomes of the trial** (as reported) **Primary outcomes** 1. 2 grade improvement in both the Clinician's Erythema Assessment (CEA) and Patient Self Assessment (PSA) 6 hours after application on day 15 (scale 0 to 4, higher indicating worse)✴ **Secondary outcomes** 1. 2 grade improvement in CEA and PSA and changes in chromameter readings 6 hours after application on day 15✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared, investigators employed by Galderma Laboratories, L.P., Fort Worth, TX
Notes	Poster, limited data Quote: "The results of the second period were discarded as there was significant treatment carryover from the first period" One of our primary outcomes was addressed (participants-assessed changes in rosacea severity (PSA)) See comparison 23 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page A182): "Subjects were randomized 1:1 to.." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement

Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page A181): "double-masked" Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page A181): "double-masked". Investigator and participant assessed outcomes Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	2/70 (2.9%) in brimonidine group; adverse event (1) and protocol deviation (1). Poster abstract, limited information Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available on clinicaltrials.gov (NCT01659853). Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data. Comment: There was insufficient information to permit a clear judgement

Kim 2011

Methods	RCT, prospective, active-controlled, open label, within-patient comparison Date of study August 2009 to March 2010 Setting Department of Dermatology and Cutaneous Biology Research Institute, Yonsei University College of Medicine, Seoul, Korea
Participants	**Randomised:** 18 participants (mean age 31.1 years, 5 male, 13 female) **Inclusion criteria** • Rosacea subtype I and II **Ocular involvement:** Unclear **Exclusion criteria** • Age under 20 years • Previous treatment with laser or light-based devices for rosacea • Known photodermatoses or photosensitivity

	• Current use of known photosensitising pharmaceuticals • Known allergy to niacin • Pregnancy • Topical treatments with corticosteroids, metronidazole or calcineurin inhibitors during the prior 2 weeks • Systemic treatments with corticosteroids or antibiotics (tetracycline, doxycycline or minocycline) during the prior 2 months. **Dropouts and withdrawals** • 3/18 (16.6%); due to difficulty in attending follow-up because of distance **Baseline data mean** Nothing reported
Interventions	Three treatments at three weekly intervals **Intervention** Pulsed dye laser + pretreatment of niacin cream 20 min before laser **Comparator** Pulsed dye laser
Outcomes	Assessments (5), baseline, week 3, 6, 9 and 15 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Improvement in rosacea-associated erythema at 6 weeks (polarization colour imaging system (Dermavision; OptoBioMed Co., Kangwon, Korea, scale from 100 to 1000)✴ **Secondary outcomes** 1. Clinical improvement of the erythema at six weeks after the last treatment compared with the initial erythema based on the blinded investigators' and patients' own evaluations (0, ≤ 25% improvement (poor); 1, 26% to 50% improvement (fair); 2, 51% to 75% improvement (good); 3, 76% to 100% improvement (excellent))✴ 2. Participants' overall rate of satisfaction (VAS) (0 = lowest and 10 highest)✴ 3. Adverse events✴ ✴Denotes outcomes pre-specified for this review

Funding source	None reported
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 90 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 575): "According to a computer-generated randomization, each cheek was randomly assigned to.." Comment: Probably done
Allocation concealment (selection bias)	High risk	Quote (page 575): "The randomization schedule was not concealed from physicians who carried out the treatment" Comment: We judged this as at a high risk of bias
Blinding of participants and personnel (performance bias)	High risk	Quote (page 574): "randomized, open, split-face.." Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 574): randomized, open, split-face.." and "Photographs were taken by the same blinded physician at baseline".. "on the blinded investigators' and patients' own evaluation. Three blinded dermatologists assessed.." Comment: These statements are contradictory. Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	3/18 (16.6%); due to difficulty in attending follow-up because of distance. Per-protocol analysis Comment: The moderate dropout rate with per-protocol analysis represents a potential risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias

Other bias	Low risk	Pre-study wash-out period adequate, study duration adequate Comment: The study appeared to be free of other forms of bias

Kim 2017

Methods	RCT, prospective, active-controlled, single-blinded, within-patient comparison Date of study Unreported Setting Department of Dermatology, School of Medicine, Chungnam National University, Daejeon, Korea
Participants	**Randomised:** 30 participants (mean age 43.4 years (range 35 to 69 years), 11 male, 19 female) **Inclusion criteria** • Erythematotelangiectatic rosacea and papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • Any previous treatment with topical ointment, oral medications, or laser treatment in the previous 2 months • History of inserting filler into the face or a metal device into the body • Pregnancy or lactation in women **Dropouts and withdrawals:** Not reported **Baseline data mean** Rosacea severity score; radiofrequency group 13.9, pulsed dye laser group 13.8
Interventions	Three treatments at four weekly intervals **Intervention** Radiofrequency **Comparator** Pulsed dye laser (595 nm)
Outcomes	Assessments (3), baseline, week 4, 8, and 12 **Outcomes of the trial** (as reported) **Primary outcomes**

	1. Rosacea severity score (National Rosacea Society Expert Committee's guidelines, Wilkin 2004)✴ 2. Erythema index (Minolta CR-400 chromameter)✴ 3. Physician's assessment ("poor" (0%–25% improvement), "fair" (26%–50% improvement), "good" (51%–75% improvement), or "excellent" (76%–100% improvement))✴ 4. Subjective evaluation (very satisfied, satisfied, slightly satisfied, or dissatisfied)✴ **Secondary outcomes** 1. Adverse events and pain scores (10-cm visual analogue scales (VASs) ranging from 0 (no pain) to 10 (extremely painful)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 204): "Supported by a grant of the Korea Healthcare Technology R&D Project, Ministry of Health & Welfare, Republic of Korea (Grant No. HI14C1379)"
Declaration of interest	Quote (page 204): "The authors have indicated no significant interest with commercial supporters"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 92 in Effects of interventions The 595-nm PDL (V-beam Perfecta; Candela, Boston, MA) treatment was performed with a 7-mm spot, a fluence ranging from 8 to 9 J/cm2, a pulse duration of 6 milliseconds, and a dynamic cooling device setting of a 30-millisecond spurt delivered 30 milliseconds before the laser pulse. The monopolar RF (Davinci Doubles; Daiwha, Seoul, Korea) treatment was delivered with a 2-cm2 tip at a fluence of 80 to 120 J/cm2, with contact cooling using electric diode set at 3ºC

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 205): "randomized" and "The laterality of treatment was randomly allocated" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 205): "single-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No drop-outs reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Pre-study wash-out period adequate, study duration adequate Comment: The study appeared to be free of other forms of bias

Kircik 2018

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study May to December 2014 Setting Multicentre (20) in US
Participants	**Randomised:** 440 participants (mean age 50 years, 93 male, 347 female) **Inclusion criteria** • ≥ 18 years of age with a diagnosis of moderate to severe persistent facial erythema associated with rosacea, defined as grade 3 or higher on both the CEA scale with photonumeric guide and the Subject Self-

	Assessment for rosacea facial redness (SSA) scale with photo guide **Ocular involvement:** Unclear **<u>Exclusion criteria</u>** • > 3 inflammatory lesions on the face • Facial hair, tattoos, or other characteristics that would interfere with erythema assessments • Other dermatologic conditions within the treatment area • Uncontrolled systemic disease • Raynaud syndrome • Narrow-angle glaucoma • Orthostatic hypotension • Cerebral or coronary insufficiency • Thromboangiitis obliterans • Scleroderma • Sjögren's syndrome • History of current or past drug or alcohol abuse • Severe, unstable, or uncontrolled cardiovascular disease • Known hypersensitivity to oxymetazoline • Current treatment with monoamine oxidase inhibitors or niacin (2500 mg/d) • Treatment with oxymetazoline-containing products, topical glucocorticosteroids applied to the face, systemic or nasal corticosteroids, or any product for the treatment of acne, rosacea, or facial redness in the past 14 days • Systemic antibiotics for rosacea in the past 28 days • Isotretinoin, laser light, or other energy-based therapy to the face in the past 180 days • Currentty receiving or with a history of receiving brimonidine **<u>Dropouts and withdrawals</u>** • 17/440 (3.9%); oxymetazoline group (12), vehicle group (5) • Adverse event; oxymetazoline group (4), vehicle group (1) • Lost to follow-up; oxymetazoline group (4), vehicle group (0) • Personal reasons; oxymetazoline group (4), vehicle group (4) **Baseline data (n)**

	Clinician's Erythema Assessment (CEA) 3: oxymetazoline group 194, vehicle group 191 Clinician's Erythema Assessment (CEA) 4: oxymetazoline group 28, vehicle group 27 Subject Self Assessment (SSA) 3: oxymetazoline group 206, vehicle group 194 Subject Self Assessment (SSA) 4: oxymetazoline group 16, vehicle group 24
Interventions	29 days **Intervention** Oxymetazoline hydrochloride cream 1% - QD (222) **Comparator** Vehicle cream - QD (218)
Outcomes	Assessments (3), baseline, day 15 and 29 (and 28-day posttreatment for worsening and rebound) **Outcomes of the trial** (as reported) **Primary outcomes** 1. 2-grade or greater decrease (improvement) from baseline on both CEA and SSA) **Secondary outcomes** 1. At least a 2-grade decrease (improvement) from baseline on the individual components, CEA and SSA (scale 0 to 4, higher is worse)✴ 2. Percent change from baseline in facial erythema assessed using digital image analysis of photographs (Canfield Scientific, Inc, Fairfield, NJ) 3. Safety and tolerability✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 104): "Funding Disclosures: This study was sponsored by Allergan plc, Dublin, Ireland. Writing and editorial assistance was provided to the authors by Peloton Advantage, Parsippany, NJ, and was funded by Allergan plc. Neither honoraria nor other form of payments were made for authorship
Declaration of interest	Quote (page 104): "LH Kircik, J DuBois, ZD Draelos, P Werschler, K Grande, and FE Cook-Bolden are investigators for Allergan plc. E Weng, DR Berk, and G Ahluwalia are employees of Allergan plc and may own stock/stock options in that company"

Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 5 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 98): "were randomly assigned". "Randomization took place using an interactive voice or web response system" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 98): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	17/440 (3.9%); oxymetazoline group (12), vehicle group (5) Comment: Low number of drop-outs. We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on www.clinicaltrials.gov (NCT02131636). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, wash-out period before study started adequate, groups treated equally All authors were investigators of employees for Allergan Comment: We judged this as at an unclear risk of bias

Koca 2010

Methods	RCT, prospective, active-controlled, open-label Date of study Unreported Setting Dermatology department, Zonguldak Karaelmas University, Turkey
Participants	**Randomised:** 49 participants (age 50.7 ± 9.1 years in metronidazole group versus 48.4 ± 9.4 years in pimecrolimus group, 16 male and 8 female in metronidazole group and 13 male and 12 female in pimecrolimus group) **Inclusion criteria** • Participants (at least 18 years of age) with papulopustular rosacea with at least 10 inflammatory lesions (papules and pustules) No ocular rosacea **Exclusion criteria** • Erythematotelangiectatic rosacea • Ocular rosacea • Concomitant dermatological disorders • Steroid-induced rosacea • Allergy to component of study medication • Medication that might interfere with course rosacea • Pregnancy or nursing **Dropouts and withdrawals:** 1 in pimecrolimus group (deterioration of disease) **Baseline data mean (SD)** Inflammatory lesions: metronidazole group 16.0 (4.6), pimecrolimus group 26.0 (14.4)
Interventions	12 weeks **Intervention** Metronidazole cream 1% - BID (24) **Comparator** Pimecrolimus cream 1% - BID (25)
Outcomes	Assessments (5): baseline, week 3, 6, 9 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in number of lesions✴

	2. Severity of rating of erythema and telangiectasia from baseline to last visit✴ **Secondary outcomes** 1. Change in inflammatory lesions count and in severity rating of erythema and telangiectasia from baseline to each of weeks 3, 6, 9. Erythema and telangiectasia scored on a 4-point scale (0 = none to 3 = severe)✴ 2. Physicians global evaluation (6-point scale, 1 = complete improvement, 2 = marked improvement (75% to 99% clearance), 3 = moderate improvement (50% to 74% clearance), 4 = insufficient improvement (< 50% clearance), 5 = no detectable improvement from baseline, and 6 = deterioration)✴ 3. Adverse events e.g. dryness, increased erythema, pruritus, stinging and burning)✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (adverse events) Conclusions do not reflect data reported, therefore the data could not be included in the meta-analysis See comparison 36 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "Patients were randomly assigned to receive either pimecrolimus 1% cream or metronidazole 1% cream twice daily for 12 weeks." "Randomization was carried out using random-number generation from standard tables." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and	High risk	Quote (251): "Open-label"

personnel (performance bias)		Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	Quote (251): "Open-label" Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	ITT analysis, all participants were accounted for. One lost to follow up in pimecrolimus group (deterioration of disease) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	High risk	Substantial baseline imbalance between groups: mean of inflammatory lesion count at baseline was higher in pimecrolimus group, 26.0 ± 11.7, versus 16.0 ± 4.6 in metronidazole group and disease duration was also longer in pimecrolimus group, 33.7 ± 33.4 months versus 16.8 ± 18.3 months in metronidazole group Study duration adequate, wash-out period before study adequate, groups treated equally, sponsorship or support and other potential conflicts of interest not reported Comment: Baseline imbalance may be a result of 'failed' randomisation. We judged this as at a high risk of bias

Koch 1999

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Dermatological Practice Kassel, Germany
Participants	**Randomised:** 30 participants (age unclear, 11 male, 19 female) **Inclusion criteria** • Participants with facial rosacea **Ocular involvement**: Unclear **Exclusion criteria:** • None reported

	Dropouts and withdrawals: Not stated **Baseline data mean (SD)** Nothing reported
Interventions	Six weeks **Intervention** Dark sulphonated shale oil 200 mg, 2 tablets TID - after 2 weeks, 2 tablets BID **Comparator** Placebo Unclear how many in each group
Outcomes	Assessments (3): baseline, week 3 and 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in inflammatory lesions✶ 2. Reduction in erythema✶ 3. Reduction of scaling 4. Investigator's Global Assessment (IGA)✶ **Secondary outcomes** 1. Tolerance 2. Side effects✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	Poster, very limited reporting of trial details and outcomes data One of our primary outcomes was addressed (adverse events) See comparison 79 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 143-4): "A double-blind, randomised, placebo controlled clinical study..." and "Patients randomly received either..."

		Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 143-4): "Double-blind" and "...coated tablets with 200 mg sodium salt of dark sulfonated shale oil, died substance per tablet, or optically identical coated tablets without any active ingredient." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 143-4): "Double-blind." and "...coated tablets with 200 mg sodium salt of dark sulfonated shale oil, died substance per tablet, or optically identical coated tablets without any active ingredient." Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	Poster with a lot of missing data Comment: Insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Quote (page 143): "To evaluate the efficacy and tolerance..." Primary and secondary outcomes unclear, difficult to judge if all outcomes were addressed. Subjective reporting of several outcomes unsupported by data Comment: Insufficient information to permit a clear judgement
Other bias	Unclear risk	Study duration adequate, wash-out period unclear, unclear if groups were treated equally, sponsorship, support unreported

		Comment: Inadequate trial details to enable a clear judgement

Koçak 2002

Methods	RCT, prospective, active- and placebo-controlled (3-armed study), double-blind Date of study 1999 to 2000 Setting Outpatient Clinic of Dermatology at Ankara Education and Research Hospital, Turkey
Participants	**Randomised:** 63 participants (mean age 51 years (range 20 to 80), 15 male, 48 female) **Inclusion criteria** • Participants with papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • No erythematotelangiectatic rosacea • Those who did not receive treatment for ocular rosacea • Use of oral coagulants • Fulminant rosacea **Dropouts and withdrawals:** 0 **Baseline data mean (SEM)** Erythema score; permethrin group 2.60 (0.48), metronidazole group 2.85 (0.36), placebo group 2.65 (0.48) Papules; permethrin group 6.04 (7.60), metronidazole group 8.00 (6.70), placebo group 4.85 (4.10) Pustules; permethrin group 2.30 (3.73), metronidazole group 4.90 (4.78), placebo group 2.60 (3.36) *Demodex folliculorum;* permethrin group 2.20 (1.04), metronidazole group 2.60 (0.74), placebo group 2.70 (0.80)
Interventions	Two months **Intervention** Permethrin 5% cream - BID (23) **Comparator 1** Metronidazole 0.75% gel - BID (20) **Comparator 2** Placebo (vehicle) - BID (20)

Outcomes	Assessments (5): baseline, day 15, 30, 45 and 60 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean difference in erythema (0 = none, 3 = severe), telangiectasia, oedema, and rhinophyma (0 = absent and 1 = present)✴ 2. Mean difference in number of papules, pustules, and *Demodex folliculorum*✴ **Secondary outcomes** 1. Side effects✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported. However, investigators thanked Glaxo-Wellcome, quote (page 269): "The authors thank Glaxo-Wellcome for their contributions to packaging the two drugs and the placebo in identical boxes."
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (adverse events) Data on number of papules, pustules and *Demodex folliculorum* were skewed See comparison 6, 18 and 19 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 266): "They were randomly assigned to three groups to receive permethrin (n = 23), metronidazole (n = 20) and placebo (n = 20)." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 266): "Patients were given permethrin 5% cream, metronidazole 0.75% gel, placebo cream in packages looking identical." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 266): "Patients were given permethrin 5% cream, metronidazole 0.75% gel, placebo cream in packages looking identical." Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	No withdrawals reported. ITT analysis Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Appears to have been in part sponsored by Glaxo Wellcome (page 269). Wash-out period unreported. Unclear if concomitant therapy that might influence rosacea was allowed Comment: Insufficient information to assess whether important risk of bias exists

Krishna 2015

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Three centres, US
Participants	**Randomised:** 60 participants (mean age 56 years (range 31 to 86), 9 male, 51 female) **Inclusion criteria** • >18 years of age with a clinical diagnosis of moderate to severe erythematotelangiectatic rosacea (at least 3 and a total score of 6–20 on the CEA scale of all five

	facial areas; telangiectasia (minimum score of 1 on the telangiectasia assessment scale); and no more than 5 facial inflammatory lesions (papules/pustules) • Women of childbearing potential (excluding women who were surgically sterilized or postmenopausal for at least 2 years) must have had a negative serum pregnancy test at screening, negative urine pregnancy test at baseline, and, if sexually active, must have agreed to use a reliable method of contraception **Ocular involvement:** Unclear **Exclusion criteria** • Systemic retinoids within 3 months of baseline • Systemic antibiotics or topical acne/rosacea treatments within 4 weeks of baseline • Systemic treatment for acne, including spironolactone • Use on the face of any of the following: topical steroids, topical retinoids, topical acne treatments including prescription and over-the-counter (OTC) preparations, topical anti-inflammatory agents, topical antibiotics, and topical imidazole antimycotics **Dropouts and withdrawals:** Not reported, but data seem to be missing for 3 patients in laropiprant group and 1 in placebo group **Baseline data mean (SD)** Clinician's Erythema Assessment (CEA) score; laropiprant group 10.2 (1.8), placebo group 10.0 (1.5) Patient Self Assessment (PSA) score; laropiprant group 42.4 (24.0), placebo group 36.8 (22.0)
Interventions	28 days **Intervention** Laropiprant 100 mg tablet - QD (30) **Comparator** Placebo tablet - QD (30)
Outcomes	Assessments (3): baseline, week 2 and 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in Clinician's Erythema Assessment (CEA) scale score from baseline (maximum score = 20)✴ **Secondary outcomes**

	1. Change in Patient Self Assessment (PSA) score from baseline✴ 2. Rosacea symptom questionnaire 3. Clinical laboratory tests for hematology, blood chemistry, and urinalysis and ECGs 4. Telangiectasia Asssessment 5. Lesion count✴ 6. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 142): "This study was funded by Merck & Co., Inc"
Declaration of interest	Quote (page 142): "Authors who are employees of Merck & Co., Inc. may hold stock or stock options in the company" The first three authors are employees of Merck & Co
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 83 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 138): "randomly assigned" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 138): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement

Incomplete outcome data (attrition bias)	Low risk	No drop-outs reported, but data seem to be missing for 3 patients in laropiprant group and 1 in placebo group
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was available on clinicaltrials.gov (NCT01451619) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported except for lesion count. This was one of our prespecified outcomes but the study was conducted in patients with erythematotelangiectatic rosacea with only very few inflammatory lesions Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Kuang 2018

Methods	RCT, prospective, active- and placebo-controlled, double-blind Date of study December 2012 to June 2013 Setting Multicentre (15), US
Participants	**Randomised:** 357 participants (mean age 51 years, 71 male, 285 female, 1 gender unreported) **Inclusion criteria** • ≥18 years of age with moderate to severe facial erythema associated with rosacea, defined as grade ≥3 on the investigator-rated 5-point Clinician's Erythema Assessment (CEA) scale with photonumeric guide and as "more redness than I prefer" or "completely unacceptable redness" on the patient-rated 5-point Subject Self - Assessment of erythema (SSA) scale • Subjective stable facial erythema with minimal variation between days and within each day • Females of childbearing potential were required to use reliable contraception **Ocular involvement:** Unclear **Exclusion criteria** • ≥3 inflammatory facial lesions • Facial characteristics that might interfere with study assessments, including acne, signs of actinic damage, or excessive facial hair

	• Uncontrolled systemic disease • Narrow-angle glaucoma • Clinically unstable hypertension, clinically unstable cerebral insufficiency, orthostatic hypotension, coronary insufficiency, cardiac arrhythmia, Ischaemic heart disease, benign prostatic hypertrophy, or Raynaud syndrome • Current use of monoamine oxidase inhibitors or niacin 2500 mg/day • Known hypersensitivity or allergies to any study treatment component • Drug or alcohol abuse within the past 12 months • Pregnancy or nursing • Any topical products applied to the face within 2 hours except cleansers • Oxymetazoline-containing products (eg, eye drops, nasal spray) • Topical glucocorticosteroids applied to the face, any prescription or over-the-counter product for acne or rosacea, or any redness-reducing product on the face within 14 days • Systemic antibiotics known to affect rosacea within 28 days • Isotretinoin within 180 days • Laser, light-source, or other energy-based therapy to the face within 6 months prior to baseline erythema assessment **<u>Dropouts and withdrawals</u>** • 17/356 (4.8%); once daily treatment group (6/177), twice daily group 11/179 • Adverse events 10 • Personal reason 1 • Protocol violation 1 • Other reasons 5 **Baseline data mean (n)** Clinician's Erythema Assessment scale 3; 0.5% oxymetazoline QD 37, 1.0% oxymetazoline QD 34, 1.5% oxymetazoline QD 38, vehicle QD 35, 0.5% oxymetazoline BID 38, 1.0% oxymetazoline BID 37, 1.5% oxymetazoline BID 33, vehicle BID 40 Clinician's Erythema Assessment scale 4; 0.5% oxymetazoline QD 8, 1.0% oxymetazoline QD 10, 1.5% oxymetazoline QD 6, vehicle QD 9, 0.5% oxymetazoline BID 7, 1.0% oxymetazoline BID 8, 1.5% oxymetazoline BID 12, vehicle BID 4

	Subject Self-Assessment of erythema scale 3; 0.5% oxymetazoline QD 28, 1.0% oxymetazoline QD 36, 1.5% oxymetazoline QD 30, vehicle QD 33, 0.5% oxymetazoline BID 31, 1.0% oxymetazoline BID 32, 1.5% oxymetazoline BID 34, vehicle BID 28 Subject Self-Assessment of erythema scale 4; 0.5% oxymetazoline QD 17, 1.0% oxymetazoline QD 8, 1.5% oxymetazoline QD 14, vehicle QD 11, 0.5% oxymetazoline BID 13, 1.0% oxymetazoline BID 13, 1.5% oxymetazoline BID 11, vehicle BID 16
Interventions	28 days **Intervention** Oxymetazoline 0.5% - QD (45) **Comparator 1** Oxymetazoline 1% - QD (44) **Comparator 2** Oxymetazoline 1.5% - QD (44) **Comparator 3** Vehicle - QD (44) **Comparator 4** Oxymetazoline 0.5%% - BID (45) **Comparator 5** Oxymetazoline 1% - BID (45) **Comparator 6** Oxymetazoline 1.5% - BID (45) **Comparator 7** Vehicle - BID (44) Patients were instructed to apply a pea-sized amount (0.5 g) to cover all facial redness, avoiding contact with the eyes, eyelids, scalp, neck, ears, mucous membranes, and open wounds, and to wash their hands before and after application
Outcomes	Assessments (4): baseline, day 2, 14 and 28 (various measurements during the day)

	Outcomes of the trial (as reported) **Primary outcomes** 1. Oxymetazoline plasma concentrations **Secondary outcomes** 1. Adverse events✴ 2. Facial tolerability (0 (none), 1 (mild), 2 (moderate), 3 (severe)) ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 219): "This study was sponsored by Allergan plc, Dublin, Ireland. Writing and editorial assistance was provided to the authors by Peloton Advantage, Parsippany, NJ, USA, and funded by Allergan plc"
Declaration of interest	Quote (page 219): "AW Kuang, M Attar, and G Ahluwalia are employees of Allergan plc, Irvine, CA, USA"
Notes	One of our primary outcomes was addressed (adverse events). However, all adverse events of all concentrations and dosages were combined, and therefore no fair comparisons between concentrations could be made (see Table 6). 30/268 adverse events were reported in all oxymetazoline groups versus 5/88 in the two vehicle groups

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 214): "Eligible patients were randomly assigned" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "The randomization scheme was prepared by Allergan's Biostatistics group. Patients were then randomized via automated interactive voice response system/interactive web response system (IVRS/IWRS), which was used to manage the randomization and treatment assignment" Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen

		in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: "The IVRS/IWRS was used to manage the randomization and treatment assignment. At the time of randomization, the IVRS/IWRS provided the site with specific study medication kit number(s) for each randomized patient, corresponding to the treatment" Comment: Adequate, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 214): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "Study medication was provided in identical tubes and cartons and labeled with medication kit numbers. At time of randomization, the IVRS/IWRS provided the site with specific study medication kit number(s) for each randomized patient, corresponding to the treatment group assigned via central randomization Sites dispense study medication according to IVRS/IWRS instructions Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement After e-mail communication (see performance bias): Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	17/356 (4.8%); once daily treatment group (6/177), twice daily group 11/179. Per-protocol analysis Comment: Low number of drop-outs and although analysis per protocol considered at low risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Layton 2015

Methods	RCT, prospective, placebo-controlled, double-blind Date of study July to November 2013 Setting Multicentre (14), Germany, UK and Sweden
Participants	**Randomised:** 92 participants (mean age 54.1 years (SD 12.8), 36 male, 56 female) **Inclusion criteria** • ≥ 18 years of age • Erythema associated with facial rosacea • Patient Self-Assessment score of 4 (severe) at baseline prior to the study drug application • Clinician's Erythema Assessment (CEA) score of 3 (moderate) or 4 (severe) at baseline prior to the study drug application **Ocular involvement:** Unclear **Exclusion criteria** • More than five facial inflammatory lesions (papules or pustules) of rosacea • Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin) • Concomitant facial dermatoses (e.g. perioral dermatitis), demodicidosis, facial keratosis pilaris, seborrhoeic dermatitis, acute lupus erythematosus or actinic telangiectasia • Prior treatment with brimonidine gel 0.33% • Any other treatment for erythema of rosacea within 4 weeks prior to inclusion • Any current treatment of a formulation containing brimonidine tartrate • Known or suspected allergies or sensitivities to any component of the study drugs, including the active ingredient brimonidine tartrate

	• Female who is pregnant or lactating **Dropouts and withdrawals** • 4/92 (4.3%), two from each group • Patient request; brimonidine group (1), vehicle group (1) • Adverse event; brimonidine group (1), vehicle group (0) • Protocol violation; brimonidine group (0), vehicle group (1) **Baseline data N (%)** CEA 3 = moderate; brimonidine group 20 (41.7), vehicle group 25 (56.8) CEA 4 = severe; brimonidine group 28 (58.3), vehicle group 19 (43.2)
Interventions	Eight days **Intervention** Brimonidine tartrate 0.33% gel - QD (48) **Comparator** Vehicle gel - QD (44) Concomitant treatment for inflammatory lesions of rosacea was allowed provided the subject had received a stable dose for at least 3 months
Outcomes	Assessments (3): baseline, day 2, and day 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Satisfaction with the overall study treatment (Facial Redness Questionnaire, Subject Satisfaction Questionnaire and Subject Diary)✴ **Secondary outcomes** 1. Change from baseline in satisfaction with appearance of facial skin (PSA) (0 no redness, 4 severe redness)✴ 2. Change from baseline in mean CEA (0 = clear, no signs of erythema, 4 = severe erythema with fiery redness)✴ 3. Percentage of subject reporting a treatment-related adverse event✴ ✴Denotes outcomes pre-specified for this review

Funding source	Quote (2405): "This study was funded by Galderma R & D."
Declaration of interest	Quote (2405): "All clinical trial investigators or their institutes received payment for conducting the studies. AML, BH, MS and DBS have served as consultants to Galderma. BH, APB, PL and MS have served as members on the Rosacea advisory board of Galderma, and MAH and MS have received honoraria as speakers for Galderma. NK and YMM are employees of Galderma R & D."
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 4 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2406): "A randomization list was generated prior to study initiation using the Ranuni routine of the Statistical Analysis System and the kit number was transmitted to the assigned clinical packaging organization for labelling" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 2406): "A randomization list was generated prior to study initiation using the Ranuni routine of the Statistical Analysis System and the kit number was transmitted to the assigned clinical packaging organization for labelling" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 2406): "The double-blind design was achieved by using indistinguishable primary packaging (tubes) and secondary packaging for brimonidine gel 0.33% and its vehicle, and they were dispensed by a third party so the evaluators (Investigator or designee) did not come into contact with the study medication." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 2406): "The double-blind design was achieved by using indistinguishable primary packaging (tubes) and secondary packaging for brimonidine gel 0.33% and its vehicle, and they were dispensed by a third party so the evaluators

		(Investigator or designee) did not come into contact with the study medication." Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	4/92 (4.3%), two from each group, reasons reported. ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT01885000) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were consultants or employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Lebwohl 1995

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Department of Dermatology, Mount Sinai Medical Center, New York and Chicago, Illinois, US
Participants	**Randomised:** 63 participants (age range 25 to 80, 21 male, 42 female) **Inclusion criteria** • Adults > 18 years with moderate rosacea, symptoms of overall severity, erythema, telangiectasia, and papulopustules were scored from none (0) to severe (3) and all participants had initial summed symptoms scores for these parameters of no less than 5 **Ocular involvement:** Unclear **Exclusion criteria** • Rhinophyma

	• Topical rosacea medications within 2 weeks • Systemic rosacea medications within 4 weeks **Dropouts and withdrawals** • 6/63 (9.5%); sulphacetamide and sulphur group (5, reported 6 adverse events as reason for discontinuation) and metronidazole group (1) • Itch and irritation; sulphacetamide and sulphur group (2) and metronidazole group (0) • Contact dermatitis; sulphacetamide and sulphur group (2) and metronidazole group (0) • Excessive dryness; sulphacetamide and sulphur group (2) and metronidazole group (0) • Worsening of the condition; sulphacetamide and sulphur group (0) and metronidazole group (1) **Baseline data mean** Number of papules; sulphacetamide and sulphur group 12.1 and metronidazole group 13.5 Number of pustules; sulphacetamide and sulphur group 4.6 and metronidazole group 3.3
Interventions	Eight weeks **Intervention** Sulphacetamide and 10%/sulphur 5% - BID (31) **Comparator** Metronidazole 0.75% gel - BID (32)
Outcomes	Assessments (5): baseline, week 2, 4, 6 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Physician's Global Assessment (on a "ruler scale at 5% intervals of improvement")✴ 2. Overall severity of rosacea (0 = none to 3 = severe)✴ 3. Papulopustules (0 = none to 3 = severe)✴ 4. Erythema (0 = none to 3 = severe)✴ 5. Telangiectasia (0 = none to 3 = severe)✴ 6. Number of lesions (papules and pustules)✴ **Secondary outcomes** 1. Adverse events✴

	2. Participants evaluation of overall response, cosmetic acceptability and willingness to use again✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 191): "This study was supported by a grant of Dermik laboratories."
Declaration of interest	Two of the investigators are employed by Dermik Laboratories, however none declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events), however data were not reported, only that there was no statistical difference between the two groups See comparison 34 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (192): "...were randomly assigned to the two treatment groups." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 191): "...investigator blinded." The report provided insufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 191): "...investigator blinded." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers/participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Six participants withdrawn, 5 in the sulphacetamide and sulphur group, 1 in metronidazole group Comment: Unclear whether dropouts were included in analysis. Insufficient information to permit a clear judgement

Selective reporting (reporting bias)	High risk	No data were available for "participants evaluation of overall response", "cosmetic acceptability as considered by participant", and "willingness to use again by participant". Only information reported that "there was no statistical difference between the 2 groups" Comment: We judged this as at a high risk of bias. Participant's evaluation is one of the principal outcome measures
Other bias	Unclear risk	Study duration adequate, wash-out period before study adequate, groups were treated equally. The sodium sulphacetamide group tended to have greater overall severity scores and greater number of pustules but this was not statistically significant. Supported by a grant from Dermik Laboratories, 2 investigators were employees of Dermik Laboratories Comment: Insufficient information to assess whether important risk of bias exists

Leyden 2011

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Unspecified, US
Participants	**Randomised:** 30 participants (mean age 45 years, all female) **Inclusion criteria** • Females ≥ 18 years with mild to moderate erythema of rosacea on the malar area of their face • Willingness to refrain from using any non-study products on the face including medication, cosmetics, sunscreen etc • Willingness to avoid having facial procedures (facials, botox, peels, laser, dermal fillers etc), tanning booth treatments and excessive sun exposure **Ocular involvement:** Unclear **Exclusion criteria** • History of any facial condition or disease that might interfere with diagnosis or evaluation • Nodular lesion or more than 2 inflammatory lesions • Known allergy or hypersensitivity to any ingredient of the study products • History or evidence of blood dyscrasia or Crohn's disease

	• Use of coumarin or warfarin • Anticipated need of concurrent use of medicated drugs on the face • Facial sunburn at baseline or sunbathing < 2 weeks prior to study entry • Facial tattoos • Pregnancy, lactating or planning pregnancy • Facial cleanser or facial hair removal < 1 week prior to study entry • Topical medications, photosensitising agents or procedures or UV therapy < 2 weeks prior to study entry • Topical tretinoin < 3 weeks prior to study entry • Vasodilatators < 4 weeks prior to study entry • Participation in an investigational drug or device study < 30 days prior to study entry • Use of systemic steroids < 12 weeks prior to study entry • Drugs know to be toxic to a major organ < 3 months prior to study entry • Laser resurfacing, use acitretin, isotretinoin, methotrexate, photo-allergic, phototoxic or photosensitising drugs < 6 months prior to study entry **Dropouts and withdrawals** • 1/30 (3.3%); metronidazole plus standard skin care group due to unwillingness to apply multiple creams **Baseline data mean** Nothing reported
Interventions	Four weeks **Intervention** Rosacea treatment system (gentle cleanser, metronidazole 0.75% gel, hydrating complexion corrector and skin balancing sunscreen SPF 30) - BID (10) **Comparator 1** Rosacea treatment system without metronidazole - BID (10) **Comparator 2** Metronidazole 0.75% gel + standard skin care regimen (standard gentle cleanser, standard moisturizer, sunscreen) - BID (10)

	The women were instructed to apply the supplied sunscreen daily and to wear protective clothing when exposed to sun
Outcomes	Assessments (3): baseline, week 2 and 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (7-point Likert scale from clear to worse)✶ 2. Investigator's assessment on erythema (0 = none, 4 = severe)✶ 3. Patient assessment of severity of rosacea (0 = none, 4 = severe)✶ 4. Patient assessment on effectiveness in reducing dryness (very effective, effective, somewhat effective, ineffective) 5. Patient assessment on skin feeling comfortable (4-point Likert scale from agree completely to disagree) 6. Patient assessment on skin easily irritated (never, rarely, sometimes, often) 7. Patient satisfaction (4-point Likert scale from very satisfied to very dissatisfied)✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 1185): "The study was funded by OMP, Inc"
Declaration of interest	Quote (page 1185): "Dr Leyden has been an investigator and consultant for OMP, Inc"
Notes	One of our primary outcomes was addressed (participant assessed changes in rosacea severity) See comparison 38, 39 and 40 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1180): "patients were randomly assigned (in a 1:1:1 ratio)" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1179): "...investigator blinded." Comment: The report provided insufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 1179): "...investigator blinded." Comment: Investigator and participant assessed outcomes Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	1/30 (3.3%); metronidazole plus standard skin care group, reason reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period before study started adequate Comment: The study appeared to be free of other forms of bias

Leyden 2014

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre in US
Participants	**Randomised:** 92 participants (mean age 51.2 years (SD 12.8, range 23 to 82 years), 25 male, 67 female) **Inclusion criteria:**

	• Participants with papulopustular rosacea (minimum of 12 inflammatory lesions) **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** None reported **Baseline data mean** Inflammatory lesions: vehicle 19.9, BPO 1% 28.6, BPO 5% 22.9
Interventions	12 weeks **Intervention** Vehicle - QD (30) **Comparator 1** Encapsulated benzoyl peroxide 1% gel - QD (32) **Comparator 2** Encapsulated benzoyl peroxide 5% gel - QD (30)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment✶ 2. Lesion count✶ **Secondary outcomes** 1. Inflammatory lesion erythema assessment 2. Erythema assessment✶ 3. Telangiectasia assessment✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 688): "The author has not disclosed any relevant conflicts"
Notes	None of our primary outcomes was addressed See comparison 25 and 26 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 685): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 685): "...double-blind" Comment: The report provided insufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 685): "...double-blind" Comment: Only investigator assessed outcomes Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No dropouts reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available (NCT00940992), and the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, no wash-out period before study started described. Limited information Comment: There was insufficient information to permit a clear judgement

Luger 2015

Methods	RCT, prospective, placebo-controlled Date of study

	Unreported Setting Multicentre (4) Germany
Participants	**Randomised:** 61 participants (mean age 51.7 years, 13 male, 48 female) **Inclusion criteria** • 18 to 65 years with rosacea subtype 1 (Wilkin 2004) • Patients with concomitant use of rosacea treatments were taken off their medication and returned for a baseline visit at the end of the wash-out period. The length of the wash-out period was five times the half-life of the rosacea medication or the time defined in the exclusion criteria, with a minimum of 14 and a maximum of 28 days No ocular involvement **Exclusion criteria** • Papulopustular rosacea or ocular rosacea • Pregnant or lactating women • Women with the menopausal symptoms of excessive sweating • Flushing or mood changes within 2 years prior to screening • Patients undergoing treatment or planned treatment with another investigational product within 30 days prior to study entry • Patients with peripheral location of rosacea, severe facial skin dryness or xerosis, keratoconjunctivitis sicca, flushing due to conditions other than rosacea, other abnormal facial skin conditions (e.g. eczema or perioral dermatitis), diabetes mellitus, systemic lupus erythematosus, Sjögren's syndrome, congenital or acquired immunodeficiency, or malignancy within the past 2 years except for in situ removal of basal cell carcinoma • Use of systemic or topical corticosteroids, antibiotics or retinoids < 2 months prior to study entry • Laser treatment, chemical peeling or any other product for the treatment of rosacea within 28 days prior to study entry • Change in the use of cosmetics, drugs or food supplements containing vitamin A or ß-carotin was permitted within 14 days prior to randomisation or whilst on study

	• Use of medicated skin care products, or drugs, cosmetics or skin care products known to exacerbate the symptoms of rosacea throughout the study **Dropouts and withdrawals** • 6/61 (9.8%); TDT 068 (3), vehicle (3) • No assessment of RosaQOL; TDT 068 (2), vehicle (1) • Adverse event; TDT 068 (1), vehicle (2) **Baseline data mean (SD)** Total RosaQoL score (Nicholson 2007); TDT 068 2.9 (0.71), vehicle 2.9 (0.67) Total rosacea standard grading system (Wilkin 2004); TDT 068 7.8 (1.66), vehicle 8.1 (1.73)
Interventions	Four weeks **Intervention** TDT 068 gel (topical formulation containing drug-free ultra-deformable phospholipid vesicles) - BID (40) **Comparator** Vehicle gel - BID (21)
Outcomes	Assessments (3): baseline, week 2 and 4 (and 2 phone calls, one at week 1 and one at week 5) **Outcomes of the trial** (as reported) **Primary outcomes** 1. Assessment of quality of life (RosaQoL, Nicholson 2007)✴ 2. Investigators rating of efficacy (rosacea standard grading system, Wilkin 2004)✴ 3. Adverse events, physical change, vital signs✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1): Editorial assistance with the preparation of the manuscript was provided by Bollin Strategies Ltd., UK, and was funded by Pro Bono Bio Entrepreneur Ltd., UK
Declaration of interest	Quote (page 1): "T. Luger and N. Peukert have no conflict of interest to declare. M. Rother is a paid consultant of Pro Bono Bio Entrepreneur Ltd"

Notes	Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 46 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2): "..were stratified in a 4:1 female/male ratio and randomized according to a random permuted block scheme in a 2:1 ratio .." Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: Patients were subsequently randomised and the study centre was notified of the treatment number of the patient via telefax by the randomisation center. Sets of sealed individual code envelopes were prepared for emergency procedures Comment: Adequate, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 2): "The investigator and other study team members involved in the evaluation of the safety and efficacy end-points, the patients, the monitors, the sponsor and clinical research organization staff remained blinded to treatment until database lock." Comment: The report provided insufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: The investigational product and its matching vehicle had a similar appearance and all subject kits were packaged in the same way Comment: Blinding ensured
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 2): "The investigator and other study team members involved in the evaluation of the safety and efficacy end-points, the patients, the monitors, the sponsor and clinical research organization staff remained blinded to treatment until database lock." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare

		providers, participants) during the study. Insufficient information to permit a clear judgement After e-mail communication: The investigational product and its matching vehicle had a similar appearance and all subject kits were packaged in the same way Comment: Blinding ensured, risk of detection bias low
Incomplete outcome data (attrition bias)	Low risk	6/61 (9.8%); TDT 068 (3), vehicle (3), reasons reported. Per-protocol analysis Comment: Low number of dropouts and although per-protocol analysis judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available (NCT01666509), and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Lupin 2014

Methods	RCT, prospective, active-controlled, open-label Date of study Unreported Setting The Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada
Participants	**Randomised:** 12 participants (mean age 49.8 years, gender unreported) **Inclusion criteria** • Subjects with subtype 1 rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** None reported **Baseline data mean** Nothing reported
Interventions	One or two treatments **Intervention**

	Microfocused ultrasound with visualization (MFU-V) treatment with 15 lines on each cheek (one treatment) **Comparator** Microfocused ultrasound with visualization (MFU-V) treatment with 15 lines on each cheek (two treatments with 2 weeks in between) Unclear how many were randomised to each group
Outcomes	Assessments (4): baseline, week 2, 4 and week 12/13 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Improvement in erythematotelangiectatic rosacea✴ 2. Patient assessed improvement✴ 3. Patient Satisfaction Questionnaire✴ **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page AB43): "Supported by Ulthera"
Declaration of interest	None declared
Notes	Two of our outcomes were addressed (participant-assessed changes in rosacea severity, and adverse events). Poster abstract, limited data, unclear how many were randomised to each group, after 3 attempts failed to contact PI for further details (see Table 3 and Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page AB 43): "were randomized.." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been

		foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding reported Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding reported. Investigator and participant assessed outcomes Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Unclear risk	No dropouts reported There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided. Protocol available at clinicaltrials.gov NCT01756027 Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Maddin 1999

Methods	RCT, prospective, active-controlled, double-blind, within-patient comparison Date of study Unreported Setting Division of Dermatology Skin Care Centre at University of British Columbia, Canada
Participants	**Randomised:** 40 participants (mean age 52.2 years for males and 49.6 years for females, 11 male, 29 female) **Inclusion criteria** • Participants at least 21 years of age and of any race or gender, with papulopustular rosacea with persistent symmetrical erythema affecting the cheeks and at least 10 inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • Non-symmetric distribution of inflammatory lesions between each side of the face • Significant concomitant dermatologic disorders

	• Presence of other conditions that could affect study results • Allergy to component of study medication • History of non-compliance • Pregnant and nursing female • Female with childbearing potential and not practicing a reliable method of birth control **Dropouts and withdrawals** • 3/40 (7.5%) • Cardiac arrest (1), personal reasons (2) **Baseline data mean (SEM)** Number of inflammatory lesions; azelaic acid treated site 11.3 (0.88), metronidazole treated site 11.40 (1.03)
Interventions	15 weeks **Intervention** Azelaic acid 20% cream - BID **Comparator** Metronidazole 0.75% cream - BID
Outcomes	Assessments (5): baseline, week 3, 6, 8 and 9 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Self-assessed changes in rosacea severity decrease in redness, participant overall impression of improvement (six-point Likert scale, higher rating worse)✶ 2. Decrease in lesion count✶ 3. Decrease in erythema, telangiectasia (four-point Likert scale)✶ 4. Physician's global evaluation of improvement (six-point Likert scale, higher rating worse)✶ **Secondary outcomes** 1. Adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 961): "Supported by a grant provided by Allergan, Inc."
Declaration of interest	None declared

Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 16 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 962): "A single-center, randomized, double-blind, contralateral, split-face..." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 962): "...double-blind." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 962): "...double-blind." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	The 3 withdrawals were accounted for and reasons for withdrawal reported. ITT analysis (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias

Other bias	Low risk	Study duration adequate, wash-out period before study adequate, additional medications that might influence outcome were not allowed Comment: We judged this as at a low risk of bias

Marks 1971

Methods	RCT, prospective, active-controlled and placebo-controlled (3-armed study), double-blind Date of study Unreported Setting Institute of Dermatology, St John's Hospital for Diseases of the Skin, London, UK
Participants	**Randomised:** 64 participants (mean age 47.8 years, 27 male, 29 female and 8 gender unreported) **Inclusion criteria** • Participants with rosacea including persistent erythema, papules, and pustules **Ocular involvement:** Unclear **Exclusion criteria** • Participants without easily definable papules **Dropouts and withdrawals** • 56 participants completed the trial, but the report indicates that at least 64 participants were randomised with the possibility of 8 or more participants who dropped out **Baseline data mean (SD)** Number of lesions; tetracycline group 21.05 (12.79), ampicillin group 21.06 (20.48), placebo group 18.47 (13.14)
Interventions	Six weeks **Intervention** Tetracycline TID 250 mg for 1 week and then BID in weeks 2 to 6 (20) **Comparator 1** Ampicillin dosage unknown TID for 1 week and then BID in weeks 2 to 6 (17) **Comparator 2**

	Placebo TID for 1 week and then BID in weeks 2 to 6 (19) Number of participants reported as having completed the trial, but unclear how many were initially randomised to each group
Outcomes	Assessments (8): baseline, week 1, 2, 3, 4, 5, 6 and 7 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Lesion count post-treatment✴ 2. N of participants with > 50% improvement✴ **Secondary outcomes** 1. Extent or depth of erythema (subjective assessment by investigator)✴ 2. Participant's opinion (four-point Likert scale, worse to much better)✴ 3. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1051): "We are grateful to Pfizer Ltd. for supplying the tetracycline, ampicillin, and placebo packed in identical capsules; and to Miss C. Pullin, of the Wellcome Research Laboratories, for statistical analysis of the results. R. M. is in receipt of a grant from the Medical Research Council."
Declaration of interest	None declared
Notes	Total number randomised not explicitly stated. 56 participants completed the trial, but at least 64 participant numbers were allocated so it is possible that eight or more participants dropped out Dosage of ampicillin not reported Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events). Data on lesions counts were quite skewed See comparison 56, 61 and 62 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1049): "Dispensing of study medications randomly allocated to one of 3 coded treatment groups by hospital dispensary." Comment: Appears to have been done centrally by the dispensary. Probably done

Allocation concealment (selection bias)	Low risk	Quote: Central allocation by the dispensary Comment: Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 1049): "The placebo, tetracycline, and ampicillin were supplied in identical capsules." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 1049): "The placebo, tetracycline, and ampicillin were supplied in identical capsules." Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	Total number randomised not explicitly stated. 56 participants completed the trial, but at least 64 were allocated, so eight or more participants dropped out. Unclear how many participants were initially randomised in each group. Further one withdrawal in the placebo group Comment: Insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration short (6 weeks), wash-out period at start of the study adequate, no concomitant medication that might influence rosacea were allowed Quote (page 1051): "We are grateful to Pfizer Ltd. for supplying the tetracycline, ampicillin, and placebo packed in identical capsules;.... R. M. is in receipt of a grant from the Medical Research Council." Comment: We judged this as at a low risk of bias

Martel 2017a

Methods	RCT, prospective, vehicle-controlled, investigator-blinded Date of study 1999-2002 Setting

	Multicentre (20), US
Participants	**Randomised**: 416 participants (mean age 47.8 years, 105 male, 311 female) **Inclusion criteria** • Moderate to severe rosacea with erythema, telangiectasia, and at least 8 inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 47/416 (11.2%); unclear from which groups • Patient request 19/47 • Lost to follow-up 11/47 • Remainder unknown **Baseline data mean** Number of inflammatory lesions: clindamycin 1% BID group 23.3, clindamycin 1% QD group 20.7, clindamycin 0.3% QD group 21.6, vehicle QD group 22.2, vehicle BID group 19.4 Erythema severity score; clindamycin 1% BID group 8.1, clindamycin 1% QD group 7.8, clindamycin 0.3% QD group 8.0, vehicle QD group 7.7, vehicle BID group 7.7 Investigator Global Rosacea severity score; clindamycin 1% BID group 2.4, clindamycin 1% QD group 2.3, clindamycin 0.3% QD group 2.3, vehicle QD group 2.3, vehicle BID group 2.2
Interventions	12 weeks **Intervention** Clindamycin 1% cream - BID (81) **Comparator 1** Clindamycin 1% cream - QD (87) **Comparator 2** Clindamycin 0.3% cream - QD (85) **Comparator 3** Vehicle cream - BID (81)

	Comparator 4 Vehicle cream - QD (82)
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Inflammatory lesion count✶ 2. Investigator global rosacea severity score ((0=none/clear; 1=mild, detectable erythema with ≤7 papules/pustules; 2=moderate, prominent erythema with ≥8 papules/pustules; 3=severe, intense erythema with ≥10 to <50 papules/pustules; 3.5 very severe, intense erythema with >50 papules/pustules)✶ 3. Investigator global improvement assessment (photographs taken at baseline, were graded on a 7-point scale (from –1 [worse], 0 [no change], and 1 [minimal improvement] to 5 [clear])✶ 4. Erythema severity score (ESS)(7-point scale in increments of 0.5 (from 0=no erythema to 3.5=very severe redness, very intense redness)✶ 5. Skin irritation (none, mild, moderate, or severe) **Secondary outcomes** 1. Adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 53): "The studies were sponsored by Galderma R&D"
Declaration of interest	Quote (page 53): "Dr. Martel and Ms. Carlavan are employees of Galderma R&D. Dr. Jarratt has been a consultant, investigator, and received honoraria from Allergan; Galderma R&D; and Valeant Pharmaceuticals International, Inc. He also is a consultant for Athenex. Dr. Weiss has been an advisory board member and researcher for Foamix; Galderma R&D; and Valeant Pharmaceuticals International, Inc. He also has been a researcher for Allergan, Inc."
Notes	One of our primary outcomes was addressed (adverse events) See comparison 27 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 54): "were randomized into 5 treatment arms' Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 53): "investigator-blinded" Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator as well as participant-assessed. Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	47/416 (11.2%); unclear from which groups. ITT analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, no wash-out period described, groups treated equally. Study sponsored by Galderma and several investigators were employees of Galderma Comment: We judged this as at an unclear risk of bias

Martel 2017b

Methods	RCT, prospective, vehicle-controlled, investigator-blinded Date of study

	1999-2002 Setting Multicentre (10), US
Participants	**Randomised**: 213 participants (mean age 48.1 years, 66 male, 147 female) **Inclusion criteria** • Moderate to severe rosacea and at least 8 inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 20/213 (9.4%); unclear from which group • Patient request 6/20 • Lost to follow-up 4/20 • Remainder unknown **Baseline data mean** Number of inflammatory lesions: clindamycin 1% BID group 17.8, vehicle BID group 19.2 Erythema severity score; clindamycin 1% BID group 8.2, vehicle BID group 8.1 Investigator Global Rosacea severity score 2 = moderate; clindamycin 1% BID group 81, vehicle BID group 83 Investigator Global Rosacea severity score 3 = severe; clindamycin 1% BID group 27, vehicle BID group 21 Investigator Global Rosacea severity score 4 = very severe; clindamycin 1% BID group 1, vehicle BID group 0
Interventions	12 weeks **Intervention** Clindamycin 1% gel - BID (109) **Comparator 1** Vehicle gel - BID (104)
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Inflammatory lesion count✶

	2. Investigator global rosacea severity score ((0=none/clear; 1=mild, detectable erythema with ≤7 papules/pustules; 2=moderate, prominent erythema with ≥8 papules/pustules; 3=severe, intense erythema with ≥10 to <50 papules/pustules; 4 very severe, intense erythema with >50 papules/pustules)✴ 3. Investigator global improvement assessment (photographs taken at baseline, was graded on a 7-point scale (from –1 [worse], 0 [no change], and 1 [minimal improvement] to 5 [clear])✴ 4. Erythema severity score (ESS)(7-point scale in increments of 0.5 (from 0=no erythema to 3.5=very severe redness, very intense redness)✴ 5. Skin irritation (none, mild, moderate, or severe) **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 53): "The studies were sponsored by Galderma R&D"
Declaration of interest	Quote (page 53): "Dr. Martel and Ms. Carlavan are employees of Galderma R&D. Dr. Jarratt has been a consultant, investigator, and received honoraria from Allergan; Galderma R&D; and Valeant Pharmaceuticals International, Inc. He also is a consultant for Athenex. Dr. Weiss has been an advisory board member and researcher for Foamix; Galderma R&D; and Valeant Pharmaceuticals International, Inc. He also has been a researcher for Allergan, Inc."
Notes	One of our primary outcomes was addressed (adverse events) See comparison 27 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 54): "were randomized into 5 treatment arms "Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been

		foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 53): "investigator-blinded" Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator as well as participant-assessed. Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	20/213 (9.4%); unclear from which group. ITT analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, no wash-out period described, groups treated equally. Study sponsored by Galderma and several investigators were employees of Galderma Comment: We judged this as at an unclear risk of bias

Monk 1991

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Participants from 4 different centres, Department of Dermatology, Bedford General Hospital, Bedford; Department of Dermatology, Bridgend General Hospital, Bridgend; Department of Dermatology, Queen Alexandra Hospital, Cosham; Department of Dermatology, Royal South Hants Hospital, Southampton, UK
Participants	**Randomised:** 33 participants (mean age 46.9 years in metronidazole 0.75% gel + placebo capsules group, and 50.7

	years in placebo gel + oxytetracycline group, 8 male and 8 female versus 9 male and 8 female) **Inclusion criteria** • Participants with rosacea with mild to severe erythema and a minimum of 3 papules or pustules on the face **Ocular involvement:** Unclear **Exclusion criteria** • Contraindications to either oxytetracycline or metronidazole **Dropouts and withdrawals** • 6/33 (18.2%); metronidazole group (4) and oxytetracycline group (2) • Lost to follow-up (3), broken leg (1), withdrawn (2) **Baseline data mean** Number papules and pustules; metronidazole group 25 and oxytetracycline group 20 Erythema grade; metronidazole group 2.5 and oxytetracycline group 2.4
Interventions	Nine weeks **Intervention** Metronidazole gel 0.75% + placebo capsules - BID (16) **Comparator** Placebo gel + oxytetracycline 250 mg - BID (17)
Outcomes	Assessments (4): baseline, week 3, 6 and 9 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Number of papules and pustules (as absolute number on scale of 1 ≤ 10, 2 = 11 to 20, 3 = 21 to 30, 4 = 31 to 40, 5 = 41 to 50, and 6 ≥ 50)✴ 2. Assessment of erythema (0 = absent, 3 = severe)✴ 3. Participant's and doctor's global assessment of improvement (1 = worse, 2 = unchanged, 3 = possible improvement, 4 = definite improvement)✴ **Secondary outcomes**

	1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 91): "We wish to thank Bioglan Laboratories for kindly providing the materials for this study"
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 72 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 91): "The patients were randomly allocated in a double-blind fashion of treatment." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 91): "...placebo gel (having the same base as the active preparation)." Comment: Assuming the placebo capsules were similar. The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 91): "Double-blind" "...placebo gel (having the same base as the active preparation)." Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias

Incomplete outcome data (attrition bias)	Unclear risk	6/33 (18.2%); metronidazole group (4) and oxytetracycline group (2). Incomplete outcome data were adequately addressed, reasons for withdrawal were reported. Per-protocol analysis Comment: We judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out period before start of the study adequate, no concomitant rosacea therapy was allowed. Additional therapy was noted Comment: We judged this as at low risk of bias

Montes 1983

Methods	RCT, prospective, placebo-controlled, double-blind Date of study "Winter months", Dermatology Department in Buenos Aires, Argentina Setting Only data from the first 4 weeks included. Study biased after 4 weeks
Participants	**Randomised:** 64 participants (age unclear, 19 male, 39 female, 6 gender unreported) **Inclusion criteria** • Participants with classic signs of rosacea (papulopustular) **Ocular involvement:** Unclear **Exclusion criteria** • Rhinophyma • Treatment with other topical or systemic treatment and or dietary restrictions • Sensitivity to ingredients of study medication **Dropouts and withdrawals** • 36/64 (56%); benzoyl peroxide group (14), placebo group (22) • Withdrawal during first four weeks due to protocol violations; benzoyl peroxide group (2), placebo group (4) • Withdrawal after four weeks; benzoyl peroxide group (12), placebo group (18)

	• Adverse events; benzoyl peroxide group (1), placebo group (1) • Sensitivity to benzoyl peroxide; benzoyl peroxide group (4), placebo group (0) • Lack of improvement; benzoyl peroxide group (7), placebo group (17) **Baseline data mean (SD)** Nothing reported
Interventions	Four weeks, then a further four weeks for participants who showed improvement **Intervention** Benzoyl peroxide (BZP) acetone gel 5% QD first 4 weeks and 10% last 4 weeks (33) **Comparator** Placebo (acetone gel vehicle) (31)
Outcomes	Assessments (5): baseline, week 2, 4, 6 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Papule and pustule score after 4 and 8 weeks (0 to 3, higher score worse)✶ 2. Overall response after 4 and 8 weeks (1 to 4, higher score worse)✶ **Secondary outcomes** 1. Erythema and telangiectasia (0 to 3, higher score worse)✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed. Only first 4 weeks included. Study biased after 4 weeks as people who did not respond to treatment "were dropped from the study" (page 187) See comparison 25 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 186): "This randomized, double-blind...". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 186) : "...matching placebo gel." "double-blind" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 186) : "...matching placebo gel." "double-blind" Outcomes were investigator assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	High risk	Participants who showed no improvement at end of the first 4 weeks were dropped from the study. Per-protocol analysis (page 186-7). Only data up to week 4 are considered Comment: We judged this as at a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate (bit short), sponsorship or support unreported. Other topical or systemic treatment were not allowed Comment: The study appeared to be free of other forms of bias

Mostafa 2009

Methods	RCT, prospective, active-controlled, 3-armed, double-blind, within-patient comparison Date of study Unreported Setting Department of Dermatology and Venereology, Faculty of Medicine, Zagazig University, Zagazig, Egypt
Participants	**Randomised:** 24 participants (mean age 51.08 ± 5.9 years (range 42 to 61), 1 male, 23 female) **Inclusion criteria** • Participants with rosacea on the face (on cheeks, nose, chin, and forehead) **Ocular Involvement:** Unclear **Exclusion criteria** • Participants with known allergy to medications used in the study • Participants with systemic diseases or on systemic medications which may affect interpretation of the results • Pregnant or lactating female **Dropouts and withdrawals:** Nothing reported **Baseline data mean (SD)** Inflammatory lesion count; azelaic acid group 4.2 (2.7), metronidazole 5.4 (3.3), permethrin group 4.5 (3.7)
Interventions	15 weeks **Intervention** Azelaic acid 20% cream - BID **Comparator 1** Metronidazole 0.75% cream - BID **Comparator 2** Permethrin 5% cream - BID
Outcomes	Assessments (11): baseline, week 3, 6, 9 and 15, and then monthly for another 6 months **Outcomes of the trial** (as reported) **Primary outcomes**

	1. Physician's assessment (including counting of inflammatory lesions, and scoring erythema and telangiectasia)✶ 2. Photographic assessment (with "same scoring systems") 3. Participant's assessment (acceptability of treatment, regarding dryness, cosmetic appearance, and greasiness) 4. Assessment of side effects✶ 5. Recurrence✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 22): "None declared"
Notes	One of our primary outcomes was addressed (adverse events). Participant' assessment was evaluated but not regarding rosacea severity. Investigators conclusions were based on the analysis of skewed and unreliable data analysis See comparison 17 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 23): "The 24 patients were randomly allocated to three groups." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 23): "...double-blind comparison of azelaic acid 20% cream, metronidazole 0.75% cream and permethrin 20% cream."

		Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 23): "...double-blind comparison of azelaic acid 20% cream, metronidazole 0.75% cream and permethrin 20% cream." Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Dropouts unclear Comment: Insufficient information to permit a clear judgement
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes are addressed adequately or reported completely, e.g. photographic assessment and Physician's Gobal Assessment Comment: We judged this as at a high risk of bias
Other bias	Unclear risk	Study duration adequate, wash-out period unclear, and unclear if groups were treated equally Comment: Insufficient information to assess whether an important risk of bias exists

Mrowietz 2018

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study October 2015 to August 2016 Setting Multicentre (18), Germany
Participants	**Randomised:** 232 participants (mean age 52.5 years, 87 male, 145 female) **Inclusion criteria** • ≥18 years with moderate-to-severe rosacea that had been diagnosed at least 6 months before screening and consisted of ≥12 facial papules or pustules • Subjects were willing to minimize external factors that might trigger rosacea flare-ups, including prolonged sun exposure. **Ocular involvement**: Unclear

	Exclusion criteria • Pregnant, lactating, or planning to become pregnant during the study • Use of oral retinoids or therapeutic vitamin A supplements of > 10,000 units/day within 6 months was prohibited • Use of topical retinoids, methoxyflurane, or systemic antibiotics or corticosteroids within 1 month • Use of topical corticosteroids, antibiotics, or other topical medications for rosacea (e.g., metronidazole) within 2 weeks of baseline • Subjects with an active nodule > 5 mm in diameter or any skin conditions on the face that would interfere with the diagnosis or assessment of rosacea, including but not limited to eczema, psoriasis, seborrhoeic dermatitis, or perioral dermatitis **Dropouts and withdrawals** • 19/232 (8.2%; FMX103 1.5% group (2), FMX103 3% group (10), vehicle group (7) • Adverse events; FMX103 1.5% group (0), FMX103 3% group (3), vehicle group (1) • Lost to follow-up; FMX103 1.5% group (1), FMX103 3% group (0), vehicle group (0) • Subject request; FMX103 1.5% group (1), FMX103 3% group (6), vehicle group (3) • Protocol deviation; FMX103 1.5% group (0), FMX103 3% group (1), vehicle group (1) • Other; FMX103 1.5% group (0), FMX103 3% group (0), vehicle group (2) **Baseline data mean** Investigator's Global Assessment (IGA) 3 (%); FMX103 1.5% group 43, FMX103 3% group 38.7, vehicle group 51.3 IGA 4 (%); FMX103 1.5% group 57, FMX103 3% group 61.3, vehicle group 48.7 Number inflammatory lesions; FMX103 1.5% group 34.5, FMX103 3% group 34.1, vehicle group 30.6
Interventions	12 weeks **Intervention** FMX103 1.5% foam - QD (79) **Comparator 1** FMX103 3% foam - QD (75)

	Comparator 2 Vehicle foam - QD (78)
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in inflammatory lesion count✶ 2. Overall response after 4 and 8 weeks (1 to 4, higher score worse)✶ **Secondary outcomes** 1. Proportion of participants with at least 2 grade improvement in IGA (clear, almost clear, mild, moderate, severe)✶ 2. Proportion of participants with score clear (0) or almost clear (1) of IGA 3. Percentage change in inflammatory lesion count 4. Change in erythema (0 = clear skin with no signs of erythema; 1 = almost clear of erythema, slight redness; 2 = mild erythema, definite redness; 3 = moderate erythema, marked redness; and 4 = severe erythema, fiery redness)✶ 5. Quality of life (RosaQoL, Nicholson 2007)✶ 6. Adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 10): "Funding This study was funded by Foamix Pharmaceuticals"
Declaration of interest	Quote (page 10): "Tal Hetzroni Kedem is an employee of, and has stocks in, Foamix Pharmaceuticals and has a patent or intellectual property interest to disclose at Foamix Pharmaceuticals. Rita Keynan is an employee of, and has a few patents written for, Foamix Pharmaceuticals. Dov Tamarkin and Mitchell Shirvan are employees of Foamix Pharmaceuticals. Meir Eini receives stock options and royalties from Foamix Pharmaceuticals."
Notes	Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 29, 30 and 31 in Effects of interventions FMX103 is minocycline

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 3): "Assignment of eligible, enrolled subjects to a treatment group followed a predetermined list of randomization numbers, with each successive number receiving one of the three treatments in random order. Randomization was done within each investigational site. The Interactive Response Technology (IRT) system was used to assign a kit number that corresponded to the randomization schedule" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 3): "Assignment of eligible, enrolled subjects to a treatment group followed a predetermined list of randomization numbers, with each successive number receiving one of the three treatments in random order. Randomization was done within each investigational site. The Interactive Response Technology (IRT) system was used to assign a kit number that corresponded to the randomization schedule" Comment: Form of central allocation, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 3): "The vehicle foam contained dyes that were added so the vehicle matched the active concentration foam in appearance. Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	19/232 (8.2%; FMX103 1.5% group (2), FMX103 3% group (10), vehicle group (7). ITT analysis. Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT02601963). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally The study was sponsored by Foamix Pharmaceuticals, several investigators were employees of Foamix Pharmaceuticals.

		Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

NCT00249782

Methods	RCT, prospective, active and placebo-controlled, single-blind Date of study November 2005 to May 2006 Setting Multicentre (27), US
Participants	**Randomised:** 400 participants (mean 51 years (range 22 to 87 years), 144 male, 256 female) **Inclusion criteria** • Participants with papulopustular rosacea (with ≥ 10 inflammatory lesions (papules and/or pustules) above the mandibular line at baseline) • Men or women ≥ 18 years of age • Investigator's Global Assessment (IGA) score ≥ 2 • In good physical and mental health No ocular involvement **Exclusion criteria** • A skin examination reveals the presence of another skin disease or condition (excessive facial hair, excessive scarring, sunburn, or other disfigurement) located on the face that would confound the evaluation of the rosacea condition • Current or past ocular rosacea, such as conjunctivitis, iritis, and keratitis, of sufficient severity to require topical or systemic antibiotics • Topical antibiotics, topical steroids and other topical rosacea treatments on the face within 14 days of baseline and throughout the study • Systemic steroids within 30 days of baseline and throughout the study • Systemic antibiotics within 30 days of baseline and throughout the study • Systemic medication or therapy known to affect inflammatory responses within the 30 days prior to baseline or throughout the study • Topical retinoids within 30 days or systemic retinoids within 180 days of baseline and throughout the study • Treatment with physical modalities that could benefit rosacea are prohibited within 30 days of baseline and throughout the study

	Dropouts and withdrawals: One participant randomised in error but did not receive treatment, for rest nothing reported **Baseline data mean (SD)** Nothing reported
Interventions	12 weeks **Intervention** Dapsone gel 5% - BID **Comparator 1** Dapsone gel 5% - QD **Comparator 2** Metronidazole gel 1% - QD **Comparator 3** Dapsone gel 5% - QD and metronidazole gel 1% - QD **Comparator 4** Vehicle gel - BID Unclear how many were randomised to each group
Outcomes	Assessments (6): baseline, week 2, 4, 8, 12 and 13 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Efficacy: per cent change and change from baseline in inflammatory lesion counts✶ 2. "Success" rate, defined as proportion of subjects with a score of 0 or 1 and at least a 2 point improvement from baseline on the IGA scale✶ 3. Erythema and telangiectasia scores✶ 4. Lesion counts over time✶ **Secondary outcomes** 1. Safety: adverse events✶ 2. Dapsone concentrations ✶Denotes outcomes pre-specified for this review
Funding source	Allergan sponsored the study

Declaration of interest	No information on clinicaltrials.gov
Notes	Study has been completed May 2006. Website accessed 19-7-2014 additional information on http://www.allerganclinicaltrials.com/results/medical_aesthetics.htm One of our primary outcomes was addressed (adverse events). Unclear how many were randomised to each group (see Table 6), no reply from Allergan after several email attempts (see Table 3)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (published as pdf on Allergan website): "Randomization: Subjects were assigned in a 1:1:1:1:1 ratio to the five treatment groups" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (clinicaltrials.gov): "...single-blind." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (clinicaltrials.gov): "...single-blind." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	No dropout reported. ITT. Limited data available Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	No exact data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Limited data are provided Comment: There was insufficient information to permit a clear judgement

NCT00560703

Methods	RCT, prospective, placebo-controlled, double-blind Date of study November 2007 to May 2009 Setting Multicentre (8), US
Participants	**Randomised:** 70 participants (mean age 55.7 years, 27 male, 43 female) **Inclusion criteria** • ≥ 18 years with facial rosacea and blepharitis **Ocular involvement:** Yes **Exclusion criteria** • Pregnant or nursing women • Allergy to tetracyclines • Recent eye surgery • Past or current use of isotretinoin • Patients who are achlorhydric • Patients who have had gastric by-pass surgery **Dropouts and withdrawals** • 6/70 (8.6%); all of placebo group • Adverse events; doxycycline 40 mg (0), placebo group (2) • Protocol violation; doxycycline 40 mg (0), placebo group (2) • Withdrawal by subject; doxycycline 40 mg (0), placebo group (1) • Non-compliance; doxycycline 40 mg (0), placebo group (1) **Baseline data mean** Nothing reported
Interventions	12 weeks **Intervention** Doxycycline 40 mg - QD (46) **Comparator** Placebo - QD (24)
Outcomes	Assessments (2): baseline and week 12 **Outcomes of the trial** (as reported)

	Primary outcomes 1. Change in ocular surface disease index (OSDI-quality of life)(range of OSDI is 0 to 100 (higher score indicates worse condition)✴ 2. Change in bulbar conjunctival hyperemia (none (0) = normal, mild (1) = slight localized injection, moderate (2) = pink colour, severe (3) = red colour, very severe (4) = marked dark redness) **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Galderma
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed 13-3-2018. Taken over by Galderma, contact person Michael Graeber Two of our primary outcomes were addressed (quality of life and adverse events) See comparison 57 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel and participants from knowledge of which intervention a participant received

		Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	6/70 (8.6%); all from the placebo group, reasons reported. ITT analysis. Comment: Low but unbalanced number of drop-outs, considered as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started unclear, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

NCT00617903

Methods	RCT, prospective, placebo-controlled, double-blind Date of study January to June 2008 Setting Multicentre (7), US
Participants	**Randomised:** 83 participants (mean age 50.5 years, 35 male, 48 female) **Inclusion criteria** • ≥ 18 year with papulopustular rosacea with a minimum of 10 and a maximum of 50 papules and/or pustules, persistent erythema, and telangiectasia • Ability and willingness to accept and comply with treatment and required medical examinations **Ocular involvement:** Unclear **Exclusion criteria** • Known non-responders to azelaic acid

	• Erythematotelangiectatic, rhinophymatous, ocular, or steroid rosacea • Presence of dermatoses that could interfere with the rosacea diagnosis • Treatment with isotretinoin in the six months prior to randomisation • Treatment of the face with topical retinoids during the two weeks prior to randomisation • Treatment with oral antibiotics during the four weeks prior to randomisation • Treatment with topical antibiotics • Treatment with systemic corticosteroids during 4 weeks prior to randomisation • Treatment of the face with topical corticosteroids during 2 weeks prior to randomisation • Treatment of the face with topical imidazole antimycotics during 2 weeks prior to randomisation • Treatment of the face with topical azelaic acid formulations during 2 weeks prior to randomisation • Use of a sauna during 2 weeks prior to randomisation and during the study • Facial laser surgery for telangiectasia during 6 weeks prior to randomisation • Planned concurrent use of any treatment other than study medication that affects rosacea • History of hypersensitivity to propylene glycol or any other ingredient of the study drugs • Participation in another clinical trial during the last 4 weeks **<u>Dropouts and withdrawals</u>** • 10/83 (12.0%); azelaic acid 15% foam group (3), vehicle foam group (7) • Withdrawal by subject; azelaic acid 15% foam group (2), vehicle foam group (3) • Lost to follow-up; azelaic acid 15% foam group (1), vehicle foam group (1) • Lack of efficacy; azelaic acid 15% foam group (0), vehicle foam group (1) • Adverse event; azelaic acid 15% foam group (0), vehicle foam group (1) • Non-compliance; azelaic acid 15% foam group (0), vehicle foam group (1) **Baseline data mean (SD)** Investigator's Global Assessment (IGA): azelaic acid 15% foam group 4.0 (0.9), vehicle foam group 3.9 (0.9)

	Number of inflammatory lesions; azelaic acid 15% foam group 18.0 (10.61), vehicle foam group 17.6 (8.36) Erythema intensity score; azelaic acid 15% foam group 3.1 (0.5), vehicle foam group 3.0 (0.5)
Interventions	12 weeks **Intervention** Azelaic acid 15% foam - BID (41) **Comparator** Vehicle foam - BID (42)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in inflammatory lesion count✴ 2. IGA dichotomised into success and failure (0 - clear; 1 - minimal; 2 - mild; 3- mild to moderate; 4 - moderate; 5 - moderate to severe; 6 - severe; therapeutic success is defined as an IGA score of clear or minimal (0 to 1))✴ 3. Change in erythema rating on a 4-point scale (1 - clear or almost clear; 2 - mild; 3 - moderate; 4 - severe)✴ **Secondary outcomes** 1. Mean of inflammatory lesion count per participant 2. Nominal change from baseline in inflammatory lesion count per participant 3. Percentage change from baseline for the inflammatory lesion count per participant 4. Absolute values and nominal change from baseline for the IGA of rosacea 5. Absolute values and rating changes of erythema and telangiectasia 6. Investigator's and participant's rating of overall improvement and the participant's opinion on cosmetic acceptability✴ ✴Denotes outcomes pre-specified for this review
Funding source	Bayer
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed 13-3-2018, some outcome data reported on clinicaltrials.gov. Information Bayer that study is not published yet

	One of our primary outcomes was assessed (participant-assessed changes in rosacea severity) See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel and participants from knowledge of which intervention a participant received Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	10/83 (12.0%); azelaic acid 15% foam group (3), vehicle foam group (7), reasons reported. ITT analysis (LOCF) Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been

		reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started adequate, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

NCT00697541

Methods	RCT, prospective, active-controlled, double-blind, cross-over Date of study May to June 2008 Setting One centre, Broomall, Pennsylvania, US
Participants	**Randomised**: 20 participants (mean age 45.1 years, all female) **Inclusion criteria** • Male or female ≥18 years of age • Clinical diagnosis of rosacea • Score of ≥ 3 on the CEAS • Score of ≥ 3 on the PSA • IOP ≥ 10 mm Hg • Non-pregnant and non-lactating females **Ocular involvement:** Unclear **Exclusion criteria** • History of hypersensitivity or allergies to any ingredient of the study drugs, unless approved by the Investigator • Use of brimonidine prescription medications within 14 days prior to check-in • Use of any over-the-counter (OTC), non-prescription preparations (including vitamins, minerals, and phytotherapeutic/herbal/plant-derived preparations) within 7 days prior to check-in, unless deemed acceptable by the Investigator • Use of systemic or topical steroids applied to the face 14 days prior to check in • The use of any Rx or OTC products for the treatment of acne or rosacea within 14 days prior to check in • The use of isotretinoin within 180 days prior to check in **Dropouts and withdrawals**

	• 3/20 (15%); 0.18% COL-118 facial gel + saline drops first group (2), vehicle facial gel + brimonidine eyedrops first group (1), reasons not reported **Baseline data mean (SD)** Nothing reported
Interventions	3 days **Intervention** 0.18% COL-118 facial gel (1.8 mg brimonidine) 1 g administered topically plus one drop of Advanced Eye Relief™ in each eye - QD; 1 g of 0.18% COL-118 facial gel is reapplied once after four hours then one day wash-out and then cross-over (10) **Comparator** COL-118 facial gel vehicle (0.0 mg brimonidine tartrate) 1 g administered topically plus one drop of 0.2% brimonidine ophthalmic solution (0.1 mg brimonidine tartrate/drop) in each eye- QD; Four hours after the first application 1-g of COL-118 facial gel vehicle (0.0 mg brimonidine) is administered topically then one day wash-out and then cross-over (10)
Outcomes	Assessments (3): baseline, day 1 and 3 (several measurements per day) **Outcomes of the trial** (as reported) **Primary outcomes** 1. To assess the relative bioavailability of 0.18% Col-118 facial gel and 0.2% brimonidine ophthalmic solution under conditions of maximum use in participants with moderate to severe erythematous rosacea - 0 hour (prior to dose) and at 1, 2, 3, 4 (just prior to the 2nd dose), 5, 6, 7, and 8 hours post-morning dose 2. AUC - Area Under the Curve of Brimonidine - 0 Hour (prior to dose) and at 1, 2, 3, 4, 5, 6, 7, and 8 hours post-morning dose 3. Time to Maximum Plasma Concentration - 0 Hour (prior to dose) and at 1, 2, 3, 4, 5, 6, 7, and 8 hours post-morning dose **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review

Funding source	Galderma
Declaration of interest	No information on clinicaltrials.gov
Notes	Study completed June 2008, website accessed 13-3-2018 None of our outcomes was assessed (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel and participants from knowledge of which intervention a participant received Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (website): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. However, the outcomes were objective, therefore we judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	3/20 (15%); 0.18% COL-118 facial gel + saline drops first group (2), vehicle facial gel + brimonidine eyedrops first group (1), reasons not reported Comment: We judged this as at an unclear risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was available, and the pre-specified outcomes appeared to have been reported, although the study has not been published in full Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out phase before study started adequate, study duration adequate, groups treated equally Comment: This study appears to be free of other forms of bias

NCT01426269

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre (US)
Participants	**Randomised:** 130 participants (mean age 49.4 years, 44 male, 86 female) **Inclusion criteria** • Participants with papulopustular rosacea who achieved an Investigator's Global Assessment (IGA) score of clear or near clear after 12 weeks of treatment with doxycycline 40 mg modified release and metronidazole 1% gel • 18 to 80 years old **Ocular Involvement:** Unclear **Exclusion criteria** • Female subjects who are pregnant, nursing or planning a pregnancy during the study • Subject has any other active dermatological condition on the face that may interfere with the conduct of the study • Subject uses or has recently used any medication which may interfere with the absorption, distribution, or elimination of study medications, or may interfere with the assessments of efficacy or safety of the study medications • Subject has a known allergy to any of the components of the study products, or a known hypersensitivity to tetracyclines or metronidazole **Dropouts and withdrawals**

	• 85/130 (65%); 38/65 in doxycycline group, 47/65 in placebo group • Adverse events; doxycycline group (1), placebo group (2) • Withdrawal by subject; doxycycline group (9), placebo group (11) • Protocol violation; doxycycline group (5), placebo group (5) • Lost to follow-up; doxycycline group (8), placebo group (6) • Site closed; doxycycline group (6), placebo group (5) • Relapse; doxycycline group (9), placebo group (18) **Baseline data mean (SD)** Nothing reported other than "(IGA) score of clear or near clear" for all that entered the second phase
Interventions	All participants receive doxycycline 40 mg and metronidazole gel 1% once daily during phase 1 (baseline to week 12) Second phase 40 weeks **Intervention** Doxycycline 40 mg - QD (65) **Comparator** Placebo - QD (65)
Outcomes	Assessments (11): baseline, every 4 weeks up to 40 weeks **Outcomes of the trial** (as reported) **Primary outcomes** 1. Percentage of subjects who relapse during phase 2 of the study (return to the baseline lesion count or return to the baseline IGA score)✴ 2. RosaQoL✴ 3. Subject questionnaire (satisfaction)✴ **Secondary outcomes** 1. Investigator's Global Assessment success (clear or near clear score)✴ 2. Clinician's Erythema Assessment (0 = clear, no signs of erythema, 4 = severe erythema with fiery redness)✴ 3. Change from baseline in inflammatory lesion counts✴

	4. Number of participants with adverse events as a measure of safety and tolerability✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (clinicaltrials.gov) "Sponsor: Galderma Laboratories, L.P."
Declaration of interest	Quote (clinicaltrials.gov) "Principal Investigators are not employed by the organization sponsoring the study"
Notes	Study includes two phases; first phase (12 weeks) all participants (230) received doxycycline 40 mg combined with topical metronidazole gel. We only included the randomised second phase. All our primary outcomes were addressed Information found on clinicaltrial.gov and of a poster provided by Galderma See comparison 58 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (clinicaltrials.gov): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (clinicaltrials.gov): "...double-blind." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (clinicaltrials.gov): "...double-blind." Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers/participants) during the study Insufficient information to permit a clear judgement

Incomplete outcome data (attrition bias)	High risk	85/130 (65%); 38/65 in doxycycline group, 47/65 in placebo group, reasons reported and 27 were due to relapse (primary endpoint for this study) Comment: We judged this as at a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol was available at clinicaltrials.gov. The pre-specified outcomes appeared to have been reported in addition to RosaQol scores and a patient satisfaction questionnaire Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Treatment duration adequate, groups treated equally. Not all study data are available as study is not published yet Comment: There was insufficient information to permit a clear judgement

NCT01449591

Methods	RCT, prospective, active and placebo-controlled, double-blind Date of study September 2011 to February 2012 Setting Multicentre (5), US
Participants	**Randomised:** 36 participants (mean age 47.4 years, 12 male, 24 female) **Inclusion criteria** • Participants with erythematotelangiectatic rosacea • Male and female (women of non-childbearing potential only) patients, 18 to 65 years of age inclusive No ocular involvement **Exclusion criteria** • Ocular, phymatous or other types of specific rosacea (other than subtype 1 and 2) requiring treatment ➢ 12 inflammatory lesions on the face • Any other facial dermatosis that may interfere with the assessments on the face such as seborrhoeic dermatosis, acne vulgaris, perioral dermatitis, Morbihan's disease, cutaneous sarcoid or lupus erythematosus and /or flushing diseases, such as climacteric flushing, mastocytosis, carcinoid syndrome or pheochromocytosis **Dropouts withdrawals** • 4/36 (11.1%); BFH772 (1), vehicle (1), metronidazole (2) • Withrew consent; BFH772 (1), vehicle (1), metronidazole (1)

	• Lost to follow-up; BFH772 (0), vehicle (0), metronidazole (1) **Baseline data mean (SD)** Nothing reported
Interventions	12 weeks **Intervention** BFH772 1% (betamethasone and calcipotriol) ointment (12) **Comparator 1** Vehicle ointment (12) **Comparator 2** Metronidazole 1% cream (12) Application frequency not reported
Outcomes	Assessments (8): baseline, week 1, 2, 4, 8, 10, 12 and 14 **Outcomes of the trial** (as reported) **Primary outcomes** 1. To assess the effect of BFH772 treatment compared to vehicle on non-transient facial erythema using the Investigator's assessment of facial erythema score (10 point scale)✶ **Secondary outcomes** 1. Investigator’s Global Assessment of rosacea✶ 2. Investigator’s assessment of facial telangiectasia and inflammatory lesion count✶ 3. Participants' assessment of flushing frequency✶ 4. Participants' assessment of facial redness✶ ✶Denotes outcomes prespecified for this review
Funding source	Sponsor: Novartis Pharmaceuticals
Declaration of interest	No information on clinicaltrials.gov
Notes	Study was completed December 2012. Website accessed 19-7-2014. Data reported on: http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public One of our primary outcomes was addressed (participant-assessed changes of rosacea severity) See comparison 44 and 45 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (on Novartis website): "This was a multicenter, randomized, blinded, comparator- and vehicle-controlled study". Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (clinicaltrials.gov): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (clinicaltrials.gov): "double-blind" Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers/participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	4/36 (11.1%); BFH772 (1), vehicle (1), metronidazole (2), reasons reported. Per-protocol analysis Comment: Low and balanced number of dropouts and although per-protocol analysis judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, no wash-out period before start of study reported, groups treated equally Comment: The study appeared to be free of other forms of bias

NCT01579084

Methods	RCT, prospective, active and placebo-controlled, double-blind Date of study April to June 2012 Setting One centre, Austin, Texas, US
Participants	**Randomised**: 64 participants (mean age not reported, 15 male, 49 female) **Inclusion criteria** • 18 years and older with facial erythema associated with rosacea on both sides of the face **Ocular involvement**: Unclear **Exclusion criteria** • Laser light-source or other energy based therapy in the last 6 months • Excessive hair around the treatment area **Dropouts and withdrawals:** None **Baseline data mean (SD)** Nothing reported
Interventions	5 days **Intervention** AGN-199201 Formulation A applied to one side of the face and Formulation B applied to the other side of the face - BID (8) **Comparator 1** AGN-199201 Formulation B applied to one side of the face and Formulation C applied to the other side of the face - BID (8) **Comparator 2** AGN-199201 Formulation C applied to one side of the face and Formulation A applied to the other side of the face - BID (8) **Comparator 3** AGN-199201 Formulation A applied to one side of the face and AGN-199201 Vehicle applied to the other side of the face - BID (8) **Comparator 4**

	AGN-199201 Formulation B applied to one side of the face and AGN-199201 Vehicle applied to the other side of the face - BID (8) **Comparator 5** AGN-199201 Formulation C applied to one side of the face and AGN-199201 Vehicle applied to the other side of the face - BID (8) **Comparator 6** AGN-199201 Formulation A applied to both sides of the face - BID (4) **Comparator 7** AGN-199201 Formulation B applied to both sides of the face - BID (4) **Comparator 8** AGN-199201 Formulation C applied to both sides of the face - BID (4) **Comparator 9** AGN-199201 Vehicle (Placebo) applied to both sides of the face - BID (4)
Outcomes	Assessments (2): baseline, day 5 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Percentage of responders with at least a 2-grade decrease from baseline on both Clinician's Erythema Assessment (CEA) and Subject Self-Assessment (SSA) at day 1 2. Percentage of responders with at least a 2-grade decrease from baseline on both Clinician's Erythema Assessment (CEA) and Subject Self-Assessment (SSA) at day 5 **Secondary outcomes** 1. Percentage of responders with at least a 2-grade decrease from baseline on Clinician's Erythema Assessment (CEA)✴

	2. Percentage of responders with at least a 2-grade decrease from baseline on Subject Self-Assessment (SSA)✶ ✶Denotes outcomes prespecified for this review
Funding source	Allergan
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed 15-3-2018. Probably dose finding study of oxymetazoline One of our primary outcomes was assessed (participant-assessed changes of rosacea severity) Unclear what the concentrations were of AGN-199201. No response of Allergan (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel and participants from knowledge of which intervention a participant received Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness

		of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, no wash-out period before start of study reported, groups treated equally Comment: The study appeared to be free of other forms of bias

NCT01735201

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study May to June 2013 Setting One centre, Austin, Texas, US
Participants	**Randomised**: 356 participants (mean age unreported, 71 male, 285 female) **Inclusion criteria** • Male or female aged 18 years or older with redness of the skin caused by rosacea **Ocular involvement**: Unclear **Exclusion criteria** • ≥3 inflammatory lesions • Laser light-source or other energy based therapy in the last 6 months • Any prescription or over the counter product for the treatment of acne or rosacea in the last 14 days **Dropouts withdrawals** • 18/356 (5.1%); AGN-199201 dose A QD (3), AGN-199201 dose B QD (1), AGN-199201 dose C QD (0), AGN-199201 vehicle QD (2), AGN-199201 dose A BID (1), AGN-199201 dose B BID (5), AGN-199201 dose C BID (2), AGN-199201 vehicle BID (2)

	• Adverse event; AGN-199201 dose A QD (1), AGN-199201 dose B QD (1), AGN-199201 dose C QD (0), AGN-199201 vehicle QD (1), AGN-199201 dose A BID (1), AGN-199201 dose B BID (2), AGN-199201 dose C BID (2), AGN-199201 vehicle BID (1) • Personal reasons; AGN-199201 dose A QD (1), AGN-199201 dose B QD (0), AGN-199201 dose C QD (0), AGN-199201 vehicle QD (0), AGN-199201 dose A BID (0), AGN-199201 dose B BID (0), AGN-199201 dose C BID (0), AGN-199201 vehicle BID (0) • Protocol violation; AGN-199201 dose A QD (1), AGN-199201 dose B QD (0), AGN-199201 dose C QD (0), AGN-199201 vehicle QD (0), AGN-199201 dose A BID (0), AGN-199201 dose B BID (0), AGN-199201 dose C BID (0), AGN-199201 vehicle BID (0) • Other reasons; AGN-199201 dose A QD (0), AGN-199201 dose B QD (0), AGN-199201 dose C QD (0), AGN-199201 vehicle QD (1), AGN-199201 dose A BID (0), AGN-199201 dose B BID (2), AGN-199201 dose C BID (1), AGN-199201 vehicle BID (1) **Baseline data mean (SD)** Nothing reported
Interventions	28 days **Intervention** AGN-199201 Dose A - QD (45) **Comparator 1** AGN-199201 Dose B - QD (44) **Comparator 2** AGN-199201 Dose C - QD (44) **Comparator 3** AGN-199201 Vehicle - QD (44) **Comparator 4** AGN-199201 Dose A - BID (45) **Comparator 5** AGN-199201 Dose B - BID (45) **Comparator 6**

	AGN-199201 Dose C - BID (45) **Comparator 7** AGN-199201 Vehicle - BID (44)
Outcomes	Assessments (2): baseline, day 28 (several measurements a day) **Outcomes of the trial** (as reported) **Primary outcomes** 1. Percentage of responders with at least a 2-grade decrease from baseline on both Clinician's Erythema Assessment (CEA) and Subject Self-Assessment (SSA) at day 28✶ **Secondary outcomes** 2. Percentage of responders with at least a 2-grade decrease from baseline on both Clinician's Erythema Assessment (CEA) and Subject Self-Assessment (SSA) at 0.5 hours post dose day 28✶ 3. Percentage of responders with at least a 2-grade decrease from baseline on both Clinician's Erythema Assessment (CEA) and Subject Self-Assessment (SSA) at 1 hours post dose day 28✶ ✶Denotes outcomes prespecified for this review
Funding source	Allergan
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed again 16-3-2018, AGN-199201 is oxymetazoline One of our primary outcomes was assessed (participant-assessed changes of rosacea severity) Concentrations are unclear, no response Allergan (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "double-blind" Not clear what measures were used to blind study personnel and participants from knowledge of which intervention a participant received Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "double-blind" Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	18/356 (5.1%); AGN-199201 dose A QD (3), AGN-199201 dose B QD (1), AGN-199201 dose C QD (0), AGN-199201 vehicle QD (2), AGN-199201 dose A BID (1), AGN-199201 dose B BID (5), AGN-199201 dose C BID (2), AGN-199201 vehicle BID (2). ITT analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period before start of study adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

NCT02147691

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study January to February 2015 Setting

	One centre, Louisville, Kentucky, US
Participants	**Randomised:** 22 participants (mean age unreported, 4 male, 18 female) **Inclusion criteria** • Male or female • Between 18 years and 85 years of age • Female subjects of childbearing potential must have a negative urine pregnancy test at Baseline • Female subjects of childbearing potential must practice a reliable method of contraception throughout the study • Moderate or severe rosacea with an Investigator's Global Assessment (IGA) score of 3 or 4 • Able to understand and comply with the requirements of the study and sign Informed Consent/Health Insurance Portability and Accountability Authorization forms **Ocular involvement:** Unclear **Exclusion criteria** • Female subjects who are pregnant, breast feeding or who are of childbearing potential and not practicing a reliable method of birth control • History of hypersensitivity or idiosyncratic reaction to any component of the test medications • Subjects who have not completed the proper wash-out periods for prohibited medications and/or procedures • Medical condition that contraindicates the subject's participation in the study • Alcohol or drug abuse is evident within the past 5 years • History of poor cooperation, non-compliance with medical treatment, unreliability • Participation in an investigational drug study within 30 days of the baseline visit **Dropouts withdrawals** • 5/22 (22.3%); azelaic acid plus brimonidine group (4), brimonidine only group (1) • Withdrawal by subject; azelaic acid plus brimonidine group (2), brimonidine only group (0) • Adverse event; azelaic acid plus brimonidine group (2), brimonidine only group (0) • Lost to follow-up; azelaic acid plus brimonidine group (0), brimonidine only group (1)

	Baseline data mean (SD) Nothing reported
Interventions	12 weeks **Intervention** Azelaic acid 15% gel - BID + brimonidine 0.33% gel - QD (10) **Comparator** Brimonidine 0.33% gel - QD (12)
Outcomes	Assessments (4): baseline, week 4, 8, and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in Investigator's Global Assessment (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate and 4 = severe)✶ **Secondary outcomes** 1. Lesion counts✶ 2. Clinician's Erythema assessment (0 = none, 1 = mild, 2 = moderate, 3 = severe, 4 = very severe)✶ 3. Erythema VAS Assessment (subject)✶ 4. Dermatology Life Quality Index (DLQI)✶ 5. Adverse events✶ ✶Denotes outcomes prespecified for this review
Funding source	Bayer
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed 16-3-2018 All our primary outcomes were assessed See comparison 24 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "investigator-blinded" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received. Participants were not blinded Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "investigator-blinded" Outcomes were investigator as well participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	High risk	5/22 (22.3%); azelaic acid plus brimonidine group (4), brimonidine only group (1). Per protocol analysis Comment: The high number of drop-outs is considered at a high risk of bias
Selective reporting (reporting bias)	Low risk	The prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period before start of study adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

NCT02300129

Methods	RCT, prospective, vehicle-controlled, investigator blinded, cross-over (5 periods)

	Date of study April to June 2014 Setting One centre, Hamburg, Germany
Participants	**Randomised;** 34 participants (mean age 50.2 years, male 2, female 31, 1 gender unreported) **Inclusion criteria** • Male or female, who is at least 18 years of age or older at Screening visit. • Clinical diagnosis of mild to moderate erythematotelangiectatic rosacea or mild to moderate papulopustular rosacea according to the National Rosacea Society grading (Wilkin 2004) • At least five flushing episodes during the last week before screening and baseline visits **Ocular involvement:** Unclear **Exclusion criteria** • Particular forms of rosacea (rosacea conglobata, rosacea fulminans, isolated rhinophyma, isolated pustulosis of the chin), or other concomitant facial dermatoses that are similar to rosacea such as peri-oral dermatitis, demodicidosis facial keratosis pilaris, seborrhoeic dermatitis, acute lupus erythematosus or actinic telangiectasia • Current treatment with monoamine oxidase inhibitors, barbiturates, opiates, sedatives, systemic aesthetics, or alpha-agonists; • Less than 3 months stable dose treatment with tricyclic anti-depressants, cardiac glycosides, beta blockers or other antihypertensive agents **Dropouts withdrawals** • 2/34 (5.6%); 1 withdrawal by subject, 1 adverse event **Baseline data mean (SD)** Nothing reported
Interventions	Period 1 includes a cross-over design (first and third sessions) and a split face design (second session). During this period, 34 subjects received on site the study drugs as follows (the order of each session being randomized) **Intervention** CD07805/47 0.5% gel on both sides of the face - QD

	Comparator 1 One side of the face treated with CD07805/47 0.5% gel, the other side treated with the CD07805/47 placebo gel (the allocation of treatment on each half-face will be determined according to a randomisation list) - QD **Comparator 2** CD07805/47 placebo gel on both sides of the face - QD A 2-days wash-out period (between Period 1 and Period 2) with no treatment on either side of the face Period 2 (4 weeks) corresponding to a cross-over design during which the subjects will apply themselves the study drugs at home on the whole face, once daily 7 days per week
Outcomes	Assessments (3): baseline, day 22 and 36 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Total number of flushes for each 2-week period **Secondary outcomes** 1. None ✴Denotes outcomes prespecified for this review
Funding source	Galderma
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed 19-3-2018, CD07805/47 is brimonidine. None of our outcomes were assessed, complicated study design, see Table 6 but there seemed no difference in number of flushes (15.3 (12.1) versus 16.3 (14.0) for each two week period

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been

		foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "investigator-blinded" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received. Participants were not blinded Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	High risk	Quote (website): "investigator-blinded" Outcomes were participant-assessed Comment: Participants were not blinded. We judged this as at a high risk of bias
Incomplete outcome data (attrition bias)	Low risk	2/34 (5.6%); 1 withdrawal by subject, 1 adverse event. Per-protocol analysis Comment: Low number of drop-outs, we judged this as a low risk of bias
Selective reporting (reporting bias)	Low risk	The prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period before start of study and between study periods adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

NCT03035955

Methods	RCT, prospective, controlled with "no treatment", investigator-blinded, within-patient comparison Date of study December 2010 to February 2012 Setting One centre, Wake Forest University, Winston-Salem, NC, US
Participants	**Randomised:** 20 participants (age range 18-65 years, 3 male, 17 female) **Inclusion criteria**

	• Male and female subjects, ages 18 and over, with mild to moderate papulopustular rosacea with bilateral facial involvement • Positive Demodex folliculorum SSSB, defined as >5 mites/cm² on at least on of two different SSSB specimens on bilateral sides of the face • Have an IGA of mild to moderate rosacea, rating between 2 and 5 **Ocular involvement:** Unclear **Exclusion criteria** • Use of topical therapy for rosacea or other skin conditions on the face within two weeks of baseline • Use of oral medications for the treatment of rosacea that have been started or altered within the past three months • Presence of a concurrent medical condition or skin condition, which is determined by the investigator to potentially interfere with study outcomes or patient assessments • Known allergy or sensitivity to azelaic acid gel or components therein, such as propylene glycol • Known allergy or sensitivity to cyanoacrylates or formaldehyde. • More than two nodules. • Female subjects who are not postmenopausal for at least 1 year, surgically sterile or willing to practice effective contraception during the study. • Nursing mothers, pregnant women and women planning to become pregnant while on study **Dropouts withdrawals** • 2/20 (10%); azelaic acid left and no treatment right group (1), azelaic acid right and no treatment left group (1) **Baseline data mean (SD)** Nothing reported
Interventions	Four weeks **Intervention** Azelaic acid 15% gel left side of the face - BID and no treatment on right side (10) **Comparator**

	Azelaic acid 15% gel right side of the face - BID and no treatment on left side (10)
Outcomes	Assessments (2): baseline, week 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in Demodex count **Secondary outcomes** 1. None
Funding source	Wake Forest University
Declaration of interest	No information on clinicaltrials.gov
Notes	Website accessed 17-3-2018 None of our outcomes were assessed. See Table 6

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (website): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (website): "investigator-blinded" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received. Participants were not blinded Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which

		intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (website): "investigator-blinded" Outcomes were investigator assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	2/20 (10%); azelaic acid left and no treatment right group (1), azelaic acid right and no treatment left group (1). Per protocol analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period before start of study adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Neuhaus 2009

Methods	RCT, prospective, active-controlled and controlled with "no treatment", investigator-blinded, within-patient comparison Date of study Unspecified Setting Dermatologic Surgery and Laser Center, Department of Dermatology, University of California, San Francisco, US
Participants	**Randomised:** 30 participants (mean age 45.8 ± 10.6 years, 9 male, 20 female and 1 gender unreported) **Inclusion criteria** • Participants had to be at least 18 years of age with moderate erythematotelangiectatic rosacea consisting of persistent background erythema and small-calibre (< 1 mm) vessels involving the central face **Ocular involvement:** Unclear **Exclusion criteria** • Previous treatment with laser or light-based device for rosacea

	• History of photosensitivity • Current treatment with a known photo-sensitising medication • Active inflammatory papules and pustules • Any changes in topical rosacea medical treatment in the preceding 3 months **Dropouts and withdrawals** • 1/30 (3.3%); 1 participant in the IPL control group dropped out after first treatment because of "excessive swelling reaction" **Baseline data mean (SD)** Nothing reported
Interventions	Three treatment sessions, each month **Intervention** Pulsed dye laser (PDL) **Comparator 1** Intense pulsed light (IPL) **Comparator 2** No treatment
Outcomes	Assessments (4): baseline, month 1, 2 and 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Erythema as scored by reflectance spectrophotometer✴ 2. Erythema grade and telangiectasia grade by investigator on a 4-point scale (0 = absent to 3 = severe)✴ 3. Quantitative telangiectasia counts by investigator✴ **Secondary outcomes** 1. Questionnaires completed by participants to evaluate efficacy and improvement of symptoms✴ 2. VAS to rate (participant's) symptoms of erythema, flushing, dryness, and overall skin sensitivity✴ 3. VAS to rate (participant's) overall improvement and tolerability after completion of all treatment sessions✴

	4. Willingness to undergo treatment again ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 927): "This study was funded by the American Society for Dermatologic Surgery Cutting Edge Research Grant."
Declaration of interest	Quote (page 920): "The authors have indicated no significant interest with commercial supporters"
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 87 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 921): "Treatment randomization was performed using a random number generator." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 921): "Only the patient and the investigator performing the therapies were aware of their treatment allocation." "A blinded investigator gave.." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 921): "Only the patient and the investigator performing the therapies were aware of their treatment allocation." "A blinded investigator gave.." Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers/participants) during the study Insufficient information to permit a clear judgement

Incomplete outcome data (attrition bias)	Low risk	Quote (page 922): "One patient in the IPL/control group dropped out after first treatment because of excessive swelling reaction. This patient did not return for follow-up. Remaining 29 patients completed all three treatment sessions." Comment: Low number of dropouts and although per-protocol analysis judged as at low risk of bias
Selective reporting (reporting bias)	High risk	No exact data are provided, only P values. All outcome measures are addressed but without exact data Comment: We judged this as at a high risk of bias
Other bias	Low risk	No wash-out period before study, study duration adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Nielsen 1983a

Methods	RCT, prospective, placebo-controlled, double-blind Date of study January to February 1982 Setting Department of Dermatology, Central Hospital, Boden, Sweden
Participants	**Randomised:** 81 participants (mean age 47 years, 32 male, 49 female) **Inclusion criteria** • Participants with rosacea in different degrees **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 4/81 (4.9%); metronidazole group (1) and placebo group (3) due to absence of improvement **Baseline data mean** Number of papules; metronidazole group 23.8 and placebo group 27.5 Number of pustules; metronidazole group 0.6 and placebo group 1.0
Interventions	Two months **Intervention** Metronidazole cream 1% - QD (41)

	Comparator Placebo (vehicle) - QD (40)
Outcomes	Assessments (3): baseline, month 1 and 2 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Physician's global evaluation (4-point Likert scale, 0% to 25% to 76% to 100% improvement)✶ 2. Lesion counts✶ 3. Reduction in erythema and telangiectasia✶ 4. Photographic evaluation 5. Participant subjective opinion of treatment (6-point Likert scale, much worse to much improved)✶ **Secondary outcomes** 1. Adverse effects✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 332): "The assays of plasma metronidazole were kindly performed by A/S Dumex Laboratories, Copenhagen, who also manufactured the test creams."
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 6 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 328): "....in accordance with a randomized administration scheme." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 327): "...double-blind." Comment: Although not explicitly stated it would appear that the active intervention and placebo cream were similar and most probably indistinguishable by participants and investigators. The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 327): "...double-blind." Outcomes were investigator- and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	4/81 (4.9%); metronidazole group (1) and placebo group (3) due to absence of improvement. Withdrawals/dropouts were accounted for but not included in the analysis. Per-protocol analysis Comment: Low number of drop-outs and although per-protocol analysis judged as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	A/S Dumex manufactured the test creams. Study duration adequate, no additional rosacea treatment allowed, adequate wash-out period before study started Comment: The study appeared to be free of other forms of bias

Nielsen 1983b

Methods	RCT, prospective, active-controlled, double-blind Date of study March to May 1982 Setting Department of Dermatology, Central Hospital, Boden, Sweden
Participants	**Randomised:** 51 participants (mean age 44 years, 17 male, 34 female) **Inclusion criteria** • Participants with rosacea **Ocular involvement:** Unclear **Exclusion criteria**

	• None reported **Dropouts and withdrawals** • 3/51 (5.9%); all in metronidazole group (2 because of pregnancy and 1 left for unknown reasons) **Baseline data mean (SD)** Nothing reported
Interventions	Two months **Intervention** Placebo cream QD and oxytetracycline BID - 250 mg (23) **Comparator** Metronidazole cream 1% QD and placebo tablets - BID (25)
Outcomes	Assessments (2): baseline and month 2 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in erythema (colour scale rating 1 to 5), number of papules and pustules and telangiectasia✴ 2. Physician's global evaluation (4-point Likert scale, 0% to 25% to 76% to 100% improvement)✴ 3. Photographic evaluation 4. Participant's subjective opinion of treatment effect (6-point scale, much improved to much worse)✴ **Secondary outcomes** 1. Side effects✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 65): "Coded tablets and test creams were kindly provided by A/S Dumex, Copenhagen"
Declaration of interest	None declared
Notes	Two of our primary outcomes was addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 72 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 63): "Fifty-one randomly selected patients etc..." "Patients were assigned at random to one of the two courses of treatment." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 65): 'Coded tablets and test creams were kindly provided by A/S Dumex." Comment: Form of central allocation. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 63): "...double-blind." Comment: Although not explicitly stated in the report it would appear that the active interventions were matched with similar and indistinguishable placebos
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 63): "...double-blind." Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	The dropouts are accounted for and included in ITT analysis Comment: Low number of dropouts combined with ITT analysis, judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Adequate study duration, adequate wash-out period before study started. No additional rosacea therapy allowed Comment: The study appeared to be free of other forms of bias

Nymann 2010

Methods	RCT, prospective, active-controlled, investigator-blinded, within-patient comparison

	Date of study Unreported Setting Dermatology Department of Bispebjerg Hospital, Copenhagen, Denmark
Participants	**Randomised:** 40 participants (mean age 54 years, gender unreported) **Inclusion criteria** • Symmetrically located facial telangiectasias **Ocular involvement:** Unclear **Exclusion criteria** • < 18 years • Asymmetry of the lesions • Immunodeficiency or photosensitivity • Pregnancy or lactation • Current use of anticoagulants, aspirins or anti-inflammatory drugs • Oral retinoid drugs within the past 6 months, • Medication known to induce photosensitivity within the past 3 months • Presence of a suntan prior to treatment **Dropouts and withdrawals** • 1/40 (2.5%); died not related to treatment **Baseline data mean** Nothing reported
Interventions	Three treatments at six week intervals **Intervention** Long pulsed dye laser (V-beam, 595 nm, Candela Laser Corp) **Comparator** Intense pulsed light therapy (Ellipse Flex, PR and VL2 applicators, Danish Dermatologic Development)
Outcomes	Assessments (2): baseline and month 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Efficacy was measured as reduction in telangiectasias on a 5 point scale (none (0%), poor (1% to 24%), fair

	(25% to 49%), good (50% to 74%), excellent (75% to 100% vessel clearance)) (photographs)✴ 2. Participants assessed intensity of pain (0 = no pain, 10 = worst imaginable pain)✴ 3. Participant satisfaction with the treatment (0 = poor, 10 = excellent)✴ 4. Participant preferred treatment **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 143): "Dermatologic Development, Hørsholm, Denmark lent the Ellipse Flex. Role of Companies: Danish Dermatologic Development,Hørsholm, Denmark, and Candela Corporation,Wayland, Massachusetts, USA, approved the treatment settings before study initiation. The companies had no role in design and conduct of the study, neither in the collection, analysis, and interpretation of data, nor in the preparation of the manuscript, review, or approval of the manuscript."
Declaration of interest	Quote (page 143): "None declared"
Notes	31 had telangiectasia related to rosacea, one had telangiectasia due to treatment with corticosteroids, and seven had idiopathic telangiectasia (and one died) Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 88 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 144): "Patients were randomly allocated.." and "Randomization was carried out by patients drawing lots between opaque sealed envelopes, containing cards with subject number and split side treatment code" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 144): "Randomization was carried out by patients drawing lots between opaque sealed envelopes, containing cards with subject number and split side treatment code" Comment: The report provides sufficient detail and reassurance that participants and

		investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	High risk	Investigators and participants were not blinded during the treatment phase Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 145): "Clinical efficacy was evaluated by one blinded trained physician" Outcomes were investigator and participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	1/40 (2.5%); died not related to treatment. Per-protocol analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period adequate before study started Comment: The study appeared to be free of other forms of bias

Park 2016

Methods	RCT, prospective, controlled with "no treatment", single-blinded, within-patient comparison Date of study January to August 2015 Setting Department of Dermatology, Seoul National University College of Medicine, Seoul, South Korea
Participants	**Randomised**: 21 participants (mean age 42.9 years, 1 male, 20 female) **Inclusion criteria** • Subjects with Fitzpatrick skin Types III or IV and those aged 20 to 60 years who had mild to moderate rosacea **Ocular involvement:** Unclear **Exclusion criteria:**

	• None reported **Dropouts and withdrawals:** None reported **Baseline data mean** Mild rosacea severity 12, moderate severity 9 Erythema Index; treated side 17.8, untreated side 17.0
Interventions	12 weeks **Intervention** Fractional microneedling radiofrequency (FMR) **Comparator** No treatment Each patient received 2 sessions of treatment with a 4-week interval between treatments. Subjects were not allowed to use any systemic or topical agent for rosacea treatment during the study
Outcomes	Assessments (2): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Clinical assessments with the photographs 2. Investigator's Global Assessment (IGA)✴ 3. Measurement of erythema was performed with 2 photometric devices (DermaSpectrometer; Cortex Technology, Hadsund, Denmark and Spectrophotometer CM-2002; Konica Minolta, Tokyo, Japan)✴ 4. Patients' subjective assessments (0, no pain; 10, the most severe pain)✴ 5. Subjective therapeutic effectiveness (0, no effect; 10, the most effective)✴ 6. Satisfaction score (0, no satisfaction; 10, the most satisfactory) 7. Skin biopsies **Secondary outcomes** • None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1362): "Supported by grant 04-2015-0350 from the SNUH Research Fund and National Research Foundation of Korea grant funded by the Korea government (MSIP) (No. 2014R1A2A1A11049397)"

Declaration of interest	Quote (page 1362): "The authors have indicated no significant interest with commercial supporters"
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 93 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1363): "randomized" Comment: Insufficient information about the method used to generate the allocation sequence to allow an assessment of whether it should produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1363): "single-blind" Not clear what measures were used to blind study personnel from knowledge of which intervention a participant received. Participants were not blinded Comment: The report did not provide sufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 1363): "single-blind" Outcomes were investigator as well as participant-assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study. Participants were not blinded Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	No drop-outs reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was not available, but the pre-specified outcomes and those

		mentioned in the methods section appeared to have been reported. However, limited data were provided regarded the untreated side Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Study duration adequate, wash-out period adequate before study started Comment: The study appeared to be free of other forms of bias

Pye 1976

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unspecified Setting Department of Dermatology, Bristol Royal Infirmary, Bristol, UK
Participants	**Randomised:** 29 participants (age 24 to 86 years, gender unreported) **Inclusion criteria** • Participants with different degrees of rosacea **Ocular involvement:** Unclear **Exclusion criteria** • Participants with comedones or acne scars, use of corticosteroid and systemic tetracyclines within 4 weeks of study entry **Dropouts and withdrawals:** 1 in each group because of headache **Baseline data mean (SD)** Nothing reported
Interventions	Six weeks **Intervention** Metronidazole 200 mg BID combined with hydrocortisone 1% cream (15) **Comparator** Lactose BID combined with hydrocortisone 1% cream (14)
Outcomes	Assessments (2): baseline and week 6 **Outcomes of the trial** (as reported) **Primary outcomes**

	1. Clinical severity assessed (with the aid of 2 full-face colour photographs) by physician (4-point Likert scale, worse to definitely improved)✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	Nothing reported
Declaration of interest	Nothing declared
Notes	None of our primary outcomes were addressed See comparison 70 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 1212): "The treatment was allocated at random..." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	Quote (page 1212): "The treatment was allocated at random without the knowledge of the doctor or the patient." The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 1211): "...double-blind" "...metronidazole 200 mg twice daily or a lactose placebo tablet.." Comment: Although not explicitly stated it would appear that the active intervention and placebo tablets were similar and most probably indistinguishable by participants and investigators. The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Low risk	Quote (page 1211): "...double-blind." "...metronidazole 200 mg twice daily or a lactose placebo tablet.." Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	2 withdrawals in each group were accounted for. Per-protocol analysis Comment: Low number of dropouts and although per-protocol analysis judged as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration short, unclear if groups were treated equally and if additional rosacea therapy was allowed, adequate wash-out period before study Comment: Insufficient information to assess whether an important risk of bias exists

Raoufinejad 2016

Methods	RCT, prospective, placebo-controlled, double-blind, within-patient comparison Date of study May 2011 to March 2014 Setting Dermatology clinic of Imam Khomeini Hospital, Tehran, Iran
Participants	**Randomised:** 34 participants (mean age 42.2 years, male 3, 17 female, 14 gender unreported) **Inclusion criteria** • ≥18 years, newly diagnosed with mild-to-severe bilateral papulopustular rosacea and ≥5 Demodex mites per cm² in the samples of both left and right sides of the face obtained by SSSB **Ocular involvement:** Unclear (at least not treated when included) **Exclusion criteria** • Pregnancy or lactation • Systemic diseases • Dermatological malignancies • Burnings

	• Infections • Systemic medications of any kind • Receiving treatment for ocular rosacea • Fulminant rosacea • Known allergy to permethrin. **Dropouts and withdrawals** • 14/34 (41.2%) • Lost to follow-up (10) • Discontinued to to adverse event (4) **Baseline data median** Demodex density/cm²; permethrin side 274.1, placebo side 217.5
Interventions	12 weeks **Intervention** Permethrin 5% gel - BID **Comparator** Placebo gel - BID All medications and cosmetics were discontinued from at least 2 weeks prior to participation to the end of the treatment course
Outcomes	Assessments (5): baseline, week 2, 5, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Demodex mites/cm² **Secondary outcomes** 1. Clinical presentations of both sides of the face were assessed by photography and the clinical criteria of the National Rosacea Society Scorecard (Wilkin 2004)✴ 2. Global Assessment by both investigators and participants (absent to severe)✴ 3. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 2105): "This study was funded through an educational grant to the researchers from the Deputy of Research, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran. Grant code: 8153"

Declaration of interest	Quote (page 2105): "Conflicts of interest: None declared"
Notes	Two of our primary outcomes were assessed (participant-assessed changes in rosacea severity and adverse events) See comparison 18 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 2107): "the random allocation sequence by the process of minimization" and "following simple randomization procedure, coin tossing, with a 1 : 1 allocation ratio" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 2107): "following simple randomization procedure coin tossing, with a 1 : 1 allocation ratio. The 'heads' were supposed as 'right half-face: permethrin 5%' (group A) and the 'tails' were assumed as 'left half-face: permethrin 5%' (group B). In each case, the reverse half-face was allocated to the placebo group. The allocation sequence was concealed from the participants, healthcare providers (KR, PM, ZN, RJ), data collector (KR) and outcome adjudicators (KR, PM). The data analyst (MR) was aware of the allocation in this double-blind trial" Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 2107): "Permethrin 5% and placebo were in gel forms pre-packed in separate, similar, sealed, aluminium tubes consecutively numbered and labelled as 'right' or 'left' for each patient's half-faces according to the allocation sequence. Each patient was assigned an order number and received the gels in the corresponding prepacked tubes. To prevent subversion of the allocation sequence, labelling and grouping were performed by a third-party (MR) Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome	Low risk	Outcomes were investigator and participant assessed

assessment (detection bias)		Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	High risk	14/34 (41.2%), reasons reported. Per-protocol analysis Comment: We judged this as at high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on http://en.irct.ir/trial/15620 (IRCT2014030416837N1) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period adequate before study started Comment: The study appeared to be free of other forms of bias

Rehmus 2006

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, US
Participants	**Randomised:** 40 participants (age and gender unreported) **Inclusion criteria** • Subjects with rosacea 18 to 70 years **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • Not reported **Baseline data mean** Nothing reported
Interventions	12 weeks **Intervention** Anti-inflammatory cream - BID **Comparator**

	Placebo cream No other skin care products or emollients were allowed for the duration of the study
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Standard quantitative and qualitative assessments of rosacea **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page AB64): "100% supported by Nu Skin Enterprises"
Declaration of interest	Quote (page AB64): "Salary support through clinical trials sponsored by Nu Skin Enterprises"
Notes	Poster abstract, no results presented, limited data (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page AB64): "Each subject was randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page AB64): "double-blind." Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page AB64): "double-blind." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study. Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	No data provided Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Outcomes unclear and no data provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Rigopoulos 2005

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre. Department of Dermatology, University of Athens, Andreas Aygros Hospital, Athens, Greece; IRIS, Institute de Recherches et d'Innovations Scientifiques, Paris, France; 4 Private Practices, Germany
Participants	**Randomised:** 246 participants (mean age 48.9 years (range 18 to 80), 34 male and 91 female in treatment group, 36 male and 85 female in placebo group) **Inclusion criteria** • Participants with clinical diagnosis of facial rosacea corresponding to grades 2 to 4 of photographic album **Ocular involvement:** Unclear **Exclusion criteria** • Use of topical facial therapy or oral therapy of any kind within 6 weeks prior to study entry • Use of any cosmetic aimed at improving rosacea within 2 weeks prior to inclusion • Pregnant and lactating women • Participants predicting some change in their lifestyle • Use of any drug, especially vasoactive or CNS drugs **Dropouts and withdrawals**

	• 17/246 (6.9%); treatment group (11) and placebo group (6) all because of adverse events **Baseline data mean (SEM)** Erythema severity; treatment group 2.71 (0.07) and placebo group 2.86 (0.07) Rosacea overall severity; treatment group 3.21 (0.1) and placebo group 3.3 (0.08)
Interventions	12 weeks **Intervention** Cream containing 1% extract of a flavonoid-rich plant *Chrysanthellum indicum* - BID (125) **Comparator** Placebo (vehicle) - BID (121)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Severity level of erythema✶ 2. The erythema surface: surface delineated by investigator on a devoted sketch in case report form (CRF), then scanned for automated computerised calculation (AutoCAD 2000)✶ 3. Investigator's Overall Assessment (taking into account erythema surface and severity, 7-point Likert scale)✶ 4. Investigator's final efficacy assessment (based on his or her experience of other treatments)✶ **Secondary outcomes** 1. Participant efficacy assessment✶ 2. Safety and tolerability by frequency of adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 568): "This study was supported by a grant from the research Division of the European Council – 5th plan."
Declaration of interest	Quote (page 568): "None of the authors has any conflict of interest to declare including financial arrangements, interest or share holding options with the company manufacturing the product."
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events).

	The review authors imputed SDs for mean reduction from baseline in rosacea severity score using 3 correlations between the baseline and final measurements See comparison 42 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 565): "This multicentre, randomized, double-blind, parallel group, placebo-controlled, study..." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 564-5): "Double-blind" and "As the active ingredient resulted in a slightly coloured final product, colour of placebo (vehicle) was adjusted accordingly." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 564-5): "Double-blind" and "As the active ingredient resulted in a slightly coloured final product, colour of placebo (vehicle) was adjusted accordingly." Outcomes were investigator- and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	High risk	Only 96 participants in the treatment group and 100 in the placebo group appear to be included in analysis. The analysis excluded the remaining participants (20%) because of "missing grade values for any examination" (quote page 566). Per-protocol analysis Comment: We judged this as at a high risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Wash-out period adequate, study duration adequate, groups treated equally. Study was supported by a grant from the research Division of The European Council - fifth plan None of the authors have any conflicts of interest to declare, including financial arrangements Comment: The study appeared to be free of other forms of bias

Rodríguez 2003

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Centro Dermatológico Pascua, Ciudad de Mexico, Mexico
Participants	**Randomised:** 34 participants (mean age unreported, 11 male, 20 female, 3 gender unreported) **Inclusion criteria** • Greater than 18 years of age with diagnosis of rosacea • No treatment 30 days prior to study entry • Positive biopsy for *Demodex folliculorum* with > 5 mites per cm² **Ocular involvement:** Unclear **Exclusion criteria** • Not reported **Dropouts and withdrawals** • 3/34 (8.8%) of benzyl benzoate group, lost to follow-up (2), pregnancy (1) **Baseline data mean** Nothing reported
Interventions	45 days **Intervention** Crotamiton 10% cream - QD (17) **Comparator**

	Benzyl benzoate 25% cream - QD (17)
Outcomes	Assessments (5): baseline, week 2, 4, 6 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in *Demodex folliculorum* (2 methods of assessment, direct microscopy and biopsy) **Secondary outcomes** 1. Tolerance, adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (adverse events) See comparison 47 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 128): "se dividieron al azar en dos grupos" (were divided at random in two groups) Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 126): "estudio doble ciego" (double-blind) Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 126): "estudio doble ciego" (double-blind) Comment: Outcomes were investigator and participant-assessed. Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	3/34 (8.8%) of benzyl benzoate group, lost to follow-up (2), pregnancy (1). Per-protocol analysis Comment: Unbalanced, but low number of follow up, judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, no wash-out period before study described, groups treated equally Comment: The study appeared to be free of other forms of bias

Saihan 1980

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Department of Dermatology, Bristol Royal Infirmary, Bristol, UK
Participants	**Randomised:** 40 participants (age and gender unreported) **Inclusion criteria** • Participants with papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 2/40 (5%); both in metronidazole group (lost to follow up) **Baseline data mean (SD)** Nothing reported

Interventions	12 weeks **Intervention** Oxytetracycline 250 mg - BID (20) **Comparator** Metronidazole 200 mg - BID (20)
Outcomes	Assessments (3): baseline, week 6 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Clinical improvement assessed by participant and two doctors (scale - 1 = worse to 3 = much improved)✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Nothing reported
Declaration of interest	None declared
Notes	Although independent assessments were made by the participant and 2 doctors these were combined and presented as a composite score See comparison 63 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 443): "...treated...on a random double-blind basis." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	Quote (page 443): "...coded tablets being issued by the pharmacist." Comment: Pharmacy-controlled, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 443): "Double-blind basis...coded tablets." Comment: Although not explicitly stated it would appear that the active intervention and placebo tablets were similar and most probably

		indistinguishable by participants and investigators. The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 443): "Double-blind basis...coded tablets." Outcomes were investigator assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Two dropouts were accounted for but not included in analyses. Per-protocol analysis Comment: Low number of dropouts and although per-protocol analysis judged as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, wash-out period before study adequate. No sponsorship or conflict of interest reported Comment: Insufficient information to assess whether an important risk of bias exists

Salem 2013

Methods	RCT, prospective, active-controlled, single-blind Date of study June 2011 to February 2012 Setting Dermatology and Ophthalmology Clinic of the Mansoura University Hospitals, Mansoura City, Egypt
Participants	**Randomised:** 120 participants (mean age 36.1 years (SD 12.4), 56 male, 64 female) **Inclusion criteria** • Subjects with acne vulgaris, rosacea, peri-oral dermatitis and anterior blepharitis • For the subjects with skin lesions: a treatment-resistant infestation, with *D. folliculorum* mite density > 5 mites/cm² **Ocular involvement:** Participants with ocular manifestations were included **Exclusion criteria**

	• A mite density ≤ 5 mites/cm² for skin lesions or with < 3 living mites/eyelash • History of systemic or topical antibacterial or anti-inflammatory drugs in the 60 days before study entry • Known hypersensitivity to ivermectin or metronidazole • Pregnant women Additionally in patients with anterior blepharitis • Posterior or mixed blepharitis • Contact lenses • Meibomian gland dysfunction • Any previous eye surgery **Dropouts and withdrawals** • "No patient missed any follow-up visit or discontinued treatment" **Baseline data mean (SD)** Demodex density acne group (30); ivermectin group 12.3 (3.2), combined group 12.9 (6.1) Demodex density rosacea group (30); ivermectin group 51.7 (20.8), combined group 51.5 (26.3) Demodex density peri-oral dermatitis group (30); ivermectin group 21.3 (7.5), combined group 21.9 (6.8) Demodex density blepharitis group (30); ivermectin group 12.8 (6.8), combined group 15 (5.7)
Interventions	Two weeks **Intervention** Metronidazole 250 mg -TID for 2 weeks and ivermectin two doses of 200 µg/kg 1 week apart (60) **Comparator** Ivermectin two doses of 200 µg/kg 1 week apart (60)
Outcomes	Assessments (5): baseline, week 1, 2, 3 and 4 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Decrease in *D. folliculorum* (standardised skin surface biopsy and for the eyes three eyelashes from each lower eyelid were epilated with fine forceps) **Secondary outcomes**

	1. Clinical improvements in itching, burning, redness, and scaling at the root of the lashes in patients with anterior blepharitis✶ 2. Clinical improvements in erythema, dryness, scaling, roughness, and/or papules/pustules in skin lesions✶ ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page e347): "Conflict of Interest: None"
Notes	None of our primary outcomes was addressed See comparison 77 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page e344): "randomly assigned to either combined therapy or ivermectin treatment at a ratio of 1:1 (15 patients for each treatment regimen from each group) using a computer-generated randomization schedule." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Quote (page e344): "The assignment was done in a single-blinded manner, in which the subjects were blinded to the treatment assignment." Comment: It looks like allocation concealment is confused with blinding, we did not receive additional information of the principal investigators. The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page e344): "The assignment was done in a single-blinded manner, in which the subjects were blinded to the treatment assignment." Comment: Investigators were not blinded. The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome	High risk	Quote (page e344): "Assessment of the outcome samples was done by two unblinded

assessment (detection bias)		parasitologists and then reviewed by another independent blinded professor of parasitology to avoid bias" Comment: The other outcomes were assessed by unblinded investigators and the measurement of those outcomes was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No losses to follow-up. Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before start of study adequate, groups treated equally Comment: The study appeared to be free of other forms of bias

Sanchez 2005

Methods	RCT, prospective, "placebo"-controlled (placebo tablets, but also topical metronidazole), double-blind Date of study Unreported Setting Unspecified, US
Participants	**Randomised:** 40 participants (mean age 41.6 years in metronidazole + doxycycline group versus 38.8 years in metronidazole + placebo group, 3 male and 17 female versus 5 male and 15 female) **Inclusion criteria** • Male and female adults > 18 years of age • Participants with rosacea, presenting with 8 to 30 papules plus pustules and no more than 2 nodules • Score 2 to 4 on Clinician's Global Severity Score • Presence of moderate to severe erythema (score 2 to 4) in at least 1 of the facial areas • Total score of 5 to 20 on the Clinician's Global Erythema assessment • Presence of telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Pregnancy and lactating female

	• Females initiating, changing hormonal contraception within four months of baseline • Systemic and topical antibiotics within four weeks of baseline **Dropouts and withdrawals** • 5/40 (12.5%); all in metronidazole group (personal reasons (2), protocol violation (1), illness (1), erythema at application site (1) **Baseline data mean (SEM)** Total inflammatory lesions; metronidazole group 25.9 (3.7), doxycycline group 27.3 (3.6) Clinician's Global severity score; metronidazole group 2.6 (0.17), doxycycline group 2.7 (0.17) Clinician's Global Erythema assessment; metronidazole group 9.8 (0.71), doxycycline group 9.5 (0.69)
Interventions	12 weeks **Intervention** Metronidazole 0.75% lotion BID + doxycycline hyclate 20 mg BID (followed by 4 weeks monotherapy of doxycycline hyclate) (20) **Comparator** Metronidazole 0.75% lotion BID + placebo tablets BID (followed by 4 weeks placebo tablets) (20)
Outcomes	Assessments (3): baseline, week 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change from baseline in total inflammatory lesion count (papules plus pustules plus nodules) at 12 and 16 week visits)✶ **Secondary outcomes** 1. Changes from baseline at weeks 12 and 16 in Clinician's Global Severity Score and Clinician's Global Erythema Assessment (both assessed on 5-point Likert scale)✶ 2. Adverse events✶ ✶Denotes outcomes pre-specified for this review

Funding source	Quote (page 791): "Supported by CollaGenex Pharmaceuticals, Inc."
Declaration of interest	Quote (page 791): "Conflicts of interest: None identified". One of the investigators was employed by CollaGenex
Notes	One of our primary outcomes was addressed (adverse events) See comparison 68 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 792): "Randomization was accomplished by assigning numbers to the sub antimicrobial dose doxycycline and placebo bottles based on the SAS statistical software randomization procedure. Each patient entering the study received the next sequentially numbered bottle." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Unclear if this was done 'centrally'. There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 792): "...double-blind." and "All study tablets were identical in size, shape, and colour (white)." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 792): "...double-blind." and "All study tablets were identical in size, shape, and colour (white)." Outcomes were investigator and participant-assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	Reasons for withdrawal were reported. ITT analysis (LOCF) was carried out Comment: Low number of dropouts, ITT analysis, judged as at low risk of bias

Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period adequate. Concomitant medications that could influence rosacea were prohibited Comment: The study appeared to be free of other forms of bias

Sauder 1997

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, Dermatology department of different centres in Canada and UK
Participants	**Randomised:** 103 participants (mean age 50 years, 40 male, 63 female) **Inclusion criteria** • Participants with moderate to severe rosacea with at least five inflammatory lesions bilaterally and and moderate to severe bilateral erythema **Ocular involvement**: Unclear **Exclusion criteria** • Participants younger than 22 years of age • > 3 nodular lesions • Other dermatological disorders **Dropouts and withdrawals** 9/103 (8.7%); treatment group (2) and placebo group (1), due to adverse events, for the remaining 6 it is unclear from which group, but were also excluded from the analysis **Baseline data mean (SD)** Inflammatory lesion count; treatment group 35.6 and placebo group 28.0
Interventions	Eight weeks **Intervention** Topical sodium sulphacetamide 10% and sulphur 5% lotion - BID **Comparator**

	Placebo (vehicle) - BID
Outcomes	Assessments (4): baseline, week 1, 4 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Physician's global evaluation (-3 = much worse, 3 = much improved)✶ 2. Lesion count reduction✶ 3. Participant's assessment of improvement of rosacea (-3 = much worse, 3 = much improved)✶ 4. Erythema (0 = none, 3 = severe)✶ **Secondary outcomes** 1. Adverse effects✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 85): "This study was funded in part by GenDerm Corporation, Lincolnshire, Illinois"
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events). Unclear how many participants in each group, although it was reported "comparable numbers". Skewed data See comparison 33 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 80): "...dispensed to patients in a randomized, double-blind fashion." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement

Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 80): "...double-blind fashion..." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 80): "...double-blind fashion..." Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers/participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	9/103 (8.7%); treatment group (2) and placebo group (1), due to adverse events, for the remaining 6 it is unclear from which group, but were also excluded from the analysis Comment: Low number of dropouts, but unclear how many started in each group and how many dropped out in each group, judged as unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration rather short, wash-out period before study adequate, no concomitant medication allowed Comment: The study appeared to be free of other forms of bias

Sbidian 2016

Methods	RCT, prospective, placebo-controlled, double-blind Date of study February 2007 to August 2009 Setting Multicentre (43), in France
Participants	**Randomised:** 156 participants (mean age 46 years, 56 male, 100 female) **Inclusion criteria** • ≥ 18 years old were included if they had difficult-to-treat papulopustular rosacea (subtype 2) with at least eight lesions (Wilkin 2004) • Difficult-to-treat rosacea was defined as being resistant to at least 3 months of cycline use, combined or not

	with topical metronidazole or azelaic acid application within the last 2 years or relapsing after that cycline regimen • For women of childbearing age, effective contraception for at least one month and pregnancy tests before starting the study treatment, monthly under treatment, and 5 weeks after stopping treatment were required **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 33*/156 (21.2%); isotretinoin group (21), placebo group (12) • Unassessable primary endpoint; isotretinoin group (17), placebo group (13) • Failed to meet the inclusion criteria; isotretinoin group (2), placebo group (2) • < 70% compliance; isotretinoin group (2), placebo group (2) • Treatment contraindication; isotretinoin group (1), placebo group (0) • Prohibited medication during study; isotretinoin group (0), placebo group (1) • Randomisation error; isotretinoin group (1), placebo group (1) *Patients could have one or several major deviation(s). **Baseline data median** Number of lesions; isotretinoin group 17, placebo group 15 Skindex; isotretinoin group 39.7, placebo group 33.2 Difficult to treat rosacea - cycline-refractory (n); isotretinoin group 49, placebo group 16 Difficult to treat rosacea - frequently relapsing (n); isotretinoin group 59, placebo group 32
Interventions	4 months **Intervention** Isotretinoin 0.25 mg/kg/day - QD (108) **Comparator** Placebo tablets - QD (48)

	Treatment with cyclines, vitamin A derivatives, metronidazole, azelaic acid, or ivermectin was prohibited during the study period
Outcomes	Assessments (5): baseline, month 1, 2, 3 and 4 (+ week 6 and 8 for responders at month 4) **Outcomes of the trial** (as reported) **Primary outcomes** 1. To determine number of participants responding to treatment for 4 months with isotretinoin (participants were considered as responders if their number of papular-pustular lesions fell by at least 90% after 4 months of treatment)✶ **Secondary outcomes** 1. Absolute changes from baseline of the number of lesions✶ 2. Improvement in participant's quality of life using the reduced Skindex-France QoL scale (30 items)✶ 3. Change in severity of other symptoms of rosacea (burning sensation, erythema, telangiectasia, vasomotor flush, etc)✶ 4. Patient satisfaction (VAS) 5. Investigator-assessed global treatment efficacy (global assessment)✶ 6. Quantity of emollients used 7. Relapse rates at 8 months (after start of treatment)✶ 8. Safety (number of adverse events)✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 1128): "This trial was funded by Bailleul Laboratory. The funding sources had no role in the study design, data collection, data analysis and interpretation, or writing of the report."
Declaration of interest	Quote (page 1129): "The authors declare that OC, BC, BD, and EV have support from Bailleul for the submitted work; BC and BD have support from Galderma that might have an interest in the submitted work in the previous 3 years. HC and EA were employees in Bailleul during the conduct of this study"
Notes	Two of our primary outcomes were assessed (quality of life and adverse events) See comparison 75 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1128); "Using permuted blocks of six randomly assigned at a 2:1 ratio, patients were to receive isotretinoin or placebo. The randomization schedule was generated by SAS software v9.2 (SAS Statistical Institute) leading to a random allocation sequence without foreknowledge of treatment assignment by the investigators and was delivered to the sponsor (Laboratoire Bailleul), who provided the treatment kits Comment: Probably done
Allocation concealment (selection bias)	Low risk	Pharmacy controlled allocation of the test kits provides reasonable reassurance that the allocation sequence was adequately concealed and that the investigators enrolling patients as well as the patients were unable to foresee the upcoming assignment
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 1124): "double-blind" and "to the sponsor (Laboratoire Bailleul, Paris, France), who provided the treatment kits" After e-mail communication: "isotretinoin and placebo capsules looked similar, and had similar packages" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	33/156 (21.2%); balanced between groups, reasons reported. ITT with LOCF Comment: High number of drop-outs but ITT analysis judged as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available on clinicaltrials.gov (NCT00882531). The pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period adequate before study started

		Study funded by Bailleul Laboratory and several investigators were employees or received payment by Bailleul Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship or support represented any additional bias

Schachter 1991

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Multicentre, Women's College Hospital, Toronto, Ontario; General Practice in Ontario, and Rhône Poulenc Rorer Canada, Montreal, Quebec, Canada
Participants	**Randomised:** 125 participants (mean age 45.4 ± 1.3 (SEM), 40 male, 61 female, 24 gender unreported) **Inclusion criteria** • Male and female participants > 18 years with a diagnosis of papulopustular rosacea limited to the face **Ocular involvement:** Unclear **Exclusion criteria** • Participants who received antibiotics, vasodilatators, or any type of treatment for rosacea in the month preceding the trial • Hypersensitivity to the study drugs **Dropouts and withdrawals:** • 24/125 (19.2 %) withdrew for reasons not related to treatment, unclear from which group **Baseline data mean (SEM)** Number of papules; metronidazole group 18.35 (1.9), tetracycline group 21.04 (1.9) Number of pustules; metronidazole group 4.67 (0.7), tetracycline group 4.40 (0.7)
Interventions	Two months **Intervention** Metronidazole 1% cream BID and placebo capsules - TID (49) **Comparator**

	Placebo cream BID and tetracycline 250 mg - TID (52) Only number of participants that completed the study
Outcomes	Assessments (3): baseline, month 1 and 2 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Clinical evaluation, including count of the numbers of pustules, papules, and telangiectasia, and an assessment of the degree of erythema (0 = no erythema, 5 = severe erythema)✴ 2. Adverse events✴ 3. Global evaluations by participant taking into account treatment efficacy and adverse effect profile (1 = very much improved, 7 very much worse) 4. Efficacy index was calculated from scores based on investigator's assessments of therapeutic and adverse effects. The therapeutic effect was rated on a scale of 1 to 4 (4 = marked improvement, 1 = unchanged or worse). Efficacy index was calculated as the therapeutic score divided by the adverse effect score✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported, but one investigator was employed by Rhone Poulenc Rorer Canada, manufacturer of metronidazole
Declaration of interest	None declared
Notes	Two of our primary outcomes were assessed (participant-assessed changes in rosacea severity and adverse events) See comparison 72 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 221): "Patients were randomly administered either metronidazole cream and placebo capsules or placebo cream and tetracycline capsules." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 221): "Placebo and active cream and capsules were matched as appropriate." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 221): "Placebo and active cream and capsules were matched as appropriate." Outcomes were investigator- and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	High risk	Unclear how many participants were actually allocated to each group. After randomisation 24/125 (19%) withdrew from the study for reasons unrelated to treatment. Additional withdrawals occurred during the course of the study (9) Metronidazole group 2/49 discontinued treatment because of lack of efficacy, or adverse events (5) Tetracycline group 2/52 discontinued because of adverse events The dropouts and withdrawals were not included in the analysis Comment: The high dropout rate and the per-protocol analysis represents a potentially high risk of bias
Selective reporting (reporting bias)	Unclear risk	Data presented in graphs had to be extracted from figures All pre-specified outcomes appear to have been addressed Comment: Insufficient information to permit a clear judgement
Other bias	Low risk	Wash-out period adequate, study duration adequate, groups treated equally, sponsorship or support not reported

		Comment: The study appeared to be free of other forms of bias

Schechter 2009

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Florida Eye, Microsurgical Institute, Florida, US
Participants	**Randomised:** 37 participants (age 75.6 years in ciclosporin group and 69.6 years in artificial tears group, 15 males and 6 females in ciclosporin group and 9 males and 7 females in artificial tears group) **Inclusion criteria** • Participants with ocular associated rosacea (lid margin telangiectasia, meibomian gland inspissation, or fullness of the lid margin) • **Exclusion criteria** Eyelid defects, lagophthalmos, sensitivity to study medication **Dropouts and withdrawals** • 3/37 (8.1%); ciclosporin group (2) and artificial tear group (1) • Lost to follow-up; ciclosporin group (1) and artificial tear group (1) • Stinging; ciclosporin group (1) and artificial tear group (0) **Baseline data mean (SD)** Schirmer score; ciclosporin group 9.7 mm (5.1) and artificial tear group 10.2 mm (5.8)
Interventions	Three months **Intervention** Ciclosporin 0.05% ophthalmic emulsion - BID (21) **Comparator** Artificial tears - BID (16)
Outcomes	Assessments (2): baseline, month 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Ocular Surface Disease Index (OSDI) on a scale of 0 to 100 (100 = worst) to determine the impact of ocular

	surface disease (normal, mild, moderate, severe) on quality of life✴ 2. Schirmer test✴ 3. Measurement of corneal staining✴ 4. TBUT (tear breaking-up time)✴ 5. Corneal staining score 6. Number of Meibomian glands expressed 7. Quality of the excreta were also evaluated (1 = clear excreta or clear small particles, 2 = opaque excreta with normal viscosity, 3 = opaque excreta with increased viscosity, and 4 = secretions retain shape after expression) **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 658): "This study was funded by an unrestricted educational grant from Allergan, Inc."
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (quality of life) See comparison 37 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 653): "Patients were randomised by computer." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 653): "...double-masked clinical trial." "The vials for each product were identical, ensuring patient and clinicians masking." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Low risk	Quote (page 653): "...double-masked clinical trial." "The vials for each product were identical, ensuring patient and clinicians masking." Outcomes were investigator- and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken. Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	3/37 (8.1%) Dropouts and withdrawals reasons were clarified. Per-protocol analysis Comment: Low number of dropouts and although per-protocol analysis judged as at low risk of bias
Selective reporting (reporting bias)	Unclear risk	The pre-specified primary outcomes were addressed, other than one of the secondary outcome measures, the quality of excreta of the Meibomian glands Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Participants were in the older age group and almost exclusively Caucasians. Wash-out period before study and duration adequate, no additional medication allowed that might influence outcome. The study was funded by an unrestricted educational grant from Allergan, Inc (page 659) Comment: The study appeared to be free of other forms of bias

Seité 2013

Methods	RCT, prospective, vehicle-controlled, double-blind Date of study Unreported Setting Single-centre Europe
Participants	**Randomised:** 66 participants (mean age 52 years (SD 11), 19 males, 47 females) **Inclusion criteria** • Subjects with rosacea **Ocular involvement**: Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** None

	Baseline data mean (SD) Intensity of the rosacea; light (26), moderate (31), severe (9)
Interventions	Eight weeks **Intervention** Test formula (skin care product containing ambophenol, neurosensine and thermal spring water) - BID (32) **Comparator** Vehicle - BID (34) All participants were treated the 8 weeks before with topical metronidazole
Outcomes	Assessments (5): baseline, week 2, 4, 6 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Face sensitivity as evaluated by the physician (telangiectasia, erythema, dryness, desquamation) 2. Face sensitivity as evaluated by the participant (pruritus, tingling, burning) 3. Global improvement of rosacea assessed by physician✴ 4. Global improvement as assessed by the participant✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 924): "The studies were funded by la Roche-Posay Pharmaceutica Laboratories France"
Declaration of interest	Quote (page 924): "All the authors except M Skalikova, L. Gibejova and H. Zelenkova, are employees of L'Oréal.'
Notes	The article covers 3 studies, only study 3 is a RCT and is included in this review One of our primary outcomes was addressed (participant assessed changes in rosacea severity). Skewed data See comparison 48 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Low risk	Quote (page 922): " randomized....." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "The allocation sequence was generated by a statistician using a specific software" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement No further information after e-mail communication
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 922): "double blind...." After e-mail communication: "Both products was in the same packaging (blind white packaging) without any indication about formula reference" Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 922): "double blind...." After e-mail communication: "Both products was in the same packaging (blind white packaging) without any indication about formula reference" Comment: Outcomes were investigator and participant-assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	No dropouts Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias

Other bias	Unclear risk	The article provided only limited data Comment: There was insufficient information to permit a clear judgement

Seo 2016

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Department of Dermatology, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea
Participants	**Randomised:** 49 participants (mean age 49 years, 19 male, 18 female, 12 gender unreported) **Inclusion criteria** • ≥18 years of age with Fitzpatrick skin types III-V and a clinical diagnosis of rosacea with erythematotelangiectatic or papulopustular subtype **Ocular involvement**: Unclear, but no severe ocular rosacea **Exclusion criteria** • Severe phymatous or ocular rosacea • Concurrent skin condition affecting the face • History of keloid • History of photosensitive disease • Treatment with oral isotretinoin during the 6 months prior to the study • Any oral medication or treatment that could affect facial erythema during the month prior to the study • History of alcohol abuse • Pregnant or lactating women **Dropouts and withdrawals** • 12/49 (24.4%); PDL group (6), LPAN group (6) • Lost to follow-up; PDL group (5), LPAN group (6) • Discontinued; PDL group (1), LPAN group (0) **Baseline data mean (SD)** Baseline erythema index; PDL group 18.1 (3.8), LPAN group 17.3 (2.3)
Interventions	Four consecutive monthly treatments **Intervention** 585-nm pulsed dye laser (PDL) (25) **Comparator**

	Dual wavelength long-pulsed 755-nm alexandrite/1,064-nm neodymium: yttrium-aluminum-garnet laser (LPAN) (24)
Outcomes	Assessments (3): baseline, month 4,5 (2 weeks after last treatment) and 10 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Mean reduction of the erythema index measured by a spectrophotometer from baseline (Dermatospectrometer spectrophotometer -Cortex Technology Inc., Hadsund, Denmark)✴ **Secondary outcomes** 1. Physician's global assessment✴ 2. Subjective satisfaction assessment (1 = no change or worsening, 2 = poor, 3 = fair, 4 = good,and 5 = excellent) 3. Procedure-associated pain 4. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 613): "This research was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number : HI13C2206)"
Declaration of interest	None declared
Notes	One of our primary outcomes was assessed (adverse events) See comparison 85 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 608): "Randomization was achieved by determining the treatment laser for each subject number before assigning any subject with a subject number" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	Investigators providing the treatment and participants were not blinded Comment: We judged this as at a high risk of bias
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 609): "The physician's global assessment was evaluated by two blinded consultant dermatologists" Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	High risk	12/49 (24.4%); PDL group (6), LPAN group (6). Per protocol analysis Comment: High number of drop-outs combined with per protocol analysis judged as at a high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period adequate before study started Comment: The study appeared to be free of other forms of bias

Sharquie 2006

Methods	RCT, prospective, placebo-controlled, double-blind, cross-over Date of study Recruitment between October 2002 and August 2004 Setting Department of Dermatology, College of Medicine, University of Baghdad, Iraq
Participants	**Randomised:** 25 participants (age 48.2 ± 9.3 years (range 21 to 64), 9 male, 16 female)

	Inclusion criteria • Participants with grade I, II, and III rosacea, including eye involvement **Ocular involvement:** Yes in nine participants **Exclusion criteria** • Pregnant women • Participants with severe steroid induced rosacea **Dropouts and withdrawals** • 6/25 (24%) for unknown reasons, 5 from placebo group and 1 from treatment group **Baseline data mean** Sharquie rosacea severity score; zinc group 8, placebo group 7
Interventions	Three months (thereafter cross-over) **Intervention** Zinc sulphate 100 mg - TID (13) **Comparator** Placebo - TID (12)
Outcomes	Assessments (7): baseline, each month up to month 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Disease severity score (Sharquie Score). This scale gives an individual score for severity of erythema (as measured according to colour chart), the number of papules and pustules, telangiectasia, and the presence or absence of rhinophyma. Photographic assessment✶ **Secondary outcomes** 1. Side effects✶ 2. Ophthalmological examination to assess eye condition ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared

Notes	We only included data for the first three months of the study. One of our primary outcomes was addressed (adverse events) See comparison 76 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 858): "Patients were randomly allocated." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 858): "Zinc sulphate or the identical placebo capsules were given in a double-blind manner." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 858): "Zinc sulphate or the identical placebo capsules were given in a double-blind manner." Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	High risk	6/25 (24%) participants dropped out for unknown reasons and were not included in the analysis Comment: We judged this as at a high risk of bias
Selective reporting (reporting bias)	Unclear risk	For intermediate outcomes only means reported, no SDs. Inadequate reporting of lesion counts

		Comment: Insufficient information to permit a clear judgement
Other bias	Low risk	Wash-out period adequate, study duration adequate, groups treated equally, sponsorship or support unreported Comment: The study appeared to be free of other forms of bias

Sneddon 1966

Methods	RCT, prospective, placebo-controlled, double-blind Date of study December 1964 for 1 year Setting Department of Dermatology of Royal Infirmary, Sheffield and Doncater Gate Hospital, Rotherham, UK
Participants	**Randomised:** 85 participants (mean age 47 years, 26 male, 52 female, 7 gender not reported) **Inclusion criteria** • Participants with erythematous and papular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 7/85 (8.2%); unclear how many from each group • 2 failed to attend, 2 refused to continue with tetracycline, 3 had other diagnoses than rosacea **Baseline data mean (SD)** Nothing reported
Interventions	Four weeks **Intervention** Tetracycline 250 mg - BID (36) **Comparator** Placebo - BID (42) Number of participants that completed the study (78)
Outcomes	Assessments (3): baseline, week 2 and 4 **Outcomes of the trial** (as reported) **Primary outcomes**

	1. Assessable improvement after 1 month✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed See comparison 56 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 649): "...dispensed by the pharmacist according to a random table." Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: Form of central allocation, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (649): "...tetracycline 250 mg twice daily or a dummy placebo indistinguishable in appearance." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (649): "...tetracycline 250 mg twice daily or a dummy placebo indistinguishable in appearance." Outcomes were investigator-assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	Unclear how many participants were actually randomised to each group. Withdrawals were

		accounted for for first month. Per-protocol analysis Comment: We judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Older study of short duration. Unreported if wash-out period before study, if concomitant medication was allowed, sponsorship or support Comment: Insufficient information to assess whether an important risk of bias exists

Stein 2014a

Methods	RCT, prospective, placebo-controlled, double-blind Date of study December 2011 to July 2013 Setting Multicentre, US and Canada
Participants	**Randomised:** 683 participants (mean age 50.4 years (SD 12.09) 217 male, 466 female) **Inclusion criteria** • ≥ 18 years with moderate to severe papulopustular rosacea based on Investigator's Global Assessment (IGA) and 15 to 70 facial inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 59/683 (8.6%); ivermectin group (37), vehicle group (22) • Pregnancy; ivermectin group (2), vehicle group (0) • Lack of efficacy; ivermectin group (0), vehicle group (1) • Adverse event; ivermectin group (7), vehicle group (4) • Subject request; ivermectin group (18), vehicle group (7) • Protocol violation; ivermectin group (2), vehicle group (1)

	• Lost to follow-up; ivermectin group (7), vehicle group (8) • Other; ivermectin group (1), vehicle group (1) **Baseline data mean (SD)** Number of inflammatory lesions; 30.9 (14.33) IGA moderate; 560 (82%) participants IGA severe; 123 (18%) participants
Interventions	12 weeks **Intervention** Ivermectin 1% cream - QD (451) **Comparator** Vehicle cream - QD (232) Subjects were instructed to avoid rosacea triggers such as sudden exposure to heat, certain foods and excessive sun exposure
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment of disease severity (0 = clear, 4 = severe)✴ 2. Inflammatory lesion count of five facial regions (forehead, chin, nose and both cheeks)✴ 3. Safety assessments (adverse events, local tolerance, laboratory parameters)✴ **Secondary outcomes** 1. Subject's evaluation of rosacea improvement (worse, no improvement, moderate, good, excellent)✴ 2. Quality of life (DLQI and RosaQoL)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 323): "The study was funded by Galderma R&D"
Declaration of interest	Quote (page 323): "The investigators received grants for conducting the studies. Ms Liu and Dr Jacovella are employees of Galderma R&D"
Notes	All our primary outcomes were addressed See comparison 15 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: Central allocation, probably done
Allocation concealment (selection bias)	Low risk	Quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 317): "The integrity of the blinding was ensured by packaging the topical creams in identical tubes with no visible difference between the creams, and requiring a third party other than the investigator to dispense the medication." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator-assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	59/683 (8.6%); ivermectin group (37), vehicle group (22), reasons reported. Per-protocol analysis and ITT analysis (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov (NCT01493687) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started not reported, groups treated equally. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D

		Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship/support represented any additional bias

Stein 2014b

Methods	RCT, prospective, placebo-controlled, double-blind Date of study December 2011 to August 2013 Setting Multicentre, US and Canada
Participants	**Randomised:** 688 participants (mean age 50.2 years (SD 12.29) 229 male, 459 female) **Inclusion criteria** • ≥ 18 years with moderate to severe papulopustular rosacea based on Investigator's Global Assessment (IGA) and 15 to 70 facial inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 51/688 (7.4%); ivermectin group (30), vehicle group (21) • Pregnancy; ivermectin group (1), vehicle group (0) • Lack of efficacy; ivermectin group (1), vehicle group (0) • Adverse event; ivermectin group (6), vehicle group (4) • Subject request; ivermectin group (9), vehicle group (8) • Protocol violation; ivermectin group (4), vehicle group (0) • Lost to follow-up; ivermectin group (8), vehicle group (8) • Other; ivermectin group (1), vehicle group (1) **Baseline data mean (SD)** Number of inflammatory lesions; 32.9 (13.70) IGA moderate; 522 (76%) participants IGA severe; 166 (24%) participants
Interventions	12 weeks **Intervention** Ivermectin 1% cream - QD (459) **Comparator**

	Vehicle cream - QD (229) Subjects were instructed to avoid rosacea triggers such as sudden exposure to heat, certain foods and excessive sun exposure
Outcomes	Assessments (5): baseline, week 2, 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment of disease severity (0 = clear, 4 = severe)✴ 2. Inflammatory lesion count of five facial regions (forehead, chin, nose and both cheeks)✴ 3. Safety assessments (adverse events, local tolerance, laboratory parameters)✴ **Secondary outcomes** 1. Subject's evaluation of rosacea improvement (worse, no improvement, moderate, good, excellent)✴ 2. Quality of life (DLQI and RosaQoL)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 323): "The study was funded by Galderma R&D"
Declaration of interest	Quote (page 323): "The investigators received grants for conducting the studies. Ms Liu and Dr Jacovella are employees of Galderma R&D"
Notes	All our primary outcomes were addressed See comparison 15 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: Central allocation, probably done.
Allocation concealment (selection bias)	Low risk	Quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access."

		Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done.
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 317): "The integrity of the blinding was ensured by packaging the topical creams in identical tubes with no visible difference between the creams, and requiring a third party other than the investigator to dispense the medication." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement.
Blinding of outcome assessment (detection bias)	Low risk	Outcomes were investigator-assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	59/683 (8.6%); ivermectin group (37), vehicle group (22), reasons reported. Per-protocol analysis and ITT analysis (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov (NCT01493687) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started not reported, groups treated equally. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship/support represented any additional bias

Stein Gold 2014c

Methods	Extension of RCT Stein 2014a, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Multicentre, US and Canada

Participants	**Randomised:** 622 participants (mean age and gender only data reported only for first phase Study 1 (Stein 2014a) **Inclusion criteria** • ≥ 18 years with moderate to severe papulopustular rosacea based on Investigator's Global Assessment (IGA) and 15 to 70 facial inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 96/622 (15.4%); ivermectin 1% group (61), in azelaic acid group (35) • Pregnancy; ivermectin 1% group (5), in azelaic acid group (1) • Lack of efficacy; ivermectin 1% group (2), in azelaic acid group (3) • Adverse event; ivermectin 1% group (5), in azelaic acid group (4) • Related adverse event; ivermectin 1% group (0), in azelaic acid group (1) • Subject request; ivermectin 1% group (27), in azelaic acid group (16) • Protocol violation; ivermectin 1% group (1), in azelaic acid group (0) • Lost to follow-up; ivermectin 1% group (16), in azelaic acid group (10) • Other; ivermectin 1% group (5), in azelaic acid group (1) **Baseline data mean (SD)** At end of Study 1 (Stein 2014a) an IGA clear, almost clear; ivermectin group 38.4% and vehicle group 11.6%
Interventions	40 weeks (Study 2) **Intervention** Ivermectin 1% cream - QD (412) **Comparator** Azelaic acid 15% gel - BID (210) The patients in the ivermectin 1% group, before the extension part, were treated over the 12 weeks with ivermectin 1% (Study 1), whilst the patients in the azelaic acid cream group

	were treated with vehicle for the 12 weeks before the extension part
Outcomes	Assessments (11): baseline, week 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Safety (adverse events, tolerability, laboratory tests)✴ **Secondary outcomes** 1. Investigator's Global Assessment (IGA)(0 = clear, 4 = severe)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1385): "Study funding/support: Galderma R&D Manuscript funding/support: Galderma Laboratories, L.P."
Declaration of interest	Quote (page 1385): "Dr. Stein Gold is an investigator for Galderma, Allergan, and Actavis and an advisor for Galderma, Allergan, Valeant, Merz, and Actavis. Dr. Fleischer is an investigator for Regeneron, Eli Lilly, Galderma, AbbVie, and a consultant for Galderma, Celgene, Kikaku International, and an employee of Merz. Dr. Draelos received funds to conduct the research presented in the manuscript. Ms Liu and Dr Jacovella are employees of Galderma R&D Dr. Tan is an advisor, consultant, speaker, and clinical trials investigator for Galderma and has received grants and honoraria for these activities. Dr. Jackson has received research support, honoraria, and consulting fees, and served as an advisor for Galderma. Dr. Fowler is a consultant and investigator for Galderma. Dr. Lynde is an investigator/ speaker/consultant for Galderma, Cipher, Stiefel, Valeant. Dr. Steinhoff is on the Rosacea advisory board Galderma. Dr. Sugarman has no conflicts
Notes	The participants treated with azelaic acid in this extension study (Study 2) were treated in the 12 weeks before with ivermectin vehicle (Study 1) and therefore were affected more at baseline of the extension study than the participants in the ivermectin treatment arm that had been treated with ivermectin in the prior 12 weeks. Therefore there is a clear baseline imbalance between intervention groups for this extension study One of our primary outcomes was assessed (adverse events) See comparison 21 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Based on Stein 2014a quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: Central allocation, probably done
Allocation concealment (selection bias)	Low risk	Based on Stein 2014a quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1381): "40-week investigator blinded" Comment: Participants were not blinded. The report did not provide sufficient detail about the measures used to blind personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	96/622 (15.4%); ivermectin 1% group (61), in azelaic acid group (35), reasons reported. Per-protocol analysis Comment: Moderate and balanced number of drop-outs combined with a per protocol analysis judged as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov (NCT01493687) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	High risk	Study duration adequate, no wash-out period before study started, groups treated equally. However, there was a serious baseline imbalance in rosacea severity at the start of the study due to

		the nature of the design of the extension study as continuation of the earlier phase. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship/support represented any additional bias

Stein Gold 2014d

Methods	Extension of RCT Stein 2014b, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Multicentre, US and Canada
Participants	**Randomised:** 636 participants (mean age and gender only data reported only for first phase Study 1 (Stein 2014b) **Inclusion criteria** • ≥ 18 years with moderate to severe papulopustular rosacea based on Investigator's Global Assessment (IGA) and 15 to 70 facial inflammatory lesions **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 124/636 (19.5%); ivermectin 1% group (75), in azelaic acid group (49) • Pregnancy; ivermectin 1% group (2), in azelaic acid group (0) • Lack of efficacy; ivermectin 1% group (1), in azelaic acid group (3) • Adverse event; ivermectin 1% group (3), in azelaic acid group (5) • Related adverse event; ivermectin 1% group (0), in azelaic acid group (2) • Subject request; ivermectin 1% group (32), in azelaic acid group (24) • Protocol violation; ivermectin 1% group (3), in azelaic acid group (5) • Lost to follow-up; ivermectin 1% group (26), in azelaic acid group (10)

	• Other; ivermectin 1% group (8), in azelaic acid group (2) **Baseline data mean (SD)** At end of Study 1 (Stein 2014b) an IGA clear, almost clear; ivermectin group 40.1% and vehicle group 18.8%
Interventions	40 weeks Study 2 **Intervention** Ivermectin 1% cream - QD (428) **Comparator** Azelaic acid 15% gel - BID (208) The patients in the ivermectin 1% group, before the extension part, were treated over the 12 weeks with ivermectin 1% (Study 1), whilst the patients in the azelaic acid cream group were treated with vehicle for the 12 weeks before the extension part
Outcomes	Assessments (11): baseline, week 4, 8, 12, 16, 20, 24, 28, 32, 36 and 40 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Safety (adverse events, tolerability, laboratory tests)✴ **Secondary outcomes** 1. Investigator's Global Assessment (IGA)(0 = clear, 4 = severe)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1385): "Study funding/support: Galderma R&D Manuscript funding/support: Galderma Laboratories, L.P."
Declaration of interest	Quote (page 1385): "Dr. Stein Gold is an investigator for Galderma, Allergan, and Actavis and an advisor for Galderma, Allergan, Valeant, Merz, and Actavis. Dr. Fleischer is an investigator for Regeneron, Eli Lilly, Galderma, AbbVie, and a consultant for Galderma, Celgene, Kikaku International, and an employee of Merz. Dr. Draelos received funds to conduct the research presented in the manuscript. Ms Liu and Dr Jacovella are employees of Galderma R&D Dr. Tan is an advisor, consultant, speaker, and clinical trials investigator for Galderma and has received grants and honoraria for these activities. Dr. Jackson has received research support, honoraria, and consulting fees, and served as an advisor for Galderma. Dr. Fowler is a consultant and investigator for

	Galderma. Dr. Lynde is an investigator/ speaker/consultant for Galderma, Cipher, Stiefel, Valeant. Dr. Steinhoff is on the Rosacea advisory board Galderma. Dr. Sugarman has no conflicts
Notes	The participants treated with azelaic acid in this extension study (Study 2) were treated in the 12 weeks before with ivermectin vehicle (Study 1) and therefore were affected more at baseline of the extension study than the participants in the ivermectin treatment arm that had been treated with ivermectin in the prior 12 weeks. Therefore there is a clear baseline imbalance between intervention groups for this extension study One of our primary outcomes was assessed (adverse events) See comparison 21 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Based on Stein 2014b quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: Central allocation, probably done
Allocation concealment (selection bias)	Low risk	Based on Stein 2014b quote (page 317): "Randomization lists were generated prior to study initiation by a statistician, and were then sent to a clinical supply group, and only personnel directly involved with labeling and packaging (not site personnel) had access." Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1381): "40-week investigator blinded" Comment: Participants were not blinded. The report did not provide sufficient detail about the measures used to blind personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study. Participants were not blinded Insufficient information to permit a clear judgement

Incomplete outcome data (attrition bias)	Unclear risk	96/622 (15.4%); ivermectin 1% group (61), in azelaic acid group (35), reasons reported. Per-protocol analysis Comment: Moderate and balanced number of drop-outs combined with a per protocol analysis judged as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov (NCT01493687) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	High risk	Study duration adequate, no wash-out period before study started, groups treated equally. However, there was a serious baseline imbalance in rosacea severity at the start of the study due to the nature of the design of the extension study as continuation of the earlier phase. Study supported by Galderma R&D. All investigators have received grants from Galderma R&D or were employees of Galderma R&D Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship/support represented any additional bias

Stein-Gold 2017

Methods	RCT, prospective, active- and vehicle-controlled, double-blind Date of study December 2015 to September 2016 Setting Multicentre (26), in US and Canada
Participants	**Randomised:** 190 participants (mean age 49.5 years, 53 male, 137 female) **Inclusion criteria** • ≥18 years with moderate to severe rosacea (Investigator's Global Assessment [IGA] 3-4), characterized by persistent diffuse moderate to severe facial erythema (Clinician's Erythema Assessment [CEA] 3-4) and inflammatory lesions (15-70 papules/pustules) **Ocular involvement:** Unclear **Exclusion criteria** • Subjects with particular forms of rosacea (rosacea fulminans, isolated rhinophyma) or other concomitant facial dermatoses that may be confounded with

	rosacea such as peri-oral dermatitis, demodicidosis, facial keratosis pilaris, seborrheic dermatitis, acute lupus erythematosus, actinic telangiectasia and acne vulgaris • Subjects with more than 2 nodules of rosacea (a circumscribed, elevated, solid lesion more than 1.0cm in diameter with palpable depth) on the face • Subjects undertaking treatment with monoamine oxidase inhibitors, barbiturates, opiates, sedatives (including H1-antihistamines, from first generation only: hydroxyzine, polaramine), systemic anesthetics, or alpha agonists at screening/baseline visit • Subjects undertaking less than 3 months of stable dose of tricyclic anti-depressants, cardiac glycosides, beta blockers or other antihypertensive agents • Subjects having untreated or unstable Raynaud's syndrome, thromboangiitis obliterans, orthostatic hypotension, severe cardiovascular disease, cerebral or coronary insufficiency, renal or hepatic impairment, scleroderma, Sjögren's syndrome, or depressionSubjects with any uncontrolled chronic or serious disease or medical condition that may either interfere with the interpretation of the clinical trial results, or with optimal participation in the study or would present a significant risk to the subject • Subjects with known or suspected allergies or sensitivities to any component of the investigational and non-investigational products, including the active ingredients brimonidine or salts of brimonidine like brimonidine tartrate and ivermectin • Any procedure on the face (e.g. laser, intense pulsed light-IPL, facial peel,dermabrasion, electrocoagulation, Thermage®) within 6 weeks prior to enrolment • Topical antibiotics, benzoyl peroxide, anti rosacea, topical immunomodulators, corticosteroids, retinoids 4 weeks prior to enrolment • Systemic antibiotics, corticosteroids, immunomodulators, oral ivermectin, inhaled corticosteroids, oxymetazoline (any route) 4 weeks prior to enrolment **<u>Dropouts and withdrawals</u>** • 19/190 (10%); IVM+ BR 8 week group (5), IVM+BR 12 week group (5), vehicle group (9) • Adverse event; IVM+ BR 8 week group (1), IVM+BR 12 week group (0), vehicle group (1) • Subject's request; IVM+ BR 8 week group (4), IVM+BR 12 week group (1), vehicle group (3)

	• Lost to follow-up; IVM+ BR 8 week group (0), IVM+BR 12 week group (3), vehicle group (3) • Other; IVM+ BR 8 week group (0), IVM+BR 12 week group (1), vehicle group (2) **Baseline data mean (SD)** IGA moderate - 3 (n); IVM+ BR 8 week group 37, IVM+BR 12 week group 40, vehicle group 78 IGA severe - 4 (n); IVM+ BR 8 week group 9, IVM+BR 12 week group 9, vehicle group 17 Inflammatory lesions; IVM+ BR 8 week group 30.6 (12.1), IVM+BR 12 week group 28.4 (12.2), vehicle group 31.1 (13.6) CEA moderate - 3 (n); IVM+ BR 8 week group 39, IVM+BR 12 week group 39, vehicle group 77 CEA severe - 4 (n); IVM+ BR 8 week group 7, IVM+BR 12 week group 10, vehicle group 18
Interventions	12 weeks **Intervention** Ivermectin 1% cream - QD in the evening for 12 weeks plus brimonidine vehicle - QD in the morning for 4 weeks followed by brimonidine - QD in the morning for the remaining 8 weeks (46) **Comparator 1** Ivermectin 1% cream - QD in the evening plus brimonidine - QD in the morning (49) **Comparator 2** Ivermectin vehicle cream - QD in the evening plus brimonidine vehicle - QD in the morning (95) All subjects received and were required to use daily, products for general skin care including a gentle skin cleanser, moisturizing lotion, and moisturizer SPF 15 sunscreen
Outcomes	Assessments (2): baseline and week 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (IGA) success (clear, almost clear) at week 12/hour 3✴ Secondary endpoints 1. IGA at each visit

	2. Clinician's Erythema Assessment (CEA) at each visit prior to and 3 h after application of brimonidine or its vehicle✶ 3. Percent change in inflammatory lesion count✶ 4. Subject global improvement and subject facial appearance (questionnaire)✶ 5. Adverse events✶ ✶Denotes outcomes pre-specified for this review
Funding source	Provided on clinicaltrials.gov: Galderma
Declaration of interest	Quote (page 915): "Dr Linda Stein Gold is an investigator, consultant and speaker for Galderma. Dr Kim Papp is a consultant, speaker, advisory board member, and investigator for Galderma. Dr Charles Lynde has been a consultant, principal investigator, and speaker for Galderma. Dr Edward Lain is a consultant and investigator for Galderma. Dr Melinda Gooderham has been an investigator, speaker, and advisory board member for Galderma. Dr Sandra Johnson is an investigator, speaker, and consultant for Galderma. Mr Nabil Kerrouche is an employee of Galderma."
Notes	Two of our primary outcomes were assessed (participant-assessed changes in rosacea severity and adverse events) See comparison 22 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 910): "A randomization list was generated by a statistician" Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 909): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 909) : "double-blind" Outcomes were investigator- and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	19/190 (10%); IVM+ BR 8 week group (5), IVM+BR 12 week group (5), vehicle group (9), reasons reported. ITT analysis and per-protocol analysis Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov (NCT02616250) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, wash-out period before study started adequate, groups treated equally. Study funded by Galderma and most authors were consultants, speakers for Galderma or employees of Galderma Comment: As the study appeared to be double-blinded and there was no selective reporting we do not consider that the sponsorship/support represented any additional bias

Taieb 2015

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Multicentre (64), 10 European countries
Participants	**Randomised:** 962 (mean age 51.5 years (SD 13.3), 335 male, 627 female) **Inclusion criteria** • Subjects (18 years or older) with moderate to severe papulopustular rosacea (IGA of 3 or 4 and between 15 and 70 inflammatory lesions) **Ocular involvement:** Unclear **Exclusion criteria**

	• Nothing reported **Dropouts and withdrawals** • 50/962 (5.2%); ivermectin group (32), metronidazole group (28) • Withdrawal on request participant; ivermectin group (21), metronidazole group (9) • Adverse event; ivermectin group (6), metronidazole group (13) • Lost to follow-up; ivermectin group (3), metronidazole group (2) • Pregnancy; ivermectin group (1), metronidazole group (1) • Protocol violation; ivermectin group (1), metronidazole group (2) • Other; ivermectin group (0), metronidazole group (1) **Baseline data mean (SD)** Mean inflammatory lesion count; ivermectin group 32.87 (13.95), metronidazole 32.07 (12.75)
Interventions	16 weeks **Intervention** Ivermectin 1% cream - QD (478) **Comparator** Metronidazole 0.75% cream - BID (484)
Outcomes	Assessments (6): baseline, week 3, 6, 9, 12 and 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Inflammatory lesion count✴ 2. Investigator's Global Assessment (5-point Likert scale; 0 = clear, no inflammatory lesions present, no erythema and 4 = severe, numerous small and/or large papules/pustules, severe erythema)✴ 3. Subjects global improvement of rosacea (5 grade self-evaluation questionnaire, worse to excellent)✴ **Secondary outcomes** 1. Adverse events✴ 2. Tolerability

	3. Subject's appreciation questionnaire (satisfaction with study drug) 4. Dermatology Life Quality Index (DLQI)✴ 5. Time to relapse (in the extension study)✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 1103): "This study was funded by Galderma R&D."
Declaration of interest	Quote (page 1103) "The investigators received grants for conducting the studies. Mrs. Peirone and Mr. Jacovella are employees of Galderma R&D."
Notes	All our primary outcomes were addressed. In a follow-up paper remission was evaluated over 36 weeks and in another paper more details on effect on quality of life were provided See comparison 20 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1103): "randomized" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "are randomized in blocks of 6. The RANUNI routine of the SAS system was used to randomly assign, in balanced blocks, kit to a treatment (Ivermectin 1% cream, Metronidazole 0.75% cream)." Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: "a randomization list was generated by the statistician and was secured with restricted access. .. and kit numbers were assigned sequentially in chronological order." Comment: Adequate, probably done
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 1103): "...investigator-blinded." Comment: The report provided insufficient detail about the measures used to blind study personnel from knowledge of which intervention a

		participant received, to permit a clear judgement After e-mail communication: "The integrity of the blinding was ensured by packaging the products in identical tubes, not allowing the investigator and subject to discuss study treatments, and requiring a third party other than the investigator to dispense the medication" Comment: Blinding investigators ensured, low risk of bias
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 1103): "...investigator-blinded." Comment: Investigator and participant assessed outcomes. Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement After e-mail communication: Blinding investigators ensured, but due to the different treatment regime once versus twice daily and participants were outcome assessors as well, we judged this as at an unclear risk of bias
Incomplete outcome data (attrition bias)	Low risk	50/962 (5.2%); ivermectin group (32), metronidazole group (28), reasons reported. Authors state to have performed an ITT analysis (LOCF) Comment: Low and balanced number of dropouts, combined with ITT analysis judged as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at clinicaltrials.gov (NCT01493947) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period not described, groups treated equally Comment: the study appears to be free of other forms of bias

Tan 2002

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre (6), Canada (Windsor, Ontario; Montreal, Quebec; Alberta, Quebec; Waterloo, Ontario; Sainte-Foy, Ontario; Winnipeg, Manitoba)

Participants	**Randomised:** 120 participants aged 27 to 85 years of age (mean 51 years (treatment group) versus 47.7 years (placebo group), 31 male, 89 female) **Inclusion criteria** • Participants with moderate to severe rosacea with moderate to severe erythema, telangiectasia, and at least six rosacea-associated papules and pustules **Ocular involvement:** Unclear **Exclusion criteria** • Use of any topical facial medication • Use of oral antibiotics, antifungals or corticosteroids within 30 days prior to study entry • Vasodilatating drugs, anticoagulants, drugs associated with flushing **Dropouts and withdrawals** • 31/120 (25.8%); metronidazole group (17) and placebo group (14) • Voluntary withdrawal; metronidazole group (1) and placebo group (2) • Adverse events;; metronidazole group (1) and placebo group (3) • Non compliance; metronidazole group (6) and placebo group (3) • Use of excluded medications; metronidazole group (9) and placebo group (6) **Baseline data mean (SEM)** Inflammatory lesion count; metronidazole group 18.5 (2.0) and placebo group 20.4 (1.7) Erythema score; metronidazole group 2.13 (0.04) and placebo group 2.10 (0.04) Telangiectasia score; metronidazole group 1.70 (0.08) and placebo group 1.73 (0.08) Rosacea severity score; metronidazole group 2.13 (0.05) and placebo group 2.20 (0.05)
Interventions	12 weeks **Intervention** Metronidazole 1% + sunscreen SPF 15 - BID (61) **Comparator** Placebo (vehicle) - BID (59)

Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Physician's global improvement✶ 2. Reduction in lesion counts✶ 3. Reduction facial erythema (0 = absent, 3 = severe)✶ **Secondary outcomes** 1. Local tolerance 2. Reduction facial telangiectasia✶ 3. Safety and tolerability✶ 4. Self-assessed global evaluation✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 529): "Sponsored by Stiefel Canada Inc", one of the investigators was employed by Stiefel
Declaration of interest	None declared
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events). Data are skewed See comparison 7 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 530): "This randomized, double-blind...study..." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment:There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (529): "...double-blind." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of

		which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (529): "...double-blind." Outcomes were investigator and participant assessed Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers, participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	High risk	31/120 (25.8%); metronidazole group (17) and placebo group (14). All participants were accounted for (including the dropouts and withdrawals). Per-protocol analysis Comment: High dropout rate combined with a per-protocol analysis judged as at high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration and wash-out period before study adequate, no concomitant medication that could influence rosacea permitted. Sponsored by Stiefel Canada Inc, manufacturer of the active intervention. One investigator was employed by Stiefel Comment: Insufficient information to assess whether an important risk of bias exists

Thiboutot 2003a

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, 13 centres in the US
Participants	**Randomised:** 329 participants (mean age 48 years (treatment group) versus 49 years (placebo group), 39 male and 125 female versus 45 male and 120 female) **Inclusion criteria** • Participants with papulopustular rosacea with a minimum of 8 and a maximum of 50 inflamed facial papules or pustules, and persistent erythema and telangiectasia

	Ocular involvement: Unclear, no participants with marked ocular involvement were included **Exclusion criteria** • Mild disease (subtype I) • Severe disease • Marked ocular rosacea • Dermatoses that might interfere with evaluation • History of hypersensitivity to ingredient study medication **Dropouts and withdrawals** • 46/329 (13.9%); azelaic group (31) and vehicle group (15) • Adverse events; azelaic group (9) and vehicle group (2) • Lack of efficacy; azelaic group (1) and vehicle group (7) • Protocol deviation; azelaic group (6) and vehicle group (1) • Withdrawal of consent; azelaic group (6) and vehicle group (2) • Other; azelaic group (9) and vehicle group (3) **Baseline data mean** Inflammatory lesion count; azelaic group 17.5 and vehicle group 17.6
Interventions	12 weeks **Intervention** Azelaic acid 15% gel - BID (164) **Comparator** Vehicle - BID (165)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (0 = clear, 6 = severe)✴ 2. Change in N of inflammatory lesions✴ 3. Overall facial erythema (0 = none, 3 = severe)✴ 4. Overall facial telangiectasia (0 = none, 3 = severe)✴ 5. Participant's assessment of rosacea severity (1 = excellent improvement, 5 = worse)✴

	Secondary outcomes 1. Safety and tolerability✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 836): "Supported by Berlex Laboratories"
Declaration of interest	Quote (page 836): "Dr Thieroff-Ekerdt is an employee of Berlex Laboratories. Dr Graupe is an employee of Schering AG. Dr Thiboutot received financial compensation from Berlex Laboratories for her role as a principal investigator in these studies"
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 837): "Patients were randomly assigned to treatment with either AzA gel or vehicle gel. The randomization list was prepared by a computer program ensuring equal numbers of patients per treatment group." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Quote (page 837): "Patients were allocated to treatment in the sequence of entry into the studies, i.e., in each center each newly admitted patient received the study medication with the lowest randomization number available." The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 836): "double-blind" Comment: Vehicle gel was used. Probably identical appearance. Although not explicitly stated it would appear that the active intervention and placebo tablets were similar and most probably indistinguishable by participants and investigators. The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Low risk	Quote (page 836): "double-blind" Comment: Vehicle gel was used. Probably identical appearance. Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	46/329 (13.9%); azelaic group (31) and vehicle group (15), dropouts and withdrawals were accounted for. ITT analysis (LOCF) Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration and wash-out period before study adequate, no concomitant medication that could influence rosacea allowed. Other medication recorded Sponsoring: Berlex Laboratories, second investigator was an employee of Berlex laboratories, third author is an employee of Schering, and first author received financial compensation from Berlex laboratories for her role as principal investigator (page 836) Comment: The review authors do not consider that the commercial sponsorship introduced any additional bias the study was double-blind, and all pre-specified outcome measures were addressed and analysis of data was according to ITT principle

Thiboutot 2003b

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Ureported Setting Multicentre, 14 centres in the US
Participants	**Randomised:** 335 participants (mean age 48 years (treatment group) versus 47 years (placebo group), 47 male and 122 female versus 46 male and 120 female) **Inclusion criteria** • Participants with papulopustular rosacea with a minimum of 8 and a maximum of 50 inflamed facial

	papules and pustules, and persistent erythema and telangiectasia **Ocular involvement:** Unclear, no participants with marked ocular involvement were included **Exclusion criteria** • Mild disease (subtype I) • Severe disease • Marked ocular rosacea • Dermatoses that might interfere with evaluation • History of hypersensitivity to ingredient study medication **Dropouts and withdrawals** • 39/335 (11.6%); azelaic group (19) and vehicle group (20) • Adverse events; azelaic group (8) and vehicle group (4) • Lack of efficacy; azelaic group (0) and vehicle group (5) • Protocol deviation; azelaic group (1) and vehicle group (0) • Withdrawal of consent; azelaic group (0) and vehicle group (3) • Other; azelaic group (10) and vehicle group (8) **Baseline data mean** Inflammatory lesion count; azelaic group 17.8 and vehicle group 18.5
Interventions	12 weeks **Intervention** Azelaic acid 15% gel - BID (169) **Comparator** Vehicle - BID (166)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (0 = clear, 6 = severe)✴ 2. Change in N of inflammatory lesions✴ 3. Overall facial erythema (0 = none, 3 = severe)✴ 4. Overall facial telangiectasia (0 = none, 3 = severe)✴

	5. Participant's assessment of rosacea severity (1 = excellent improvement, 5 = worse)✴ **Secondary outcomes** 1. Safety and tolerability✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 836): "Supported by Berlex Laboratories"
Declaration of interest	Quote (page 836): "Dr Thieroff-Ekerdt is an employee of Berlex Laboratories. Dr Graupe is an employee of Schering AG. Dr Thiboutot received financial compensation from Berlex Laboratories for her role as a principal investigator in these studies"
Notes	Same reference as Thiboutot 2003a (report of 2 studies). Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 11 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 837): "Patients were randomly assigned to treatment with either AzA gel or vehicle gel. The randomization was prepared by a computer program ensuring equal numbers of patients per treatment group." Comment: Probably done
Allocation concealment (selection bias)	Unclear risk	Quote (page 837): "Patients were allocated to treatment in the sequence of entry into the studies, ie, in each center each newly admitted patient received the study medication with the lowest randomization number available." The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 836): "double-blind" Comment: Vehicle gel was used. Probably identical appearance. Although not explicitly stated it would appear that the active intervention and placebo tablets were similar and most probably indistinguishable by participants and investigators. The report provided sufficient detail about the measures used to blind study

		participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 836): "double-blind" Comment: Vehicle gel was used. Probably identical appearance. Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	39/335 (11.6%); azelaic group (19) and vehicle group (20). Dropouts and withdrawals were accounted for and included in the analysis. ITT analysis (LOCF) Comment: We judged this as at low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported. Comment: We judged this as at a low risk of bias.
Other bias	Low risk	Wash-out period adequate, study duration adequate, no concomitant medication that could influence rosacea allowed. Other medication recorded Sponsoring: Berlex Laboratories, second investigator was an employee of Berlex laboratories, third investigator was an employee of Schering and first investigator received financial compensation from Berlex laboratories for her role as principal investigator (page 836) Comment: The review authors do not consider that the commercial sponsorship introduced any additional bias the study was double-blind, and all pre-specified outcome measures were addressed and analysis of data was according to ITT principle

Thiboutot 2005

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Multicentre, US
Participants	**Randomised:** 134 participants (mean age 44.5 years in doxycycline group and 48.9 years in placebo group, 40 male, 94 female) **Inclusion criteria**

	• Participants with 10 to 30 papules and pustules and no more than 2 nodules, scoring 2 to 4 on a clinician's global severity score (a 5-point scale in which 0 indicates no disease and 4 indicates severe disease, and a score of 2 to 4 on the 5-point Clinician's Erythema Assessment Scale (0 = none, 4 = severe; fiery redness), presence of facial telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Topical treatments for rosacea or acne and those taking corticosteroids or vasodilatators **Dropouts and withdrawals** • 25/134 (18.7%); unclear from which group **Baseline data mean** Nothing reported
Interventions	16 weeks **Intervention** Doxycycline 20 mg - BID (67) **Comparator** Placebo capsules - BID (67)
Outcomes	Assessments (5): baseline, week 3, 6, 12 and week 16 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in lesion count✴ 2. Reduction in erythema✴ 3. Overall disease severity✴ **Secondary outcomes** 1. Adverse events✴ ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 17): "100% supported by CollaGenex"
Declaration of interest	Quote (page 17): "Drs. Thiboutot, Beer, and Skidmore have received consulting and speaking fees from CollaGenex. Dr. Berman has received research grant support from

	CollaGenex. Drs. Leyden and Fowler have received consulting fees from CollaGenex."
Notes	Poster presentation, a lot of information is lacking (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 17): "A multi-center, double-blind, randomized, placebo-controlled trial was undertaken" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 17): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 17): "double-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	25/134 (18.7%); unclear from which group. Analysis unclear Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Thiboutot 2008

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Multicentre, 7 centres in US
Participants	**Randomised:** 92 participants (mean age 48.5 years in QD group versus 49.6 years in BID group, 11 male and 34 female versus 17 male and 30 female) **Inclusion criteria** • Participants aged 18 years or older having papulopustular rosacea with at least 10, and no more than 50, inflamed papules or pustules, persistent erythema, and telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 4/92 (4.3%); 2 in each group, 1 centre was excluded (20 participants, as IGA assessments were not in conformity with study protocol) • Reasons; never received study medication (1), withdrawal of consent (1), lost to follow-up (1), other (1) **Baseline data mean** Nothing reported
Interventions	12 weeks **Intervention** Azelaic acid 15% gel QD + vehicle gel - QD (45) **Comparator** Azelaic acid 15% - BID (47)
Outcomes	Assessments (4): baseline, week 4, 8 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (IGA) (0 = clear, 6 = severe), defined as treatment success (sum of clear and minimal IGA score)✴ 2. Treatment response (sum of clear, minimal, and mild IGA score)✴

	3. Change compared to baseline in inflammatory lesion count✶ 4. Erythema intensity (0 = none, 3 = severe)✶ 5. Telangiectasia intensity (0 = none, 3 = severe)✶ **Secondary outcomes** 1. Investigator's and participant's assessment of overall improvement✶ 2. Participant's opinion on cosmetic acceptability and tolerability ✶Denotes outcomes pre-specified for this review
Funding source	One of the investigators was employed by Intendis
Declaration of interest	Quote (page 545): "Dr Thiboutot has participated in clinical trials and has been a consultant/advisor for Intendis Inc,....Dr Fleischer has participated in clinical trials and has been a consultant/advisor for Intendis Inc,....Dr Del Rosso has received grant/research support/honoraria from and has been a consultant for etc and....Intendis Inc...Dr Graupe is employed by Intendis GmbH, Berlin, Germany"
Notes	1 centre (20 participants) was excluded as assessments were not in conformity with protocol One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 12 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 542): "Patients were randomized to receive either AzA 15% gel once daily or AzA 15% gel twice daily." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Low risk	As both groups received 2 tubes for each study day it is unlikely that allocation could have been foreseen Comment: The report provides sufficient detail and reassurance that participants and investigators enrolling participants could not foresee the upcoming assignment. Probably done
Blinding of participants and	Low risk	Quote (page 541): "double-blind". Both groups received a morning and evening tube for each

personnel (performance bias)		study day. The subjects in the QD group received 1 application with vehicle gel each day of the study (page 542) Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 541): "double-blind". Both groups received a morning and evening tube for each study day. The subjects in the QD group received 1 application with vehicle gel each day of the study (page 542). Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	4/92 (4.3%); 2 in each group, 1 centre was excluded (20 participants, as IGA assessments were not in conformity with study protocol). Reasons for withdrawal are reported. ITT analysis (LOCF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the prespecified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	High risk	All of the investigators in this study have received sponsorship from pharmaceutical industry. The study was designed as a superiority study, but was inappropriately reported as a successful non-inferiority study, without any reference to the number of participants recruited, the planned design, or sample size. Study duration adequate, unclear if there was a wash-out period before study or if other medications were allowed Comment: A potential risk of bias cannot be excluded

Thiboutot 2009

Methods	RCT (only second phase), prospective, placebo-controlled (only second phase), double-blind (only second phase), cross-over study (we only included second phase) Date of study Unreported Setting Multicentre in US

Participants	**Randomised:** 136 participants (mean age 46.4 years in azelaic acid gel group versus 47.5 years in vehicle group, 18 male and 49 female in azelaic acid group versus 17 male and 52 female in vehicle group) **Inclusion criteria** • Males and females ≥18 years of age with papulopustular rosacea with at least 10 inflammatory papules and/or pustules, moderate to severe facial erythema, facial telangiectasia, and an Investigator's Global Assessment score (IGA) of ≥ 4 (on a scale of 0 to 4) • Only participants who achieved ≥ 75% reduction in inflammatory lesions within 4 to12 weeks were included for second phase **Ocular involvement:** Unclear **Exclusion criteria** • Pregnancy, lactating female • Presence of other dermatoses that might interfere with evaluations • Hypersensitivity to ingredient of study treatment **Dropouts and withdrawals** • 14/136 (10.3%), 7 in both groups, reasons inadequately reported but 2 in both groups were lost to follow-up **Baseline data mean** Inflammatory lesion count; azelaic acid group 1.39, vehicle group 1.55
Interventions	24 weeks **Intervention** Azelaic acid 15% gel - BID (67) **Comparator** Vehicle - BID (69)
Outcomes	Assessments (7): baseline, every for weeks up to 24 weeks **Outcomes of the trial** (as reported) **Primary outcomes** 1. Relapse rate defined as a failure of study medication to maintain rosacea remission (deterioration in lesions

	count by at least 50% of the lesion count improvement observed in first phase, increase in erythema that was intolerable to participant, if investigator or participant thought maintenance was a failure)✴ 2. Adverse events✴ **Secondary outcomes** 1. Inflammatory lesion count✴ 2. Investigator's Global Assessment (0 = clear, to 6 = severe), furthermore a dichotomised score of success (IGA score of clear, minimal, or mild) or failure (IGA score of mild-to-moderate or worse)✴ 3. Investigator's rating of overall improvement (1 = complete remission, 6 = deterioration) and self-rating by participant (1 = excellent improvement, 5 = worse)✴ 4. Erythema and telangiectasia assessment (4-point scale)✴ 5. Rating by subject of cosmetic acceptability (rated as very good, good, satisfactory, poor, and no opinion) ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 647): "Research funding was provided by Indendis Inc"
Declaration of interest	Quote (page 647): "Dr Fleischer.... he served as a consultant for...Intendis..He has served as an investigator for...Intendis...He also served on the speaker bureaus for...Intendis..Dr Del Rosso has served as a consultant, speaker and researcher for...Intendis...Dr Thiboutot has served as an investigator and consultant for Intendis Inc..."
Notes	We only included second phase of the study (azelaic acid 15% gel versus vehicle), not the first phase (up to 12 weeks). In the first phase, all participants received doxycycline 100 mg BID + azelaic acid 15% gel BID. However, participants who did not respond in the first phase were not included in the second phase, which means these data cannot be generalised for all participants with papulopustular rosacea. Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 13 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 640): "Subjects eligible for the maintenance phase of the study were randomized to apply either AzA 15% gel or its vehicle twice daily for an additional 24 weeks." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page (640); "double-blind" Comment. Vehicle gel was used. Probably identical appearance The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page (640); "double-blind" Comment. Vehicle gel was used. Probably identical appearance. Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	We only included second phase of the study. 14/136 (10.3%), 7 in both groups. ITT analysis carried out (LCOF) Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	High risk	Not all pre-specified outcomes were addressed and reported. Data missing in the maintenance phase, self-assessment by participants Comment: We judged this as at a high risk of bias
Other bias	Unclear risk	No wash-out phase, only participants were included who had attained at least a 75% reduction in number of inflammatory lesions in the first phase on a combination of doxycycline 100 mg to 200 mg plus azelaic acid 15% gel twice daily. Study duration adequate, not allowed to use other medications that might influence rosacea. Research funding was provided by Intendis, Inc. First author served as an investigator and

		consultant for Intendis, as did second and third author Comment: Phase 1 of this study is a run-in period (equivalent to wash-out). However, insufficient information to assess whether an important risk of bias exists

Tirnaksiz 2012

Methods	RCT, prospective, active-controlled, double-blind, within-patient comparison Date of study Unreported Setting Department of Dermatology, School of Medicine, Gazi University, Ankara, Turkey
Participants	**Randomised:** 12 participants (mean age 39.8 years, 5 male, 7 female) **Inclusion criteria** • Adult subjects with moderate to severe rosacea (erythematotelangiectatic rosacea and papulopustular rosacea according to Wilkin 2004 • > 2 inflammatory lesions (papules and/or pustules), moderate to severe erythema and telangiectasia **Ocular involvement:** Unclear **Exclusion criteria** • Pregnant or nursing females • History of metronidazole hypersensitivity • ultraviolet (UV) therapy < 2 weeks prior to study entry • Systemic and topical medicines such as antibiotics, corticosteroids or anticoagulants < 30 days prior to study entry • Isotretinoin or tretinoin therapy < 6 months prior to study entry **Dropouts and withdrawals** • None reported **Baseline data mean (SEM)** Inflammatory lesion count; micro emulsion group 3.75 (0.74), commercial gel group 3.01 (0.59) Erythema score; micro emulsion group 2.50 (0.22), commercial gel group 2.08 (0.26) Telangiectasia; micro emulsion group 1.50 (0.17), commercial gel group 1.08 (0.31)

Interventions	Six weeks **Intervention** Metronidazole 0.75% in microemulsion - BID **Comparator** Metronidazole 0.75% commercial gel - BID To prevent cross-over, hands were washed between the right and left applications. None of the patients used any other kind of treatment during the study period. No restrictions were placed on diet or the use of cosmetics
Outcomes	Assessments (4); baseline, week 2, 4 and 6 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Adverse events✴ 2. Signs of rosacea, such as stinging, burning, itching, and dryness (participants' feedback and investigator's observation) 3. Cosmetic acceptability, degree of absorption, skin feel as assessed by participant 4. Inflammatory lesion count✴ 5. Erythema (0 = no perceptible erythema, 3 = severe erythema or purple hue)✴ 6. Teleangiectasia (0 = absent, 3 = severe many fine vessels and large vessels covering more than 30% of the face)✴ **Secondary outcomes** 1. Patch testing ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 591): "This study was partly supported by a Grant from Gazi University, Turkey (SBE-11-2001/10)"
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (adverse events) See comparison 10 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (page 585): "This study was designed as a randomized, double-blind, bilateral split-face paired comparison" and "Patients were assigned to receive the commercial gel and microemulsion formulation to each half of the face." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 585): "Each patient received a pair of identical-appearing vials, labeled right and left, one containing commercial gel and the other microemulsion formulation." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 585): "Each patient received a pair of identical-appearing vials, labeled right and left, one containing commercial gel and the other microemulsion formulation Comment: Outcomes were investigator- and participant assessed Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	No dropouts reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Treatment duration adequate, wash-out period before the study adequate

		Comment: The study appeared to be free of other forms of bias

Torok 2005

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Multicentre (6) in US. Trillium Creek Dermatology Center, Medina, Ohio; Department of Dermatology, Thomas Jefferson University, Pennsylvania; Radiant Research, Tucson, Arizona; International Research Services, Inc, Rockland, Maine; Derm Research, Inc, Austin, Texas
Participants	**Randomised:** 152 participants (mean age 47 years (range 19 to 77), 43 male, 109 female) **Inclusion criteria** • Participants had to be at least 16 years of age. Clinical evidence of rosacea with a minimum of 10 and a maximum of 39 lesions (papules and pustules), at least moderate erythema, and at least an investigator global severity of moderate **Ocular involvement:** Unclear **Exclusion criteria** • Participants that used medicated cleanser containing benzoyl peroxide, sodium sulfacetamide, or salicylic acid for 2 weeks before study entry • Rosacea or acne treatments, of any type, 2 weeks (topical) or 1 month (systemic) before study entry • Retinoids for 1 month (topical) or 6 months (systemic) before study entry • Systemic antibacterials within 1 month before study entry • Participants were not allowed the following medications throughout the course of the study: cimetidine, lithium, disulphiram, coumarin anticoagulants, niacin, vasodilators, or any other medication that could interfere with study results • Participants whose rosacea was unresponsive to treatment with topical metronidazole or sodium sulphacetamide and sulphur products in the past **Dropouts and withdrawals** • 14/152 (9.2%), sulphacetamide group (10), metronidazole group (4)

	• Intolerance; sulphacetamide group (7), metronidazole group (0) • Contraindicated medication; sulphacetamide group (1), metronidazole group (2) • Concurrent disease; sulphacetamide group (0), metronidazole group (1) • Protocol violation; sulphacetamide group (1), metronidazole group (1) **Baseline data mean (SEM)** Inflammatory lesion count; sulphacetamide group 18 (1), metronidazole group 17 (1)
Interventions	12 weeks **Intervention** Sulfacetamide 10% and sulphur 5% cream including sunscreen SPF 15 - BID (75) **Comparator** Metronidazole 0.75% cream group - BID (77)
Outcomes	Assessments (5): baseline, week 3, 6, 9 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Total facial inflammatory lesions✴ 2. Facial erythema (0 = no redness, 3 = intense erythema)✴ 3. Investigator global severity (0 = clear, 7 = very severe)✴ **Secondary outcomes** 1. Participant's assessment of global improvement (0 = cleared, 5 = worsening)✴ 2. Adverse events✴ 3. Tolerance (0 = poor, 3 = excellent) ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 357): "This study was supported by Stiefel Laboratories, Inc"
Declaration of interest	Quote (page 357): "Dr Torok is a consultant and advisory board member for, is on speaker's bureau and received research grants from Galderma Laboratories, LP, Stiefel Laboratories Inc....Dr Webster is a consultant and speaker for and has received a grant from ..Galderma Laboratories, LP,

	Stiefel Laboratories Inc..Dr Egan is a consultant for Stiefel Laboratories Inc". Others no conflict of interest
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 34 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 358): "Subjects were randomly assigned to treatment with either sodium sulphacetamide 10% and sulfur 5% with sunscreens or metronidazole 0.75% cream." E-mail contact with the investigator confirmed computer-generated and central allocation Comment: Probably done
Allocation concealment (selection bias)	Low risk	Method of allocation concealment not reported E-mail contact with the investigator confirmed central allocation Comment: Probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 357): "...investigator-blinded." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 357): "...investigator-blinded." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Dropouts were accounted for and included in analysis, but unclear how missing data was imputed Comment: We judged this as at unclear risk of bias
Selective reporting (reporting bias)	High risk	Participant's assessment of global improvement was not addressed Comment: As this was one of our principal outcomes, this was considered as at a high risk of bias
Other bias	Unclear risk	Study duration and wash-out period adequate, groups treated equally aside from intervention. Study sponsored by Stiefel Laboratories, Inc. The first two investigators have received grants from Stiefel Laboratories

		Comment: Sponsorship and the fact that one investigator is a consultant for the sponsor raises concerns about the potential for bias

Two 2014

Methods	RCT, prospective, placebo-controlled, double-blind Date of study July 2011 to December 2012 Setting University of California, San Diego (UCSD) Dermatology Clinic, US
Participants	**Randomised:** 15 participants (mean age 60 years, 3 male, 7 female, 5 gender unreported) **Inclusion criteria** • Papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 4/15 (26.6%) in the SEI003 group scheduling conflicts (1) no longer interested (2), starting doxycycline for ocular rosacea (1) **Baseline data mean** IGA score; SEI003 group 1.8, vehicle group 2.0 CEA score; SEI003 group 9, vehicle group 7
Interventions	12 weeks **Intervention** SEI003 cream (11) **Comparator** Vehicle cream (4) Application frequency unclear
Outcomes	Assessments (5): baseline, week 2, 6, 9 and 12 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Investigator's Global Assessment (IGA)✴

	2. Five- point Clinician's Erythema Assessment (CEA) score of five different target sites (left cheek, right cheek, nose, chin, and glabella)✶ **Secondary outcomes** Safety monitoring (adverse events) and tape strip sampling for stratum corneum protease activity (SPA)✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 1145): "In vitro analysis described in this work was supported in part by the United States National Institutes of Health (NIH) grant R01-AR052728 to RLG."
Declaration of interest	Quote (page 1145): "Neither Therapeutics nor Skin Epibiotics provided any financial compensation for the study or to any members of the study team with the exception of EH, who left his position at UCSD for employment opportunities at these companies part-way through the study"
Notes	One of our primary outcomes was addressed (adverse events) See comparison 49 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1143): " randomized, double-blind, placebo controlled study".."randomized 2:1...." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups After e-mail communication: "The allocation sequence was generated by an unblinded member of the study team who worked off-site in a separate laboratory" Comment: Probably done
Allocation concealment (selection bias)	Low risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: "The allocation sequence was created prior to enrolling any subjects in the study" by a third party Comment: Probably done

Blinding of participants and personnel (performance bias)	Low risk	Quote (page 1143): "Subjects, study coordinators, and those performing clinical assessments were blinded" Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement After e-mail communication: "study medication was placed into a bottle labeled with the participant's unique study identification number that was assigned to the participant at the time of enrolment in the trial" by a third party, and "Both the treatment and the control creams were identical in appearance and viscosity so that the two drugs could not be distinguished by look or feel." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 1143): "Subjects, study coordinators, and those performing clinical assessments were blinded" Comment: Outcomes were investigator and participant assessed. Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement After e-mail communication: "study medication was placed into a bottle labeled with the participant's unique study identification number that was assigned to the participant at the time of enrolment in the trial" by a third party, and "Both the treatment and the control creams were identical in appearance and viscosity so that the two drugs could not be distinguished by look or feel." Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	High risk	4/15 (26.6%) in the SEI003 group and per-protocol analysis Comment: High and unbalanced dropout rate combined with per-protocol analysis judged as at high risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for this study NCT01398280 was available at https://www.clinicaltrialsregister.eu/ctr-search/search and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported

		Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration adequate, no information regarding wash-out period Comment: The study appeared to be free of other forms of bias

Utaş 1997

Methods	RCT, prospective, active and placebo-controlled, double-blind Date of study Unreported Setting Department of Dermatology, Erciyes University Medical School, Kayseri, Turkey
Participants	**Randomised:** 53 participants (mean age 46.9 years (range 38 to 68 years), 7 male, 46 female) **Inclusion criteria** • Participants with rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • Not reported **Baseline data mean** Nothing reported
Interventions	Two weeks **Intervention** Ketoconazole 400 mg/day (10) **Comparator 1** Ketoconazole 2% cream (10) **Comparator 2** Ketoconazole 400 mg + 2% cream (13) **Comparator 1** Placebo cream (10) **Comparator 1**

	Placebo pills (10)
Outcomes	Assessments (2): baseline and week 2 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Number inflammatory lesions and erythema, scored 0 to 3 (0 = no lesion, 3 severe lesion)✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed Older study, described in letter, a lot of information is lacking (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 69): "Quote: "The patients were randomized into 5 groups" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 69): "double-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome	Unclear risk	Quote (page 69): "double-blind". Only investigator assessed outcomes

assessment (detection bias)		Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants/healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Not reported, no exact data were provided Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Outcomes unclear and no data provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Letter provided only limited data Comment: There was insufficient information to permit a clear judgement

van der Linden 2017

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study April 2011 to March 2015 Setting Dermatology Department of the Academic Medical Centre, Amsterdam, the Netherlands
Participants	**Randomised**: 80 participants (mean age 46 years, 21 male, 59 female) **Inclusion criteria** • ≥ 18 years; had a clinical diagnosis of papulopustular rosacea had a score ≥ 1 on Investigator's Global Assessment (IGA); had at least eight inflammatory lesions (papules and/or pustules) and had a score ≥ 1 on Clinician's Erythema Assessment (CEA). • Negative urine pregnancy test, and should have used a form of contraceptive in women **Ocular involvement:** Unclear **Exclusion criteria** • Pregnant, nursing or planning pregnancy • Initiated or changed a hormonal method of contraception within 3 months prior to baseline • Dermatosis that might interfere with rosacea or the evaluation of treatment results • Known hypersensitivity to tetracyclines • Topical therapy within 2 weeks prior to baseline • Systemic or laser therapy for rosacea within 4 weeks prior to baseline • Any investigational drug within 4 weeks

	• Isotretinoin in the 6 months prior to baseline • Known or suspected achlorhydria or had surgery to bypass or remove the duodenum; were known or suspected to have hepatic impairment or were receiving potentially hepatotoxic medicinal products • Current drug or alcohol abuse • Considered to be unsuitable to participate in this trial by their treating physicians **Dropouts and withdrawals during treatment phase (16 weeks)** • 9/80 (11.3%); minocycline group (5), doxycycline group (4) • Adverse events; minocycline group (4), doxycycline group (3) • Patient's request; minocycline group (1), doxycycline group (1) After 28 weeks • Protocol violation; minocycline group (0), doxycycline group (2) • Lost to follow-up; minocycline group (1), doxycycline group (0) **Baseline data median** Lesion count; minocycline group 20, doxycycline group 26 RosaQoL; minocycline group 3.36, doxycycline group 3.38 IGA mild (n); minocycline group 10, doxycycline group 2 IGA moderate (n); minocycline group 9, doxycycline group 12 IGA severe (n); minocycline group 21, doxycycline group 26 CEA mild (n); minocycline group 13, doxycycline group 12 CEA moderate (n); minocycline group 22, doxycycline group 24 CEA significant (n); minocycline group 3, doxycycline group 2 CEA severe (n); minocycline group 2, doxycycline group 2
Interventions	16 weeks **Intervention** Minocycline 100 mg - QD (40) **Comparator 1** Doxycycline 40 mg - QD (40) No concomitant treatment was allowed.

Outcomes	Assessments (6): baseline, week 2, 4, 8, 16 weeks and 12 weeks after end of study **Outcomes of the trial** (as reported) **Primary outcomes** 1. Change in lesion count✶ 2. Rosacea-specific Quality of life instrument (RosaQoL)✶ **Secondary outcomes** 1. Evaluate the safety of doxycycline and minocycline✶ 2. Patient's assessment of treatment (1 = excellent improvement, 5 = worse)✶ 3. Investigator's Global Assessment (IGA) (0 = clear, 4 = severe)✶ 4. Clinician's Erythema Assessment (CEA) (0 = none, 4 = severe)✶ 5. Adverse events✶ 6. Relapse rate✶ 7. Compliance ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 1565): "Funding sources: None"
Declaration of interest	Quote (page 1565): "None declared"
Notes	All our primary outcomes were addressed See comparison 59 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 1468): "Eligible patients were randomly assigned (1 : 1), after providing informed consent, by one of the treating physicians (A.R.v.R. and D.C.v.R.) using the computer- generated randomization system 'TENALEA Clinical Trial Data Management System' (Netherlands Cancer Institute) to random block sizes of four, six and eight, to minimize selection bias" Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 1468): "Treatment allocation was concealed until the end of the study and data collection and analyses were complete". The method used to conceal the allocation sequence, that is to determine whether intervention

		allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement After e-mail communication: Central allocation (via pharmacy) Comment: Adequate
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 1468): "A blinded assessor (M.M.D.v.d.L.) assessed lesion count, IGA and CEA" Comment: The report provided insufficient detail about the measures used to blind study personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 1468): "A blinded assessor (M.M.D.v.d.L.) assessed lesion count, IGA and CEA" Comment: Outcomes were investigator and participant assessed. Participants were not blinded. Uncertainty with the effectiveness of blinding of outcomes assessors (investigators) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	9/80 (11.3%); minocycline group (5), doxycycline group (4), reasons reported. ITT and per protocol analysis Comment: We judged this as at an unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was available at apps.who.int/trialsearch/ (EUCTR2010-021150-19-NL) and the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration adequate, wash-out period before study started adequate, groups treated equally. However, there was baseline imbalance in IGA with the people in the doxycycline group being more affected Comment: We judged this as at an unclear risk of bias

Van Landuyt 1997

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Service de Dermatologie, Hôpital Saint Jacques

Participants	**Randomised:** 60 participants (age and gender unreported) **Inclusion criteria** • Participants with rosacea **Ocular involvement:** Unclear **Exclusion criteria** • Minocycline < 15 days prior to study entry **Dropouts and withdrawals** • 1/60 in placebo group, reason unreported **Baseline data mean** Not reported
Interventions	30 days **Intervention** Clonidine 0.075 mg/day (30) **Comparator** Placebo (30)
Outcomes	Assessments (at least 3): baseline, 15 days and 30 days **Outcomes of the trial** (as reported) **Primary outcomes** 1. Erythema and intensity of the flushes✴ 2. Laser Doppler, chromometry and thermometry on both cheeks **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	This is a very brief interim report, full study has never been published, data only reported for 30 participants and largely unusable (see Table 6) None of our primary outcomes were addressed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 729): "randomisée" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 729): "double insu." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 729): "double insu" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Interim report on 30 participants Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement

Veien 1986

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Multicentre, Department of Dermatology, Marselisborg Hospital, Arhus; Department of Dermatology, Genthofte Hospital, Copenhagen; Odense University Hospital, Odense; and Dermatology Clinic, Aalborg, Denmark

Participants	**Randomised:** 76 participants (mean age 52.4 years, 36 male/39 female and 1 gender unreported) **Inclusion criteria** • Adults with rosacea defined as erythema, telangiectasia, pustules, papules, and recurrent disease for at least 6 months **Ocular involvement:** Unclear **Exclusion criteria** • Pregnant and nursing women **Dropouts/Withdrawals** • 6/76 (7.9%); unclear how many from each group **Baseline data mean (SD)** Means for lesions or erythema were not reported
Interventions	Eight weeks **Intervention** Metronidazole 1% cream and placebo tablets - BID (38) **Comparator** Tetracycline tablets 250 mg BID and placebo cream (38)
Outcomes	Assessments (4): baseline, week 2, 4 and 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction in lesion count✴ 2. Intensity of erythema (scale 1 to 5)✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 210); "The metronidazole cream and tetracycline tablets were supplied by the Danish drug company, Dumex Ltd."
Declaration of interest	None declared
Notes	None of our primary outcomes were addressed See comparison 72 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 209): "The study was performed in 4 centers as a double-blind, randomized trial." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 209): "double-blind" "...placebo tablets identical in appearance to the tetracycline tablets." "...placebo cream was cream base of metronidazole cream." Comment: The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 209): "double-blind" "...placebo tablets identical in appearance to the tetracycline tablets." "...placebo cream was cream base of metronidazole cream." Outcomes were investigator assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Unclear risk	6/76 (7.9%); unclear how many participants from each group, per-protocol analysis Comment: We judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias

Other bias	Unclear risk	Study duration adequate, wash-out period before study rather short for oral therapy (2 weeks), unclear if other medications were allowed Comment: Insufficient information to assess whether an important risk of bias exists

Verea Hernando 1992

Methods	RCT, prospective, active-controlled, double-blind Date of study Unreported Setting Dermatology department, Juan Canalejo Hospital, La Coruña, Spain
Participants	**Randomised:** 40 participants (mean age 57.8 (14) years in the erythromycin group and 62.2 (12) years in metronidazole group, 13 male, 27 female) **Inclusion criteria** • Participants that attended the dermatology department of the hospital that were diagnosed with rosacea **Ocular involvement:** Unclear **Exclusion criteria** • Participants that had previously used systemic antibiotics • History of hypersensitivity to the study treatments **Dropouts and withdrawals** • 6/40 (15%); erythromycin group (5) and metronidazole group (1) • Lost to follow-up; erythromycin group (3) and metronidazole group (1) • Withrawal of consent; erythromycin group (1) and metronidazole group (0) • Adverse event; erythromycin group (1) and metronidazole group (0) **Baseline data total** Number of papules; erythromycin group 571 and metronidazole group 476 Number of pustules; erythromycin group 160 and metronidazole group 63
Interventions	Three months **Intervention**

	Erythromycin gel 2% - BID (22) **Comparator** Metronidazole gel 0.75% - BID (18)
Outcomes	Assessments (2): baseline, month 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Number of inflammatory lesions✶ 2. Erythema and telangiectasia✶ 3. Global assessment by physician✶ 4. Assessment according to participant✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) See comparison 32 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote (page 474) (translation): "Patients included in the study were assigned a key number by the pharmacy service that assigned them to one of the two groups through a table of random numbers generated by computer." Comment: Probably done
Allocation concealment (selection bias)	Low risk	Quote (page 474) (translation): "They were randomised by a computer generated distribution numbered list by the pharmacy." Comment: Pharmacy-controlled randomisation. Probably done
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 474): "...doble ciego." [Translated as double-blind] Comment: The report provided insufficient detail about the measures used to blind study

		participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 474): "...doble ciego." [Translated as double-blind] Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	High risk	Dropouts and withdrawals (> 20% in erythromycin group) were reported but unclear at which time points and no evidence of ITT analysis (page 475) Comment: We judged this as at a high risk of bias
Selective reporting (reporting bias)	High risk	Physician's Global Assessment was not addressed or reported Comment: We judged this as at a high risk of bias
Other bias	High risk	Wash-out period unclear, study duration adequate, groups probably treated equally. Baseline imbalance between the groups in number of pustules and papules Comment: The baseline imbalance in the groups puts the study at serious risk of bias

Waibel 2016

Methods	RCT, prospective, active-controlled, investigator-blinded, within-patient comparison Date of the study Unreported Setting Miami Dermatology and Laser Institute, University of Miami, Miami, FL, US
Participants	**Randomised:** 22 participants (age and gender unreported) **Inclusion criteria** • Erythematotelangiectatic and/or papulopustular rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals**

	• Not reported **Baseline data mean** Nothing reported
Interventions	3 laser treatment at 4 week intervals **Intervention** KTP laser (532 nm) therapy **Comparator** Pulsed dye laser (595 nm) therapy
Outcomes	Assessments (2): baseline, with follow-up evaluation and assessment at 4–6 weeks after the final treatment **Outcomes of the trial** (as reported) **Primary outcomes** 1. Overall response to treatment (digital photography)✴ **Secondary outcomes** 1. Improvement by investigation evaluation✴ 2. Subject self evaluation✴ 3. Spectrophotometry✴ ✴Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None reported
Notes	One of our primary outcomes was addressed (participant-assessed changes in rosacea severity) Poster abstract, limited information is provided (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 426): "A comparative randomized two-arm split-face study" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No mentioning of blinding of physicians and participants Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 426): "blinded review of digital photography" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias)	Unclear risk	Quote (page 918): "single-blind" Comment: Outcomes were investigator and participant assessed. Participants were not blinded. Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers) during the study Insufficient information to permit a clear judgement.
Selective reporting (reporting bias)	Unclear risk	There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Only limited data were provided (poster abstract) Comment: There was insufficient information to permit a clear judgement

Weissenbacher 2007

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Department of Dermatology and Allergy Biederstein, Munich, Germany
Participants	**Randomised:** 40 participants (mean age 58 years, 25 male, 15 female) **Inclusion criteria** • Participants with papulopustular rosacea with a rosacea severity score of ≥ 6 as well as an erythema score of ≥ 2 and a scaling score of ≥ 1

	Ocular involvement: Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals:** None **Baseline data mean** Rosacea severity score; pimecrolimus group 6.88, vehicle group 7
Interventions	Four weeks **Intervention** Pimecrolimus 1% cream - BID (20) **Comparator** Vehicle cream - BID (20)
Outcomes	Assessments (4): baseline, week 1, 2 and 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Rosacea severity score for each sign (erythema, papules, pustules, and scaling) and a total score graded as none (0), mild (0.5 to 1), moderate (1.5 to 2), or severe (2.5 to 3)✶ 2. Subjective severity assessment on visual analogue scale (VAS 0 mm, no change to 100 mm, very severe skin changes) and a quality of life assessment using the Dermatology Life Quality Index (DLQI) and photographic documentation✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	Quote (page 728): "M.B. is employed by Novartis Pharma, the manufacturer of Elidel (pimecrolimus)."
Notes	We only included data from the first 4 weeks, second part of study was open-phase. Two of our primary outcomes were addressed (quality of life and participant-assessed changes in rosacea severity) See comparison 35 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 729): "Forty patients with papulopustular rosacea were investigated in a single-centre, randomized, double-blind vehicle-controlled study." Comment:Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Low risk	Quote (page 728): "double-blind", only first 4 weeks Comment: Vehicle cream was used. Probably identical appearance The report provided sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Low risk	Quote (page 728): "double-blind", only first 4 weeks Vehicle cream was used. Probably identical appearance. Outcomes were investigator and participant assessed. Blinding of participants and key study personnel was ensured, and it is unlikely that the blinding could have been broken Comment: We judged this as at a low risk of bias
Incomplete outcome data (attrition bias)	Low risk	There were no withdrawals reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Unclear if there was a wash-out period, duration of double-blinded part too short (4 weeks), unclear if additional medications were allowed and recorded. One of the investigators was employed by the manufacturer of Elidel (Novartis Pharma)

		Comment: Insufficient information to assess whether an important risk of bias exists

Wilkin 1989

Methods	RCT, prospective, active- and placebo-controlled, double-blind, cross-over Date of study Unreported Setting McGuire Veterans Administration Medical Center, Richmond, US
Participants	**Randomised:** 15 participants (age range 41 to 60 years, 4 male, 11 female) **Inclusion criteria** • Participants with erythematotelangiectatic rosacea and flushing reactions, that were normotensive and in good general health **Ocular involvement:** Unclear **Exclusion criteria** • Participants that used prescription or over-the-counter drugs to control flushing **Dropouts and withdrawals:** Not stated, unclear **Baseline data mean (SD)** Nothing reported
Interventions	53 days **Intervention** Placebo for 18 days (period A), placebo for 17 days (period B), and then nadolol 40 mg QD for 18 days (period C) (4) **Comparator 1** Placebo for 18 days (period A), placebo for 17 days (period B), and then nadolol 40 mg BID for 18 days (period C) (3) **Comparator 2** Nadolol 40 mg for 18 days (period A), placebo for 17 days (period B), and then placebo for 18 days (period C) (4) **Comparator 3** Nadolol 40 mg BID for 18 days (period A), placebo for 17 days (period B), and then placebo for 18 days (period C) (4)

Outcomes	Assessments for period A (2): baseline, day 18 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Reduction of flushing intensity (measuring cutaneous perfusion index method with laser-Doppler velocimetry) 2. Number and duration of flushes and intensity as assessed by participant **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 202): "Supported by a grant from E.R. Squibb & Sons, Inc, New Brunswick, New Jersey"
Declaration of interest	None declared
Notes	We included only period A, first study period, however, no separate data for this period (see Table 6) None of our primary outcomes were addressed

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 202): "All persons were randomly assigned to one of four 2-way cross-over treatment groups in a double-blind manner." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Unclear if tablets were comparable/similar in appearance Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 203): "were analyzed in a blinded manner" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Dropouts not reported, other than 1 participant who dropped out reasons unclear Comment: We judged this as at unclear risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	High risk	Wash-out period was included in study design, other rosacea treatment did not have to be stopped, study duration too short (period of 17 to 18 days), groups treated equally. Small sample size Comment: We judged this as at a high risk of bias

Wilkin 1993

Methods	RCT, prospective, active-controlled, investigator-blinded Date of study Unreported Setting Two centres in US
Participants	**Randomised:** 43 participants (age range 25 to 70 years, both male and female, numbers not specified) **Inclusion criteria** • All participants had a diagnosis of rosacea, principally papulopustular variety **Ocular involvement:** Unclear **Exclusion criteria** • Participants receiving systemic or topical therapy for their rosacea within the previous 30 days **Dropouts and withdrawals:** Unclear **Baseline data mean (SD)** Signs and symptoms of rosacea were comparable for both groups

Interventions	12 weeks **Intervention** Clindamycin 1% lotion BID + placebo capsules - 4 times daily during first 3 weeks and thereafter BID **Comparator** Vehicle lotion BID + tetracycline 250 mg - 4 times daily during first 3 weeks and thereafter BID
Outcomes	Assessments (2): baseline, week 12 **Outcomes of the trial** (as reported) **Primary outcomes:**✴ 1. Percentage change in mean lesion count 2. Skin tolerance (erythema, telangiectasia, flushing or blushing, oedema, itching, burning, dryness, scaling or peeling, and oiliness) 3. Physician's and participant's assessment of result (worse, no change, improved)✴ **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 65): "Supported by a grant of Upjohn Company, Kalamazoo, Michigan"
Declaration of interest	None declared
Notes	Unclear how many participants were assigned to each group, dropouts not mentioned, no exact data provided (see Table 6) One of our primary outcomes was addressed (participant-assessed changes in rosacea severity)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 66): "Patients were randomly assigned to one of two regimens." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups

Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 65): "...investigator-blinded." "...double-blinded." Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 65): "...investigator-blinded." "...double-blinded." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Minimal outcomes data reported, dropouts and withdrawals unreported Comment: Insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Unclear what study outcomes were, not stated in Methods section Comment: Insufficient information to permit a clear judgement
Other bias	Low risk	Study duration and wash-out period adequate, groups appear to have been treated equally Comment: The study appears to be free of other forms of bias

Wittpenn 2005

Methods	RCT, prospective, placebo-controlled, double-blind Date of study Unreported Setting Private Practice, Stony Brook, NY, Rand Eye Institute, Pompano Beach, Florida, US
Participants	**Randomised:** 20 (age and gender unreported) **Inclusion criteria** • Participants with rosacea associated lid and corneal changes after any active infections were treated with lid scrubs and antibiotics

	Ocular involvement: Yes **Exclusion criteria** • Lid defects and lagophthalmos • Doxycycline 2 weeks prior to study entry **Dropouts and withdrawals** • Not reported **Baseline data mean** Nothing reported
Interventions	Three months **Intervention** Ciclopsporin (0.05%) eye drops **Comparator** Artificial tears Unclear how many were randomised to each group, application frequency unclear
Outcomes	Assessments (at least 2): baseline and month 3 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Increase in Schirmer's test 2. Improvement of Tear Breaking-Up Time 3. Improvement in Ocular Surface Disease Index **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (in abstract): "None"
Declaration of interest	Quote (in abstract): "JR Wittpenn, Allergan, B Schechter, Allergan"
Notes	None of our outcomes were addressed. This study was part of NCT00348335 (see Table 3). Poster with very limited data (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement

Random sequence generation (selection bias)	Unclear risk	Quote (on poster): "patients were randomized to cyclosporine A or artificial tears for 3 months**.**" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (on poster): "double-masked." Comment: The report did not provide sufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (on poster): "double-masked." Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Unclear risk	Only limited data were provided, no report on dropouts Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Abstract provided only limited data Comment: There was insufficient information to permit a clear judgement

Wolf 2006

Methods	RCT, prospective, active-controlled, investigator-blind Date of study Unreported Setting Multicentre (15) in US
Participants	**Randomised:** 160 participants (mean age 51.1 ± 10.7 years (range 32 to 78) in metronidazole group and 51.1 ± 11.3 years (range 31 to 77) in azelaic acid group, 26 male and 56 female

	in metronidazole group, and 18 male and 60 female in azelaic group) **Inclusion criteria** • Participants with moderate rosacea, further defined as 8 to 50 papules, pustules and nodules on the face, with no more than 2 nodules **Ocular involvement:** Unclear **Exclusion criteria** • Pregnant and breast-feeding women. Participants that used systemic antibiotics, oral metronidazole, and corticosteroids less than 4 weeks prior to the start of the study or with retinoids 6 months prior to the start of the study **Dropouts and withdrawals** • 24/160 (15%); metronidazole group (14) and azelaic acid group (10) • Patient's request, protocol violation, lost to follow-up were most frequent reported reasons (no further details) **Baseline data median** Inflammatory lesions; metronidazole group 17 and azelaic acid group 14.5
Interventions	15 weeks **Intervention** Metronidazole 1% gel - QD (82) **Comparator** Azelaic acid 15% gel - BID (78)
Outcomes	Assessments (6): baseline, week 3, 6, 9, 12 and 15 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Inflammatory lesion counts✴ 2. Investigator global severity score (0 = cleared, no erythema or very mild erythema with no inflammatory lesions; and 4 is severe erythema, numerous small or large papules and pustules with or without nodules. Also dichotomised score for treatment success or failure by score 0 or 1)✴

	3. Erythema severity (0 = none, 4 = severe; also dichotomised score for treatment success or failure by score 0 or 1)✶ **Secondary outcomes** 1. Tolerability, including burning, stinging, dryness, scaling, and itching on a 0 to 3 scale 2. Adverse events✶ 3. Participants' satisfaction at end of 15 weeks✶ ✶Denotes outcomes pre-specified for this review
Funding source	Quote (page 3): "This study was supported by a grant from Galderma Laboratories, LP"
Declaration of interest	Quote (page 3): "Mr Kerrouche and Ms Arsonnaud are from Galderma Laboratories, LP, Sophi-Antipolis, France. Dr Wolf is an advisory board member, consultant, researcher and speaker for Galderma Laboratories
Notes	Two of our primary outcomes were addressed (participant-assessed changes in rosacea severity and adverse events) See comparison 16 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 4): "Patients were randomized in a 1:1 fashion to treatment with metronidazole 1% gel once daily or azelaic acid 15% gel twice daily for a period of 15 weeks." Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during enrolment, was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 4): 'investigator-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement

Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 4): 'investigator-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (healthcare providers and participants) during the study Insufficient information to permit a clear judgement
Incomplete outcome data (attrition bias)	Low risk	24/160 (15%); metronidazole group (14) and azelaic acid group (10). Both ITT and per-protocol analyses reported performed Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Unclear risk	Study duration and wash-out period adequate, groups treated equally. Supported by a grant from Galderma Laboratories. First investigator was an advisory board member, consultant, researcher, and speaker for Galderma Laboratories, two other investigators are from Galderma Comment: We judged this as at unclear risk of bias

Yoo 2011

Methods	RCT, prospective, active-controlled, single-blind, within-patient comparison Date of study Unreported Setting Mount Sinai Medical Center, New York, NY, US
Participants	**Randomised:** 6 participants (age and gender unreported) **Inclusion criteria** • Erythematotelangiectatic rosacea **Ocular involvement:** Unclear **Exclusion criteria** • None reported **Dropouts and withdrawals** • 1/6; personal reasons

	Baseline data mean Nothing reported
Interventions	12 weeks (4 sessions of laser with 2 week intervals) **Intervention** Pulsed dye laser therapy + calcium dobesilate (2,5-dihydroxybenzene sulfonate) gel - QD **Comparator** Pulsed dye laser therapy
Outcomes	Assessments (3): baseline, 16 and 20 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Overall response to treatment✶ 2. Safety✶ **Secondary outcomes** 1. None ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	One of our primary outcomes was addressed (adverse events) Poster abstract, limited information is provided (see Table 6)

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 918): "and concurrently received PDL treatment to one randomized side" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported

		Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	Unclear risk	Quote (page 918): "single-blind" Comment: The report provided insufficient detail about the measures used to blind study participants and personnel from knowledge of which intervention a participant received, to permit a clear judgement
Blinding of outcome assessment (detection bias)	Unclear risk	Quote (page 918): "single-blind" Comment: Uncertainty with the effectiveness of blinding of outcomes assessors (participants, healthcare providers) during the study Insufficient information to permit a clear judgement.
Incomplete outcome data (attrition bias)	Unclear risk	1/6 for personal reasons lost to follow-up. Comment: There was insufficient information to permit a clear judgement
Selective reporting (reporting bias)	Unclear risk	Only limited data were provided (protocol available at clinical trials.gov NCT00945373) Comment: There was insufficient information to permit a clear judgement
Other bias	Unclear risk	Only limited data were provided Comment: There was insufficient information to permit a clear judgement

Zhang 2017

Methods	RCT, prospective, active-controlled Date of study January 2014 to July 2015 Setting Dermatology Department, Ningbo No. 6 Hospital, Ningbo, China
Participants	Randomised: 65 participants (age range 19 to 52 years, 16 male, 49 female) **Inclusion criteria** • 18-60 years with erythematotelangiectatic or papulopustular rosacea No ocular involvement **Exclusion criteria** • Photosensitive diseases • Allergic to hydroxychloroquine • Pregnant and lactating women • Eye diseases, such as retinal diseases

	• Oral or topical vitamin A acid and corticosteroids or photosensitive drugs within recent 3 months • Seborrheic dermatitis, steroids-dependent dermatitis and other chronic non-specific skin inflammation • Family history of malignant tumour • Severe systemic disease and others not suitable for participating **Dropouts and withdrawals** • None reported **Baseline data mean** Score of papules and pustules, telangiectasia, erythema and pruritus, but method unclear
Interventions	8 weeks **Intervention** Hydroxychloroquine 0.2 gram - BID and after 4 weeks a single treatment with PDL (595 nm) (32) **Comparator** Hydroxychloroquine 0.2 gram - BID (33)
Outcomes	Assessments (2): baseline and week 8 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Improvement (digital camera) with curative effect index (100% = cured, 75-99% = markedly effective, 50-75% = improvement, <50% = ineffective)✶ **Secondary outcomes** 1. Fundus examination 2. Routine blood tests, liver and kidney function ✶Denotes outcomes pre-specified for this review
Funding source	None reported
Declaration of interest	None declared
Notes	None of our primary outcomes was addressed. Article translated (see Acknowledgements) See comparison 91 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 413): "randomly divided" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding. Outcomes were investigator-assessed Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No drop-outs reported Comment: We judged this as at a low risk of bias
Selective reporting (reporting bias)	Low risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported Comment: We judged this as at a low risk of bias
Other bias	Low risk	Study duration and wash-out period adequate, groups appear to have been treated equally Comment: The study appears to be free of other forms of bias

Zhong 2015

Methods	RCT, prospective, vehicle-controlled, within-patient comparison Date of study March to May 2011 Setting Department of Dermatology, Peking University First Hospital, Beijing, China
Participants	**Randomised:** 30 participants (mean age 39.3 years, 12 male, 18 female)

	Inclusion criteria • 18-65 years with rosacea **Ocular involvement:** Unclear **Exclusion criteria** • Facial acne • steroid- dependent dermatitis • Other skin or systemic diseases that might influence skin assessment • Using antirosacea drugs (including antibiotics), steroids, or vasodilating agents topically < 2 weeks and orally < 4 weeks prior to enrolment • Allergy for test ingredients • Gestation or lactation **Dropouts and withdrawals** • None reported **Baseline data mean**
Interventions	2 weeks **Intervention** Tranexamic acid 5% solution - BID **Comparator** Vehicle - BID During the study, no other topical or systemic agents were allowed
Outcomes	Assessments (2): baseline and week 2 **Outcomes of the trial** (as reported) **Primary outcomes** 1. Skin physiological parameters, including skin surface pH (pH meter pH900), stratum corneum hydration (Corneometer, CM825), and transepidermal water loss (Tewameter TM300)(COURAGE+KHAZAKA electronic GmbH, Köln, Germany) 2. Assessment of erythema (Chromameter CM2600d (Konica Minolta, Inc., Tokyo, Japan))✴ 3. Expression of protease-activated receptor 2 (PAR-2)(using reverse transcription polymerase chain reaction) after stimulation with tranexamic acid; Changes of intracellular calcium induced by PAR-2

	activation were measured using Fluo-4 NW calcium assay **Secondary outcomes** 1. None ✴Denotes outcomes pre-specified for this review
Funding source	Quote (page 117): "This project was supported by the National Natural Science Fund (81201217) and the Beijing Natural Science Fund (7122181)"
Declaration of interest	Quote (page 112): "The authors declare that they have no financial or nonfinancial conflicts of interest related to the subject matter or materials discussed in this article"
Notes	None of our primary outcomes was addressed See comparison 54 in Effects of interventions

Risk of bias table

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote (page 113): "A randomized, vehicle controlled, split-face study was performed on 30 rosacea patients" Comment: Insufficient detail was reported about the method used to generate the allocation sequence to allow a clear assessment of whether it would produce comparable groups
Allocation concealment (selection bias)	Unclear risk	The method used to conceal the allocation sequence, that is to determine whether intervention allocations could have been foreseen in advance of, or during, enrolment was not reported Comment: There was insufficient information to permit a clear judgement
Blinding of participants and personnel (performance bias)	High risk	No blinding Comment: The outcome was likely to be influenced by the lack of blinding
Blinding of outcome assessment (detection bias)	High risk	No blinding. Outcomes were investigator-assessed Comment: The outcome measurement was likely to be influenced by the lack of blinding
Incomplete outcome data (attrition bias)	Low risk	No drop-outs reported Comment: We judged this as at a low risk of bias

Selective reporting (reporting bias)	Unclear risk	The protocol for the study was not available, but the pre-specified outcomes and those mentioned in the methods section appeared to have been reported. However, some extra outcomes have been added which were not mentioned in the method section such as clinical signs and symptoms (lesion assessment) Comment: We judged this as at an unclear risk of bias
Other bias	Low risk	Study duration and wash-out period adequate, groups appear to have been treated equally Comment: The study appears to be free of other forms of bias

Footnotes

BID = twice a day, BZP = benzoyl peroxide, ITT = intention-to-treat analysis, N = number, n/a = not applicable, ns = not significant, no further data available, QD = once daily, RCT = randomised controlled trial, RWBT = rapid whole blood test, SD = standard deviation, SEM = standard error of the mean, TID = three times a day, UBT = urea breath test

Characteristics of excluded studies

Aitken 1983

Reason for exclusion	Not a randomised controlled trial (RCT). No description of rosacea, unclear if additional medication was allowed, no site of evaluation is recorded, no intention-to-treat analysis (ITT). Lots of information is lacking

Aizawa 1992

Reason for exclusion	Not a RCT

Altinyazar 2005

Reason for exclusion	Quote: "Patients were randomly assigned..." Page 253 Comment: The investigator confirmed by email that this consisted of "60 sealed envelopes including names of treatments, half to half. Patients selected an envelope" This is a form of quasi-randomisation. CCT

Aronson 1987

Reason for exclusion	Open allocation, "based on arrival", quasi-randomised. CCT

Bakar 2006

Reason for exclusion	Not a RCT

Bang Soon 2007

Reason for exclusion	Not a RCT

Bartholomew 1982

Reason for exclusion	CCT, no evidence of randomisation

Berardesca 2008

Reason for exclusion	After e-mail communication with the investigators to clarify aspects of trial conduct the judgement for sequence generation was changed from 'unclear' to 'high risk of bias'. The participants were allocated to the intervention by alternation. CCT

Beridze 2005

Reason for exclusion	CCT

Bernstein 1982

Reason for exclusion	Not a RCT

Bjerke 1989a

Reason for exclusion	Not a RCT. Narrative report about treatment

Bukvic-Mokos 1998

Reason for exclusion	CCT

Chu 2005

Reason for exclusion	Not a RCT. Case report

Colón 2007

Reason for exclusion	Study to assess cumulative irritation potential and not treatment effect on rosacea

Cunliffe 1977

Reason for exclusion	CCT

Del Rosso 2004

Reason for exclusion	Not a RCT. Narrative report about 2 studies

Dereli 2005

Reason for exclusion	Not a RCT. Open-label study

Draelos 2005

Reason for exclusion	Not a RCT of effects of interventions on rosacea. Unit of randomisation = barrier tests on the arms

Erdogan 1998

Reason for exclusion	Not a RCT

Fernandez-Obregon 2004

Reason for exclusion	Not a RCT

Fleischer 2005

Reason for exclusion	Open-label, observational study

Freeman 2012

Reason for exclusion	After e-mail contact appeared to be quasi-randomised

Frigerio 1969

Reason for exclusion	Not a RCT

Frucht-Pery 1993

Reason for exclusion	Quote: "Treatment (either doxycycline protocol or tetracycline hydrochloride protocol) was suggested to each patient at random. Those who refused the suggested protocol were offered the treatment with the other protocol." Page 89 Comment: Method used to randomise participants to the interventions was inadequate. Not a RCT

Garg 2008

Reason for exclusion	Not a RCT. Open-label study

Gedik 2005

Reason for exclusion	Not a RCT. Rosacea patients were given triple therapy consisting of amoxicillin, clarithromycin and lansoprazole

Go 1976

Reason for exclusion	Not a RCT

Goldsmith 1989

Reason for exclusion	Not a RCT. Narrative review

Hofer 2004

Reason for exclusion	Not a RCT, no blinding, all participants were treated with isotretinoin

Irvine 1988

Reason for exclusion	Not a RCT

Jackson 2007

Reason for exclusion	Poster, without data. Unsuccessful attempts at contacting authors

Karabulut 2008

Reason for exclusion	Contact with investigators via electronic mail, responses clear that the allocation sequence was inadequately generated

Koçak-Altintas 2005

Reason for exclusion	Quote: "...randomly divided into two groups." Comment: Following extensive email communication with the principal investigator we were unable to receive reassurances that the allocation sequence was adequately generated and therefore this study has been classified as a CCT

Laquieze 2007

Reason for exclusion	This study did not match the inclusion criteria for this review

Lee 2008

Reason for exclusion	Participants with steroid-induced rosacea, and rosacea patients were excluded

Liu 2006

Reason for exclusion	Systematic review of 5 studies, all included in present review

Loo 2004

Reason for exclusion	Not a RCT

Maxwell 2010

Reason for exclusion	After reading full text appears to be CCT

Meekin 2008

Reason for exclusion	No participants with rosacea

Mraz 2008

Reason for exclusion	Not a RCT

Määttä 2006

Reason for exclusion	Not a RCT

Nasir 1985

Reason for exclusion	Not a RCT

Nielsen 1983

Reason for exclusion	Not a RCT

Ortiz 2009

Reason for exclusion	Not a RCT. Open-label study

Parodi 2008

Reason for exclusion	Not a RCT

Ruggero 2005

Reason for exclusion	Not a RCT. Open, observational study

Sainthillier 2005

Reason for exclusion	This study did not match the inclusion criteria for this review

Seal 1995

Reason for exclusion	Participants with chronic blepharitis, few had associated rosacea. No separate data available for participants with rosacea. Many criteria were assessed as unclear or inadequate. No ITT

Sehgal 2008

Reason for exclusion	Not a RCT. Case report

Shanler 2007

Reason for exclusion	Not a RCT. Case report

Signore 1995

Reason for exclusion	Open-label pilot study with 6 participants, of which 1 dropped out Quote: "Patients were selected randomly and consecutively." "Patients were instructed to apply 0.75% metronidazole gel to the right side of the face...and 5% permethrin to the left side." Page 177 Comment: Quasi-randomised. CCT

Stoudemayer 2006

Reason for exclusion	Poster, limited data available. Not a RCT

Tierney 2009

Reason for exclusion	Ten participants with telangiectasia, no mention of rosacea at all

Togsverd-Bo 2009

Reason for exclusion	Not a RCT. Case report of 4 treated participants

Torresani 1997

Reason for exclusion	Not a RCT

Trumbore 2009

Reason for exclusion	Not a RCT, no control. Open-label

Uebelhoer 2007

Reason for exclusion	Population did not fit the inclusion criteria. Participants with photodamage without rosacea were also included. Unclear

	which participants had rosacea and no separate data available for participants with rosacea

Veien 1988

Reason for exclusion	Not a clinical trial

Veraldi 1996

Reason for exclusion	Not a RCT

Viera 2007

Reason for exclusion	Not a RCT. A narrative review on incyclinide

Yu 2006

Reason for exclusion	Not a RCT, open-label study

Öztürkcan 2004

Reason for exclusion	Not a RCT

Footnotes

RCT = randomised controlled trial
CCT = controlled clinical trial (quasi-randomised)

Characteristics of studies awaiting classification

EUCTR2010-023566-43-DE

Methods	Randomised, double-blind, active-controlled
Participants	Number of participants unclear, participants with papulopustular rosacea
Interventions	Permethrin 5% cream versus permethrin 2.5% cream versus metronidazole 0.75% cream
Outcomes	*Primary outcome measures* 1. Reduction in lesion count *Secondary outcome measures* 1. Numbers of papules, pustules 2. Erythema score 3. Participant assessment (VAS) 4. Adverse events

Notes	Website accessed 16-3-2018, no results posted. Unlikely data will be published after all this time, confirmed by Dr Wachall

EUCTR2012-005686-12-GB

Methods	Randomised, double-blind, placebo-controlled
Participants	80 participants with severe facial erythema of rosacea
Interventions	Brimonidine 0.5% gel versus placebo gel
Outcomes	*Primary outcome measures* 1. Dermatology Life Quality Index questionnaire at each visit 2. Facial Redness questionnaire at each visit 3. EuroQol-5 Dimension questionnaire at each visit 4. Subject Satisfaction questionnaire at the end of the study 5. Severity of erythema according to participants before and 3 hours after application of study drug 6. Severity of erythema according to study doctors before and 3 hours after application of study drug 7. Incidence of adverse event *Secondary outcome measures* 1. Not provided
Notes	Website accessed 19-3-2018, study completed, no results posted

IRCT201508169014N75

Methods	Randomised, open-label, active-controlled
Participants	40 participants with papulopustular rosacea
Interventions	Ivermectin 5% cream versus metronidazole 0.75% gel
Outcomes	*Primary outcome measures* 1. Number of papules and pustules *Secondary outcome measures* 1. Scoring the erythema of skin lesions
Notes	Website access 19-3-2018, study completed, no results posted

NCT00041977

Methods	Randomised, double-blind, placebo-controlled

Participants	150 men and women with rosacea, erythema, papules/pustules, and telangiectasia
Interventions	Doxycycline hyclate 20 mg tablets (Periostat(R)) administered twice daily versus placebo
Outcomes	Not specified
Notes	Study has been completed. Tried to contact CollaGenex Pharmaceuticals without success Website accessed 16-7-2014, sent e-mail to D. Pariser for more information, and asked Galderma NL and international. Website checked again 16-3-2018, no results posted. Unlikely data will be published after all this time

NCT00436527

Methods	Randomised, single blind, no treatment control, within-participant
Participants	26 participants with rosacea
Interventions	Metronidazole gel 1% versus no treatment
Outcomes	*Primary outcome measures* 1. Six replicate Corneometer CM 825 measurements *Secondary outcome measures* 1. Adverse events
Notes	Study has been completed August 2006. Website accessed 19-7-2014, sent e-mail to Galderma NL and international. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT00495313

Methods	Randomised, double-blind, active-controlled
Participants	91 participants with papulopustular rosacea, with erythema and telangiectasia
Interventions	Vibramycin plus metronidazole versus Oracea® delayed-release plus metronidazole
Outcomes	Not specified
Notes	Study completed December 2007. Tried to contact CollaGenex Pharmaceuticals without success Website accessed 16-7-2014, sent message via LinkedIn, and asked Galderma NL and international. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT00621218

Methods	Randomised, double-blind, placebo-controlled
Participants	26 with erythrophagocytotic rosacea
Interventions	Tretinoin gel 0.05% bid versus vehicle
Outcomes	*Primary outcome measures* 1. Improvement in signs and symptoms of rosacea *Secondary outcome measures* 1. Changes in various skin parameters
Notes	Study completed December 2008, no study results reported yet Website accessed 18-7-2014, sent e-mail, company is acquired by Valeant Pharmaceuticals. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT00667173

Methods	Randomised, single-blind, 3 arms, placebo-controlled
Participants	140 with facial rosacea and inflammatory lesions
Interventions	Drug: IDP-115 topical application versus vehicle versus vehicle
Outcomes	*Primary outcome measures* 1. Change from baseline in the number of inflammatory lesions 2. Improvement from baseline in global severity *Secondary outcome measures* 1. Change from baseline in erythema
Notes	Study has been completed July 2008, no published data yet, seeking initial approval September 2010 Website accessed 18-7-2014, Dow Pharmaceuticals Sciences is acquired by Valeant Pharmaceuticals, sent e-mail. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT00991198

Methods	Randomised, double-blind, placebo-controlled
Participants	49 participants with rosacea, acne vulgaris, atopic dermatitis or seborrhoic dermatitis
Interventions	Topical oxygen versus placebo

Outcomes	*Primary outcome measures* 1. Skin grading evaluation of photodamage *Secondary outcome measures* 1. Stratum corneum hydration 2. Bioinstrumental assessment of skin "melanin" lightening, and lesional erythematous sites 3. Bioinstrumental assessment of skin texture, scaliness (desquamation) 4. punch biopsy histopathologic examination (H&E, and immunohistochemistry for aquaporin 3, and filaggrin) 5. RT-PCR collagenase , and hypoxia-inducible factor-1 alpha 6. Product performance
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT01016782

Methods	Randomised, double-blind, placebo-controlled
Participants	867 participants with rosacea
Interventions	0444 gel versus placebo
Outcomes	*Primary outcome measures* 1. Reduction in the number of papules and pustules from baseline to end of treatment *Secondary outcome measures* 1. Reduction in the investigator's global evaluation, clear or almost clear
Notes	Study completed 2009, results not reported Website accessed 19-7-2014, company acquired by Sandoz in 2012, sent e-mail through website Sandoz. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01125930

Methods	Randomised, double-blind, placebo-controlled
Participants	68 participants with erythematotelangiectatic rosacea
Interventions	46 weeks, Atralin gel 0.05% versus vehicle
Outcomes	*Primary outcome measures*

	1. Severity of erythematotelangiectatic rosacea signs at 24 weeks. Severity of erythematotelangiectatic rosacea signs will be measured by taking into account the following: redness, telangiectasia, facial oedema, dry skin 2. Severity of erythematotelangiectatic rosacea symptoms at 24 weeks. Evaluation of erythematotelangiectatic rosacea symptoms includes subject reporting of flushing, burning, stinging, topical product intolerance *Secondary outcome measures* 1. Quality of life at 2, 6, 12, 18 and 24 weeks, photodamage at 24 weeks. Signs of other rosacea subtypes at 2, 6, 12, 18 and 24 weeks (ocular, phymatous or papulopustular manifestations of rosacea) 2. Molecular markers of inflammation at 24 weeks. These will be evaluated from skin biopsy from some subjects at baseline and final evaluation at 24 weeks 3. Molecular evidence of photodamage at 24 weeks. These will be evaluated from skin biopsy from some subjects at baseline and final evaluation at 24 weeks 4. Severity of erythematotelangiectatic signs at 2, 6, 12 and 18 weeks 5. Severity of erythematotelangiectatic rosacea symptoms at 2, 6, 12 and 18 weeks 6. Skin irritation at 2, 6, 12 and 18 weeks
Notes	Study completed January 2013. Website accessed 13-3-2018 (some outcome data on clinicaltrials.gov). The study has not been published yet, but they will notify us. Will be included when published. It states "Terminated (due to slow recruitment and sponsor request study ended early)" Sent e-mail 15-3-2018, but mail address no longer correct

NCT01134991

Methods	Randomised, double-blind, placebo-controlled
Participants	21 moderate to severe rosacea patients
Interventions	1% FXFM244 versus 4% FXFM244 versus placebo
Outcomes	*Primary outcome measures* 1. Improvement in signs and symptoms of rosacea at 12 weeks *Secondary outcome measures*

	1. The severity of the overall rosacea condition will be measured at baseline and at all follow-up visits. The severity will be assessed and graded based on the scales for erythema, telangiectases, and number of papulopustular lesions at 0, 3, 6, 9, and 12 weeks
Notes	Study terminated (difficulties in recruitment). Website accessed 19-7-2014, sent e-mail. Reply 21-7-2014, according to Dov Tamarkin, PhD the study is still ongoing. Website accessed again 16-3-2018 states terminated (difficulty in recruitment), no results posted. Unlikely data will be published after all this time

NCT01186068

Methods	Randomised, double-blind, placebo-controlled
Participants	175 participants with erythematous rosacea
Interventions	V-101 (oxymetazoline) versus vehicle
Outcomes	*Primary outcome measures* 1. Clinician's Erythema Assessment, physician visual evaluation at visit on day 28 *Secondary outcome measures* 1. Subject's self-assessment, patient assesses their condition at visit on day 28
Notes	Study has been completed (no data reported), but after e-mail contact not yet published. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01257919

Methods	Randomised, investigator-blind, cross-over, multiple dose phase I study
Participants	21 participants with papulopustular rosacea
Interventions	Azelaic acid foam versus azelaic acid gel
Outcomes	*Primary outcome measures* 1. Baseline corrected area under the curve (AUC)
Notes	Study has been completed March 2011. Website accessed 19-7-2014 Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01398280

Methods	Randomised, open-label, vehicle-controlled
Participants	15 participants with papulopustular rosacea and erythema
Interventions	Topical aminocaproic acid (ACA) mixed with Vanicream versus vehicle cream
Outcomes	*Primary outcome measures* 1. Cathelicidin protein analysis *Secondary outcome measures* 1. KLK5 protease activity
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT01513863

Methods	Randomised, double-blind, active and placebo-controlled
Participants	602 participants with moderate to severe rosacea
Interventions	Metronidazole topical gel 1% versus metronidazole topical gel 1% (Metrogel) versus placebo
Outcomes	*Primary outcome measures* 1. Clinical Success (a patient is considered a clinical success if the IGE is 0 (clear) or 1 (almost clear) 2. Treatment Success (a patient is considered a treatment success if the mean percent change from baseline at week 10 (Day 70) in the inflammatory (papules and pustules) lesion count of rosacea *Secondary outcome measures* 1. Change in Investigational Global Evaluation (IGE)
Notes	Study has been completed September 2012. Website accessed 19-7-2014 Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01631656

Methods	Randomised, single-blind, active-controlled, within participant
Participants	10 subjects with mild to moderate rosacea
Interventions	Azelaic acid 15% gel + Nd:YAG laser versus azelaic acid 15% gel

Outcomes	*Primary outcome measures* 1. Investigator's Global Assessment of Improvement measuring reduction in rosacea severity from baseline *Secondary outcome measures* 1. Not provided
Notes	Study was completed February 2011. Website accessed 15-3-2018. Article written-up not yet published, unclear if it is truly randomised or CCT, no further reply received in 2014 and still not published

NCT01740934

Methods	Randomised, double-blind, placebo-controlled
Participants	117 participants with mild to moderate rosacea
Interventions	Anatabloc cream versus vehicle cream
Outcomes	*Primary outcome measures* 1. Adverse effects *Secondary outcome measures* 1. Change in the appearance of the facial skin
Notes	Study has been completed August 2013. Website accessed 15-3-2018. No results posted. They are writing study down. Will be included when published. E-mailed again 15-3-2018

NCT01784133

Methods	Randomised, double-blind, placebo-controlled
Participants	240 participants with papulopustular rosacea
Interventions	Omiganan versus placebo
Outcomes	*Primary outcome measures* 1. Change in inflammatory lesion count *Secondary outcome measures* 1. Success on IGA defined as clear or almost clear
Notes	Study has been completed March 2014. Website accessed 20-7-2014 Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01828177

Methods	Randomised, single-blind, active and placebo-controlled
Participants	200 participants with rosacea
Interventions	PDI-320 versus PDI-320 monad #1 versus PDI-320 monad #2 versus vehicle
Outcomes	*Primary outcome measures* 1. Treatment "Success Rate" based on change in Investigator's Global Assessment (IGA) 2. Absolute change in inflammatory lesion count *Secondary outcome measures* 1. Treatment "Success Rate" based on change in IGA (interim time points) 2. Absolute change in inflammatory lesion count (interim time points) 3. Change in erythema severity 4. Change in telangiectasia severity
Notes	Study was ongoing. Website accessed 20-7-2014 Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01933464

Methods	Randomised, double-blind, placebo-controlled
Participants	10 participants with rosacea associated erythema
Interventions	Cromolyn sodium versus normal saline
Outcomes	*Primary outcome measures* 1. Facial erythema will be measured using the Clinician's Erythema Assessment applied to 5 areas of the subject's face (chin, nose glabella, left cheek, right cheek), as well as using measurements from a colorimeter applied to each of the 5 locations previous mentioned 2. Change in facial erythema *Secondary outcome measures* 1. Matrix metalloproteinase levels 2. Change in matrix metalloproteinase levels 3. Adverse events

Notes	This study is currently recruiting participants. Website accessed 20-7-2014. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT01993446

Methods	Randomised, double-blind, placebo-controlled
Participants	30 participants with rosacea
Interventions	DRM02 versus vehicle
Outcomes	*Primary outcome measures* 1. Change in inflammatory lesion count *Secondary outcome measures* 1. Investigator's Global Evaluation (IGE) 2. IGE dichotomized into "success" and "failure" 3. Percent change in inflammatory lesions
Notes	Study has been completed March 2014. Website accessed 20-7-2014. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT02036229

Methods	Randomised, double-blind, placebo-controlled
Participants	50 subjects with clinical and laboratory diagnosis of demodicidosis with symmetrical facial eruption (including papulopustular rosacea)
Interventions	Ivermectin 0.5% cream versus vehicle cream
Outcomes	*Primary outcome measures* 1. A decrease in mite density in skin surface biopsy after treatment with topical ivermectin (≤ 5 mites/cm^2 for skin lesions) *Secondary outcome measures* 1. Clinical improvement 2. Comparable dermoscopic improvement in the demodicidosis features
Notes	This study is not yet open for participant recruitment. Website accessed 20-7-2014 Website accessed again 16-3-2018. Study completion date June 2016. Results not posted yet

NCT02052999

Methods	Randomised, open-label, active and placebo-controlled
Participants	80 participants with erythema-telangiectatic or papulopustular rosacea
Interventions	PAC-14028 cream 1% versus metronidazole gel 0.75% versus vehicle
Outcomes	*Primary outcome measures* 1. Change in Investigator's Global Assessment (IGA) *Secondary outcome measures* 1. Erythema severity 2. Telangiectasia severity 3. Inflammatory lesion counts
Notes	Study has been completed August 2013. Website accessed 20-7-2014 Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT02120924

Methods	Randomised, double-blind, active and placebo-controlled
Participants	1100 participants wild moderate rosacea
Interventions	Generic azelaic acid gel 15% versus Finacea® (azelaic acid) gel, 15% versus vehicle
Outcomes	*Primary outcome measures* 1. Change in inflammatory lesion count *Secondary outcome measures* 1. The proportion of subjects with a clinical response of "success" at week 12 using Investigator Global Evaluation (IGE) 2. Application site reactions
Notes	Still recruiting. Website accessed 20-7-2014. Study completed September 2014. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT02144181

Methods	Randomised, single-blind, active-controlled
Participants	88 participants with erythematotelangiectatic rosacea

Interventions	Two low-density Ulthera System treatments versus three low-density Ulthera System treatments versus two high-density Ulthera System treatments versus three high-density Ulthera System treatments
Outcomes	*Primary outcome measures* 1. Clinician's Erythema Assessment (CEA) at 90 days post-treatment compared to baseline (erythema will be assessed on a 5-point CEA scale (0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe) at baseline and at 90 days post-treatment completion. Success is defined as 1-grade improvement on CEA scale) *Secondary outcome measures* 1. CEA scale at 180 days post-treatment compared to baseline 2. CEA scale at 365 days post-treatment compared to baseline 3. Patient Self-Assessment (PSA) of erythema at 90 days compared to baseline (5 point Likert scale) 4. Patient Self-Assessment (PSA) of erythema at 180 days compared to baseline 5. Patient Self-Assessment (PSA) of erythema at 365 days compared to baseline 6. Dermatology Life Quality Index (DLQI) assessment at 90 days post-treatment 7. Dermatology Life Quality Index (DLQI) assessment at 180 days post-treatment 8. Dermatology Life Quality Index (DLQI) assessment at 365 days post-treatment 9. Colorimeter at 90 days post-treatment 10. Colorimeter at 180 days post-treatment 11. Colorimeter at 365 days post-treatment
Notes	Still recruiting. Website accessed 20-7-2014. Study completed October 2016. Website accessed again 16-3-2018, still no results posted. Unlikely data will be published after all this time

NCT02268474

Methods	Randomised, open-label, active-controlled
Participants	22 participants with erythematotelangiectatic and papulopustular rosacea
Interventions	KTP laser versus PDL laser
Outcomes	*Primary outcome measures*

	1. Degree of improvement in erythematotelangiectatic rosacea and papulopustular rosacea end of study *Secondary outcome measures* 1. Degree of improvement in erythematotelangiectatic rosacea and papulopustular rosacea at other time points 2. Investigator assessed degree of improvement in erythematotelangiectatic rosacea and papulopustular rosacea 3. Patient assessed degree of improvement in erythematotelangiectatic rosacea and papulopustular rosacea 4. Subject satisfaction level 5. Change in Dermatology Life Quality Index 6. Spectrophotometer measurements 7. Subject discomfort (pain) 8. Adverse Events
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT02289352

Methods	Randomised, double-blind, active and vehicle-controlled
Participants	462 participants with rosacea
Interventions	Brimonidine topical gel, 0.33% (Watson Laboratories, Inc., USA) versus reference product Mirvaso® (Brimonidine) topical gel, 0.33% versus placebo gel
Outcomes	*Primary outcome measures* 1. Rosacea improvement or treatment success *Secondary outcome measures* 1. Proportion of patients with a clinical response of treatment success on Day 1
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT02385240

Methods	Randomised, double-blind, active and placebo-controlled
Participants	552 participants with rosacea and moderate to severe erythema

Interventions	Brimonidine 0.33% gel (Perrigo) versus brimonidine 0.33% gel (reference product) versus placebo gel
Outcomes	*Primary outcome measures* 1. 2-grade improvement on both the Clinician's Erythema Assessment (CEA) and the Patient Self Assessment (PSA) scales *Secondary outcome measures* 1. Not provided
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT02393937

Methods	Randomised, double-blind, active and vehicle-controlled
Participants	963 participants with erythematotelangiectatic and papulopustular rosacea
Interventions	Metronidazole gel 1% versus metronidazole gel 1% (Metrogel) versus placebo gel
Outcomes	*Primary outcome measures* 1. Change from baseline in inflammatory lesion counts *Secondary outcome measures* 1. Investigator's Global Evaluation
Notes	Website accessed 19-3-2018, study completed. No data posted

NCT02547441

Methods	Randomised, double-blind, vehicle-controlled
Participants	463 participants with papulopustular rosacea
Interventions	CLS001 gel (Omiganan) versus vehicle gel
Outcomes	*Primary outcome measures* 1. Efficacy; absolute change inflammatory lesion count 2. Efficacy; 2 grade reduction in Investigator Global Assessment 3. Adverse events *Secondary outcome measures* 1. The absolute change in inflammatory lesions at week 9

	2. The absolute change in inflammatory lesions at week 6 3. Efficacy; 2 grade reduction in Investigator Global Assessment at week 6
Notes	Website accessed 19-3-2018, no results posted

NCT02576860

Methods	Randomised, double-blind, vehicle-controlled
Participants	263 participants with papulopustular rosacea
Interventions	CLS001 gel (Omiganan) versus vehicle gel
Outcomes	*Primary outcome measures* 1. Efficacy; absolute change inflammatory lesion count 2. Efficacy; 2 grade reduction in Investigator Global Assessment 3. Adverse events *Secondary outcome measures* 1. The absolute change in inflammatory lesions at week 9 2. The absolute change in inflammatory lesions at week 6 3. Efficacy; 2 grade reduction in Investigator Global Assessment at week 6
Notes	Website accessed 19-3-2018, no results posted

NCT02583009

Methods	Randomised,double-blind, placebo-controlled
Participants	216 participants with rosacea
Interventions	PAC-14028 cream 0.1%, PAC-14028 cream 0.3%, PAC-14028 cream 1.0% cream versus cream vehicle
Outcomes	*Primary outcome measures* 1. Change in Investigator's Global Assessment *Secondary outcome measures* 1. Improvement in rate in Investigator's Global Assessment 2. Change in erythema severity score 3. Rate of change in inflammatory lesion count 4. Change in erythema index 5. Change in telangiectasia score
Notes	Website accessed 18-3-2018, study completing date August 2016. No data posted

NCT02795117

Methods	Randomised, double-blind, active and placebo-controlled
Participants	485 participants with moderate to severe papulopustular rosacea
Interventions	Ivermectin versus ivermectin reference product versus placebo
Outcomes	*Primary outcome measures* 1. Mean percent change from baseline in the inflammatory (papules and pustules) lesion count *Secondary outcome measures* 1. Subjects with clinical success on the Investigator's Global Assessment
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT02800148

Methods	Randomised, double-blind, active and placebo-controlled
Participants	665 participants with moderate papulopustular rosacea
Interventions	Azelaic acid foam versus azelaic acid foam (Finacea) versus placebo foam
Outcomes	*Primary outcome measures* 1. Percent reduction of lesion count *Secondary outcome measures* 1. Not provided
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT02828241

Methods	Randomised, double-blind, placebo-controlled
Participants	61 participants
Interventions	DFD-04 (itraconazole) ointment versus placebo ointment
Outcomes	*Primary outcome measures* 1. Change in inflammatory lesion counts *Secondary outcome measures*

	1. Proportion of subjects with Investigator's Global Assessment (IGA) success
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT02840461

Methods	Randomised, double-blind, active and vehicle-controlled
Participants	635 participants with papulopustular rosacea
Interventions	Ivermectin cream 1% (Actavis) versus ivermectin 1% cream (Soolantra TM), versus vehicle cream
Outcomes	*Primary outcome measures* 1. Percent change from baseline to Week 12 in the number of inflamed (papules/pustules) lesions of rosacea *Secondary outcome measures* 1. Proportion of patients with a clinical response of "success" using the Investigator's Global Evaluation (IGE) at Week 12
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT03048058

Methods	Randomised, single-blind, non-survey controlled
Participants	20 participants with persistent erythema associated with active rosacea
Interventions	Brimonidine gel plus internet surveys versus brimonidine gel only
Outcomes	*Primary outcome measures* 1. Adherence *Secondary outcome measures* 1. Investigator'ss Global Assessment 2. Lesion count 3. Clinician's Erythema Assessment 4. Quality of life
Notes	Website accessed 17-3-2018. Completed June 2017, no results posted

NCT03094403

Methods	Randomised, double-blind, active and placebo-controlled
Participants	1000 participants with moderate rosacea
Interventions	Azelaic acid 15% gel vs azelaic acid 15% gel (Finacea) versus placebo gel
Outcomes	*Primary outcome measures* 1. Change in inflammatory lesion counts *Secondary outcome measures* 1. Not provided
Notes	Website accessed 19-3-2018, study completed, no results posted

NCT03287791

Methods	Randomised, double-blind, active and vehicle-controlled
Participants	978 participants with moderate facial rosacea
Interventions	Azelaic acid 15% foam (Finacea) versus generic azelaic acid 15% foam versus vehicle foam
Outcomes	*Primary outcome measures* 1. Inflammatory lesion count *Secondary outcome measures* 1. Not provided
Notes	Website accessed 17-3-2018. Completed, no results posted

Footnotes

Characteristics of ongoing studies

ChiCTR-IPR-17012224

Study name	A multicenter, randomized, double-blind, double-mock test for the efficacy and safety of hydroxychloroquine in the treatment of rosacea
Methods	Randomised, double-blind, active-controlled
Participants	300 participants with severe erythema glaucoma dilatation, papulopustular rosacea and erythema
Interventions	Hydroxychloroquine versus doxycycline
Outcomes	*Primary outcome measures*

	1. Investigator's Global Assessment 2. Blood routine 3. Urine routine 4. Liver function 5. Renal function 6. ANA 7. Fundus examination 8. Quality of life 9. Rose Acne Scoliosis Scale (Researcher Evaluation) *Secondary outcome measures* 1. Not provided
Starting date	Recruitment pending
Contact information	Hongfu Xie, xiehongfu1964@aliyun.com
Notes	Website accessed 19-3-2018

CTRI/2017/02/007835

Study name	A comparative, randomized, two arm, multicentric, active controlled, open label, parallel group, phase III study to evaluate the efficacy, safety and tolerability of ivermectin cream 1% w/w vs. azelaic acid gel 15% w/w in patients with inflammatory lesions of rosacea
Methods	Randomised, open-label, active-controlled
Participants	240 participants with papulopustular rosacea
Interventions	Ivermectin 1% cream versus azelaic acid 15% gel
Outcomes	*Primary outcome measures* 1. Efficacy of ivermectin cream 1% w/w vs. azelaic acid gel 15% w/w *Secondary outcome measures* 1. Safety and tolerability of ivermectin cream 1% w/w vs. azelaic acid gel 15% w/w 2. Tolerance parameters
Starting date	14-2-2018
Contact information	Dr Shailesh Singh, shailesh.singh@ajantapharma.com
Notes	Website accessed (19-3-2018), recruitment closed, no results posted yet

EUCTR2006-007029-29-EE

Study name	Non inferiority study of metronidazole 0.75% cream versus reference therapy in the local treatment of papulopustular rosacea
Methods	Randomised, single-blind, placebo and active-controlled
Participants	300 participants with papulopustular rosacea
Interventions	Metronidazole 0.75% cream versus metronidazole 0.75% gel versus placebo
Outcomes	*Primary outcome measures* 1. Improvement of inflammatory lesions *Secondary outcome measures* 1. To assess the superiority of Rosiced cream in comparison to its vehicle
Starting date	08-05-2007
Contact information	Not provided, but sponsored by Pierre Fabre Dermatologie
Notes	Website accessed 15-3-2018, still ongoing in France Study results on website, study not published This 12-week, randomised, Investigator-masked, active reference- and vehicle-controlled study failed to fully demonstrate the non-inferiority of Rosiced® cream to Rozex® cream in the topical treatment of rosacea (supported on the ITT data set but not on the primary PP data set), a result to be linked to a significant Country effect and to a contradictory effect between both data sets in a Country group. The equivalent tolerability profiles of both verum creams with prevailing skin disorders were in accordance with that usually described with metronidazole topical formulations' use. Will be included when data are available

EUCTR2008-003854-13-FR

Study name	An investigator blind parallel group vehicle control study comparing the efficacy and safety of CD 5024 1% cream with metronidazole 0.75% cream in subjects with papulopustular rosacea over 16 weeks treatment
Methods	Randomised, active and vehicle-controlled, investigator-blinded
Participants	600 participants with papulopustular rosacea
Interventions	Ivermectin 1% versus placebo versus metronidazole 0.75%
Outcomes	*Primary outcome measures*

	1. Percent change in inflammatory lesions from baseline to Week 16 *Secondary outcome measures* 1. Not stated
Starting date	25-11-2008
Contact information	Galderma R&D
Notes	Website accessed 15-3-2018. No results

EUCTR2015-002920-23-GB

Study name	A phase 3, randomized, vehicle-controlled, double-blind, multicenter study to evaluate the safety and efficacy of once-daily CLS001 topical gel versus vehicle administered for 12 weeks to subjects with papulopustular rosacea with a 4 week follow-up period
Methods	Randomised, double-blind, vehicle-controlled
Participants	450 participants with papulopustular rosacea
Interventions	Omiganan topical gel versus vehicle gel
Outcomes	*Primary outcome measures* 1. The absolute change from Baseline to Week 12 in inflammatory lesions 2. IGA at Week 12: 2 grade reduction; Clear or almost Clear (IGA 0, or 1) 3. Adverse events (AE) throughout the study *Secondary outcome measures* 1. Not provided
Starting date	18-12-2015
Contact information	jphillips@cutanea.com
Notes	Website accessed 19-3-2018, authorised-recruitment may be ongoing or finished

EUCTR2015-005486-23-DE

Study name	A multi-center, randomized, double-blind, parallel-group, placebo-controlled study to assess the efficacy, safety and tolerability of DFD-04 (itraconazole) ointment, 5% in patients with inflammatory lesions of rosacea over 12-weeks
Methods	Randomised, double-blind, placebo-controlled

Participants	60 participants with papulopustular rosacea
Interventions	DFD-04 (itraconazole) 5% ointment versus placebo
Outcomes	*Primary outcome measures* 1. The absolute change from baseline to end of treatment (defined as complete clearance or after 12 weeks, whichever is earlier) of inflammatory lesion counts (papules and pustules) 2. Proportion of patients with a clinical response of “success” at end of treatment. Success based on IGA is defined as an IGA score of ‘0’ (Clear) or ‘1’ (almost clear) with at least 2 grades reduction from baseline 3. Proportion of patients with a clinical response of “success” at end of treatment. Success based on CEA is defined as a CEA score of ‘0’ (Clear) or ‘1’ (almost clear) with at least 2 grades reduction from baseline *Secondary outcome measures* 1. Not provided
Starting date	13-4-2016
Contact information	karolin.boecker@bioskinCRO.com
Notes	Website accessed 19-3-2018, study completed, no results posted

EUCTR2016-003197-41-DE

Study name	A multi-center, randomized, double-blind, parallel-group, controlled study to assess the efficacy, safety and tolerability of oral DFD-29 extended release capsules for the treatment of inflammatory lesions of rosacea over 16 weeks - efficacy, safety and tolerability of DFD-29 capsules in rosacea patients
Methods	Randomised, double-blind, active and placebo-controlled
Participants	Unclear how many participants with papulopustular rosacea
Interventions	Minocycline hydrochloride extended release capsules (DFD-29) versus doxycycline 40 mg modified release versus placebo
Outcomes	*Primary outcome measures* 1. Proportion of subjects with IGA (modified scale without erythema) ‘treatment success’ – Grade 0 or 1 at the end of study with at least 2 grade reduction from baseline to Week 16 2. Total inflammatory lesion count *Secondary outcome measures*

	1. The efficacy of the two dosage strengths of oral DFD-29 (20 mg and 40 mg) in comparison to Oraycea® (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks 2. the safety and tolerability of oral DFD-29 (20 mg) in comparison to placebo in the treatment of inflammatory lesions of rosacea for 16 weeks 3. the safety and tolerability of the two dosage strengths of oral DFD-29 (20 mg and 40 mg) in comparison to Oraycea® (doxycycline 40 mg capsules) in the treatment of inflammatory lesions of rosacea for 16 weeks 4. the efficacy of oral DFD-29 (40 mg) in comparison to oral DFD-29 (20 mg) in the treatment of inflammatory lesions of rosacea for 16 weeks 5. the safety and tolerability of oral DFD-29 (40 mg) in comparison to DFD-29 (20 mg) in the treatment of inflammatory lesions of rosacea for 16 weeks
Starting date	19-1-2017
Contact information	Dr. Reddy's Labaratories Ltd.
Notes	Website accessed 19-3-2018, authorised-recruitment may be ongoing or finished

EUCTR2017-000157-40-HU

Study name	Efficacy comparison of Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo in the treatment of severe Rosacea. - ANSWER study - oraceA soolaNtra aSsociation in patients With severE Rosacea
Methods	Randomised, single-blind, active-controlled
Participants	270 participants with papulopustular rosacea
Interventions	Ivermectin 1% topical cream associated with Doxycycline 40 mg Modified release (MR) capsules versus Ivermectin 1% topical cream associated with Placebo
Outcomes	*Primary outcome measures* 1. The percent change from baseline in inflammatory lesion count *Secondary outcome measures* 1. CEA % of subjects across scores 2. IGA % of subjects across scores

	3. Stinging/burning % of subjects across scores 4. Percent change from Baseline (medical history) in terms of flushing count 5. Change from Baseline (medical history) in terms of flushing severity score 6. Global improvement in rosacea % of subjects across scores
Starting date	15-6-2017
Contact information	Galderma R&D, cta.coordinator@galderma.com
Notes	Website accessed 19-3-2018, ongoing, no results posted as yet

JPRN-UMIN000008315

Study name	Clinical trial for development of topical rapamycin treatment for rosacea
Methods	Randomised, placebo-controlled, cross-over
Participants	5 participants with rosacea
Interventions	0.2% rapamycin ointment versus vehicle
Outcomes	*Primary outcome measures:* 1. Changes in redness and size of eruptions *Secondary outcome measures:* 1. Appearance of contact dermatitis 2. Rapamycin levels in whole blood 3. Histological findings in specimens of skin tissue in the cases who agree with skin biopsy
Starting date	It still states recruiting
Contact information	Mari Wataya-Kaneda, mkaneda@derma.med.osaka-u.ac.jp
Notes	Website accessed 16-3-2018, last follow-up date 31-3-2015, no results

KCT0001705

Study name	Multi center, double-blind, randomized, placebo controlled parallel-group, dose finding phase II clinical trial to evaluate anti-rosacea effect and safety of PAC-14028 cream (0.1%, 0.3%, 1.0%) in rosacea patients
Methods	Randomised, double-blind, placebo-controlled
Participants	216 participants with erythematotelangiectatic and papulopustular rosacea

Interventions	PAC-14028 Cream 0.1%, 0.3%, 1.0% versus vehicle
Outcomes	*Primary outcome measures* 1. Change in Investigator's Global Assessment *Secondary outcome measures* 1. Change in erythema index 2. Change in the erythema severity 3. Change in the telangiectasia severity 4. Rate of change in inflammatory lesion count
Starting date	24-11-2014
Contact information	Kim Il-Hwan, Korea University Ansan Hospital
Notes	Website accessed 19-3-2018, still recruiting

NCT02075671

Study name	Photodynamic therapy for papulopustular rosacea
Methods	Randomised, double-blind, placebo-controlled
Participants	30 participants with papulopustular rosacea
Interventions	Aminolevulinic acid topical solution 20% + Blu-U Light versus vehicle + Blu-U Light
Outcomes	*Primary outcome measures* 1. Improvement of the inflammatory lesions (papules, pustules, nodules), erythema, and telangiectasia of rosacea as assessed by the Investigator's Global Assessment (IGA) 2. Improvement of the inflammatory lesions (papules, pustules, nodules) of rosacea as assessed by the Inflammatory Lesion Investigator's Global Assessment (ILIGA) *Secondary outcome measures* 1. Evaluate improvement of rosacea associated erythema as assessed by the Clinician's Erythema Assessment (CEA) scale 2. Evaluate improvement of the inflammatory lesions (papules, pustules, nodules) of rosacea as measured by a difference in inflammatory lesion count 3. Evaluate improvement of rosacea as assessed by the Patient Overall Assessment Scale
Starting date	April 2014

Contact information	George Washington University, Jack Short, jshort@mfa.gwu.edu, as they are still recruiting, not sent mail
Notes	This study is currently recruiting participants. Website accessed 20-7-2014 Website accessed again 16-3-2018, still recruiting

NCT02204254

Study name	Prospective, open label, randomised study comparing bipolar radiofrequency potentiated by infrared light to doxycycline in patient with papulopustular rosacea
Methods	Randomised, open label, active-controlled
Participants	40 participants with papulopustular rosacea
Interventions	Bipolar radiofrequency potentiated by infrared light versus doxycycline
Outcomes	*Primary outcome measures* 1. Change in Investigator's Global Assessment *Secondary outcome measures* 1. Lesion counts
Starting date	Recruiting
Contact information	Florence le Duff, leduff.f2@chu-nice.fr
Notes	Website accessed 23-9-2014. Webiste accessed again 16-3-2018, expected completion date September 2018

NCT02659670

Study name	Internet surveys and their impact on adherence to brimonidine topical gel and QOL in patients with rosacea
Methods	Randomised, single-blind, no survey controlled
Participants	20 participants with persistent erythema associated with rosacea
Interventions	Brimonidine gel plus survey versus brimonidine gel only
Outcomes	*Primary outcome measures* 1. Clinician's Erythema Assessment 2. Patient Severity Assessment 3. Investigator Visual Analogue Scale 4. Inflammatory lesion counts *Secondary outcome measures* 1. Change in quality of life (survey)

	2. Factors that affect adherence (survey)
Starting date	January 2016
Contact information	Wake Forest University Health Sciences
Notes	Website accessed 18-3-2018. Looks bit like NCT03048058. Status still recruiting

NCT03003104

Study name	A randomized, double-blind, vehicle controlled study to evaluate the safety, tolerability, and efficacy of DMT210 gel in adult patients with moderate to severe acne rosacea
Methods	Randomised, double-blind, vehicle controlled
Participants	104 participants with papulopustular rosacea
Interventions	DMT210 topical 5% gel versus topical gel vehicle
Outcomes	*Primary outcome measures* 1. Inflammatory lesion counts 2. Investigator's Global Assessment 3. Clinician's Erythema Assessment 4. Patient Severity Assessment *Secondary outcome measures* 1. Adverse events (safety and tolerability)
Starting date	January 2017
Contact information	Dermata Therapeutics
Notes	Estimated completion date September 2017, website accessed 17-3-2018, no results posted, still active

NCT03064438

Study name	Efficacy of Accu-D1 in the treatment of acne rosacea
Methods	Randomised, double-blind, placebo-controlled
Participants	36 participants with rosacea
Interventions	ACCU-D1 cream versus placebo cream
Outcomes	*Primary outcome measures* 1. Inflammatory lesion count 2. Investigator's Global Assessment 3. Clinician's Erythema Assessment *Secondary outcome measures*

	1. Inflammatory lesion count change from baseline 2. Clinician's Erythema Assessment change from baseline 3. Responder analysis 4. Percent change in inflammatory lesion count
Starting date	Not yet recruiting
Contact information	Accuitis, Inc, rick.coulon@accuitis.com
Notes	Website accessed 18-3-2018

NCT03075891

Study name	Efficacy comparison of ivermectin 1% topical cream associated with doxycycline 40 mg modified release (MR) capsules versus Ivermectin 1% topical cream associated with placebo in the treatment of severe rosacea
Methods	Randomised, double-blind, active controlled
Participants	270 participants with papulopustular rosacea
Interventions	Ivermectin 1% cream plus doxycycline capsules versus ivermectin 1% cream plus placebo capsules
Outcomes	*Primary outcome measures* 1. Percent change from baseline in inflammatory lesion count *Secondary outcome measures* 1. Not provided
Starting date	July 2017
Contact information	Galderma
Notes	Website accessed 17-3-2018, still active

NCT03142451

Study name	A randomized, multicenter, double-blind, vehicle-controlled study to evaluate the safety and efficacy of FMX103 1.5% topical minocycline foam compared to vehicle in the treatment of facial papulopustular rosacea (FX2016-11 and 12)
Methods	Randomised, double-blind, vehicle-controlled
Participants	1500 participants with papulopustular rosacea
Interventions	Minocycline 1.5% (FMX103) foam versus vehicle foam
Outcomes	*Primary outcome measures* 1. Change in inflammatory lesion count

	2. Investigator's Global Assessment *Secondary outcome measures* 1. Percent change in inflammatory lesion count
Starting date	June 2017
Contact information	Foamix Ltd.
Notes	Website accessed 18-3-2018. Still recruiting

NCT03194698

Study name	Pilot study to examine efficacy and cytokines levels after Meibomian gland expression (MGX) with and without Intense Pulsed Light treatment (IPL)
Methods	Randomised, open-label, active-controlled
Participants	20 participants with dry eye associated with ocular rosacea
Interventions	Intense Pulsed Light plus Meibom gland expression versus Meibom gland expression only
Outcomes	*Primary outcome measures* 1. Ocular Surface Disease Index symptom survey *Secondary outcome measures* 1. Pathologic microbial load 2. TGF-B1 growth cytokine level
Starting date	August 2017
Contact information	Joanne F. Shen, M.D., Mayo Clinic
Notes	Website accessed 19-3-2018, enrolling by invitation

NCT03263273

Study name	A multicenter, randomized, double-blind, parallel group, vehicle-controlled study to evaluate the safety and efficacy of 1% and 3% topical minocycline gel (HY01) in patients with papulopustular rosacea
Methods	Randomised, double-blind, vehicle-controlled
Participants	249 participants with moderate-to-severe papulopustular rosacea
Interventions	Topical minocycline 1% gel versus topical minocycline 3% gel versus vehicle gel
Outcomes	*Primary outcome measures*

	1. Change in inflammatory lesion count *Secondary outcome measures* 1. Investigator's Global Assessment
Starting date	October 2017
Contact information	Hovione Scientia Limited
Notes	Website accessed 18-3-2018, still recruiting

NCT03340961

Study name	A Controlled Study to Assess the Efficacy, Safety and Tolerability of Oral DFD-29 Extended Release Capsules
Methods	Randomised, double-blind, active and placebo-controlled
Participants	200 participants with papulopustular rosacea
Interventions	DFD-29 extended release capsules 40 mg versus DFD-29 extended release capsules 20 mg versus doxycycline modified release 40 mg versus placebo
Outcomes	*Primary outcome measures* 1. Investigator's Global Assessment *Secondary outcome measures* 1. Inflammatory lesion counts
Starting date	October 1, 2017
Contact information	Dr. Reddy's Laboratories Limited
Notes	Website accessed 19-3-2018, still recruiting

NCT03392558

Study name	The suitability of two skin care regimens in moderate to severe facial rosacea
Methods	Randomised, double-blind, active-controlled
Participants	80 participants with facial rosacea
Interventions	Burt's Bees skin care regimen versus Cetaphil control regimen
Outcomes	*Primary outcome measures* 1. Investigator's Global Assessment *Secondary outcome measures*

	1. Overall skin quality 2. Transepidermal water loss 3. Corneometry
Starting date	January 2018 (but not yet recruiting)
Contact information	Burt's Bees Inc, zdraelos@northstate.net, hemali.gunt@burtsbees.com
Notes	Website accessed 17-3-2018

NCT03448939

Study name	A phase 3 multi-center, double-blind, randomized, vehicle-controlled study of S5G4T-1 in the treatment of papulopustular rosacea
Methods	Randomised, double-blind, vehicle-controlled
Participants	350 participants with papulopustular rosacea
Interventions	S5G4T-1 topical cream versus S5G4T-2 vehicle cream
Outcomes	*Primary outcome measures* 1. Investigator's Global Assessment 2. Change in lesion count *Secondary outcome measures* 1. Percent change in lesion count
Starting date	Not yet recruiting
Contact information	Sol-Gel Technologies, Ltd
Notes	Website accessed 17-3-2018

NTR4804

Study name	Rosacea and the Subpurpuric pulsed dye laser treatment Efficacy - RoSE
Methods	Randomised, single-blinded,
Participants	58 participants with erythematotelangiectatic rosacea
Interventions	Subpurpuric Pulsed Dye Laser (PDL) treatments until their visible telangiectasia are disappeared with a maximum of 4 treatments, separated by either a 2-week interval versus 8 week interval
Outcomes	*Primary outcome measures* 1. Health Related Quality of Life (HRQoL) measurement as a patient reported outcome (PRO) by using the RosaQol, a rosacea-specific HRQoL questionnaire

	2. Blinded evaluation of photographs by using the Investigators Global Assessment (IGA) *Secondary outcome measures* 1. Blinded evaluation of photographs by using the Clinician's Erythema Assessment (CEA) 2. Grading of severity of telangiectasia Patient's Global Assessment (PGA)
Starting date	1-3-2013
Contact information	MMD van der Linden m.m.vanderlinden@amc.uva.nl
Notes	Website accessed 19-3-2018, still recruiting

TCTR20170418002

Study name	Comparing the effects of microsecond pulse duration light system and millisecond pulse duration light system in treatment of facial erythematotelangiectatic rosacea
Methods	Randomised, active-controlled
Participants	10 participants with erythematotelangiectatic rosacea
Interventions	microsecond pulse duration light system versus millisecond pulse duration light system
Outcomes	*Primary outcome measures* 1. Mean improvement grade of patients for telangiectasia *Secondary outcome measures* 1. Pain scores
Starting date	18-3-2018
Contact information	Pouria Yazdian pouria_yazdian_a@yahoo.com
Notes	Website accessed 19-3-2018, still recruiting

Footnotes

Summary of findings tables

1 Topical brimonidine compared to vehicle for rosacea

Topical brimonidine compared to vehicle for rosacea						
Patient or population: participants with rosacea **Intervention:** topical brimonidine **Comparison:** vehicle						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with vehicle	**Risk with topical brimonidine**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of brimonidine on quality of life
Participant-assessed improvement in rosacea severity Assessed with: Patient's Self Assessment - 2 grade improvement Follow up: mean 3 hours	Study population		**RR 2.11** (1.60 to 2.78)	553 (2 RCTs) [1]	⨁⨁⨁⨁ **HIGH**	Topical brimonidine reduces erythema according to the participants (based on 2 grade improvement on Patient's Self Assessment)
	196 per 1.000	**413 per 1.000** (313 to 544)				
Proportion of participants with adverse event Follow up: mean 4 weeks	Study population		**RR 1.29** (0.98 to 1.69)	553 (2 RCTs) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Topical brimonidine probably results in little to no difference in number of participants experiencing an adverse event when compared with vehicle. Adverse events were mild and transient, and the most frequently reported were worsening of erythema, flushing, pruritus and skin irritation
	246 per 1.000	**318 per 1.000** (241 to 416)				
Physician-assessed improvement in rosacea severity - not reported	-	-	-	-	-	No reporting of data other than "No aggravations in the severity of IGA were observed"
Assessment of erythema or telangiectasia Assessed with: Clinician's Erythema Assessment - 2 grade improvement Follow up: mean 3 hours	Study population		**RR 2.21** (1.41 to 3.46)	553 (2 RCTs) [1]	⨁⨁⨁⨁ **HIGH**	Topical brimonidine reduces erythema according to physicians (based on a 2 grade improvement on Clinician's Erythema Assessment)
	199 per 1.000	**440 per 1.000** (281 to 689)				

Lesion count - not reported	-	-	-	-	-	No reporting of data other than "No aggravations in the severity of lesion counts were observed"
Time needed until improvement Assessed with: Patient's Self Assessment scale Follow up: mean 30 minutes	Study population **159 per 1.000**	**271 per 1.000** (185 to 395)	**RR 1.70** (1.16 to 2.48)	553 (2 RCTs) [1]	⨁⨁⨁⨁ **HIGH**	Topical brimonidine reduces erythema within 30 min after application according to the participants (based on 2 grade improvement of Patient's Self Assessment)
Duration of remission - not measured	-	-	-	-	-	We are uncertain about the effect of brimonidine on duration of remission. There was no rebound or worsening of erythema after treatment cessation in comparison to baseline assessments

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Fowler 2013a, Fowler 2013b

[2] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable harm (1.25)

2 Topical oxymetazoline compared to vehicle for rosacea

Topical oxymetazoline compared to vehicle for rosacea						
Patient or population: participants with rosacea **Intervention:** topical oxymetazoline **Comparison:** vehicle						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with vehicle	**Risk with topical oxymetazoline**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of oxymetazoline on quality of life
Participant-assessed improvement in rosacea severity Assessed with: Subjective Self-Assessment scale - 2 grade improvement Follow up: mean 3 hours	Study population		**RR 1.65** (1.23 to 2.21)	885 (2 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Topical oxymetazoline probably reduces erythema slightly according to the participants (based on 2 grade improvement on Patient's Self Assessment)
	134 per 1.000	**222 per 1.000** (165 to 297)				
Proportion of participants with adverse event Follow up: mean 29 days	Study population		**RR 1.32** (0.97 to 1.78)	885 (2 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [3] [4]	Oxymetazoline probably results in little to no difference in number of participants experiencing an adverse event when compared with vehicle. Application site dermatitis, pruritus, and erythema, worsening of inflammatory lesions and headache were the most reported adverse events and were considered mild or moderate in severity
	159 per 1.000	**210 per 1.000** (155 to 284)				
Physician-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of oxymetazoline on physician-assessed improvement
Assessment of erythema or telangiectasia Assessed with: Clinician's Erythema Assessment - 2 grade improvement Follow up: mean 3 hours	Study population		**RR 1.76** (1.44 to 2.15)	885 (2 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Topical oxymetazoline probably reduces erythema according to physicians (based on a 2 grade improvement on Clinician's Erythema Assessment)
	237 per 1.000	**417 per 1.000** (341 to 509)				

Lesion count - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of oxymetazoline on lesion counts
Time needed until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of oxymetazoline on time needed until improvement
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of oxymetazoline on duration of remission. During the 29 days follow-up period six patients in the oxymetazoline group experienced worsening erythema (rebound) versus two in the vehicle group
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes

[1] Baumann 2018, Kircik 2018

[2] Downgraded one level for serious risk of bias, allocation concealment and blinding were assessed as unclear for both studies

[3] Not downgraded for risk of bias, although blinding was unclear it was stated as double-blind and we already downgraded for imprecision and decided not to downgrade twice

[4] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable harm (1.25)

3 Topical metronidazole compared to placebo for rosacea

Topical metronidazole compared to placebo for rosacea						
Patient or population: participants with rosacea **Intervention:** topical metronidazole **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with topical metronidazole**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of metronidazole on quality of life
Participant-assessed improvement in rosacea severity Follow up: mean 2 months	Bjerke 1989 RR 1.68, 95% CI 1.25 to 2.28, Nielsen 1983a RR 3.05, 95% CI 1.57 to 5.94 (data of these two studies could not be pooled due to too much heterogeneity I^2 = 65%), Bleicher 1987 (within-participant study) RR 7		-	252 (3 RCTs) [1]	⨁⨁⨀⨀ **LOW** [2 3 4]	Metronidazole appears to improve rosacea severity according to the participants
Proportion of participants with adverse event Follow up: range 2 months to 10 weeks	Study population		**RR 1.19** (0.94 to 1.51)	1773 (6 RCTs) [5]	⨁⨁⨁⨀ **MODERATE** [6 7]	Metronidazole likely results in little to no difference in number of participants experiencing an adverse event compared with placebo. Most instances these adverse events were mild and consisted of pruritus, skin irritation, and dry skin
	161 per 1.000	**191 per 1.000** (151 to 243)				
Physician-assessed improvement in rosacea severity Follow up: range 2 months to 10 weeks	Study population		**RR 1.98** (1.29 to 3.02)	334 (3 RCTs) [9]	⨁⨁⨁⨀ **MODERATE** [8 10]	Metronidazole likely improves rosacea severity according to the physicians
	288 per 1.000	**570 per 1.000** (371 to 869)				
Assessment of erythema or telangiectasia Follow up: range 2 months to 6 months	In the separate studies there was a greater reduction of erythema in the groups treated with metronidazole, but data were inadequately reported, except in Koçak 2002		-	602 (7 RCTs) [12]	⨁⨁⨁⨀ **MODERATE** [11 13]	Metronidazole likely reduces erythema slightly
Lesion count Follow up: range 2 months to 6 months	No SDs reported, data were skewed, but appeared to support data of physician-assessed improvement		-	1964 (8 RCTs) [14]	⨁⨁⨁⨀ **MODERATE** [13 15]	Metronidazole likely reduces lesion counts
Time needed until improvement	Based on interim data improvement started around 4 weeks		-	514 (5 RCTs) [16]	⨁⨁⨁⨀ **MODERATE** [2]	Effect of metronidazole likely starts within 4 weeks after start treatment

Follow up: range 2 months to 10 weeks						
Duration of remission Follow up: mean 6 months	Study population **409 per 1.000**	**205 per 1.000** (102 to 405)	**RR 0.50** (0.25 to 0.99)	88 (1 RCT) [17]	⨁⨁⨁⊖ **MODERATE** [18] [19]	Metronidazole probably maintains remission longer than vehicle after treatment success is obtained. 9/44 in metronidazole group relapsed, versus 18/44 in vehicle group during 6 months follow-up
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio						
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

Footnotes

[1] Bjerke 1989, Nielsen 1983a, Bleicher 1987

[2] Downgraded one level for serious imprecision (small sample sizes in the individual studies)

[3] Although for two studies the sequence generation and allocation concealment was unclear (Bjerke 1989 and Nielsen 1983a), the blinding was ensured for both Bleicher 1987 and Nielsen 1983a, and stated as double-blind for Bjerke 1989 and therefore we considered it unlikely that this would have an impact on this outcome assessment and decided only to downgrade for imprecision and inconsistency

[4] Downgraded one level for serious inconsistency (I^2 = 65%) when data of Bjerke 1989 and Nielsen 1983a would have been pooled

[5] Beutner 2005, Bitar 1990, Bjerke 1989, Breneman 1998, Koçak 2002, Nielsen 1983a

[6] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable harm (1.25)

[7] Although we judged the domains for sequence generation and allocation concealment as unclear for 5 of the 6 studies, 5 of the 6 studies were double-blind and we considered it unlikely this would have an impact on this outcome assessment and decided only to downgrade for imprecision

[8] Downgraded one level for serious imprecision (wide confidence intervals due to low sample size)

[9] Bjerke 1989, Breneman 1998, Nielsen 1983a

[10] Although for two studies the sequence generation and allocation concealment was unclear (Bjerke 1989 and Nielsen 1983a), the blinding was ensured for Nielsen 1983a, and stated as double-blind for Bjerke 1989 and Breneman 1998 and therefore we considered it unlikely that this would have an impact on this outcome assessment and decided only to downgrade for imprecision

[11] Not downgraded for risk of bias, although blinding of outcome assessment was only ensured for 4 of the 7 studies, they were all stated as double-blind and we considered there was no risk of bias for this outcome

[12] Bitar 1990, Bjerke 1989, Bleicher 1987, Breneman 1998, Dahl 1998, Koçak 2002, Nielsen 1983a

[13] Downgraded one level for serious imprecision (small sample sizes in the individual studies, pooling not possible due to missing SDs)

[14] Beutner 2005, Bitar 1990, Bjerke 1989, Bleicher 1987, Breneman 1998, Dahl 1998, Koçak 2002, Nielsen 1983a

[15] Not downgraded for risk of bias, although blinding of outcome assessment was only ensured for 5 of the 8 studies, they were all stated as double-blind and we considered there was no risk of bias for this outcome

[16] Bitar 1990, Bjerke 1989, Bleicher 1987, Breneman 1998, Nielsen 1983a

[17] Dahl 1998

[18] Although we judged the domains for sequence generation, allocation concealment as unclear and the method of blinding of participants and physicians was not reported, there was no attrition bias nor selective reporting and therefore we concluded there was no serious risk of bias for this outcome assessment

[19] Downgraded one level for serious imprecision (low sample size, optimal sample size is not met)

4 Topical azelaic acid compared to vehicle for rosacea

Topical azelaic acid compared to vehicle for rosacea						
Patient or population: participants with rosacea **Intervention:** azelaic acid **Comparison:** vehicle						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with vehicle	**Risk with topical azelaic acid**				
HRQoL Assessed with: different instruments Follow up: mean 3 months	In Draelos 2013a authors report "There were no statistically significant differences between the 2 groups in end-of-treatment or end-of-study ....or QOL scores". Draelos 2015 used RosaQoL, DLQI and EuroQOL. At baseline the DLQI was 5.4 in both groups and it decrease by 2.6 in the azelaic group compared to 2.1 in the vehicle group. The authors reported "P = 0.018", but a difference of 0.5 on the DLQI is not clinically important (Basra 2008; Basra 2015). Improvements were also seen in the RosaQoL, but less in the EuroQOL. The authors reported "(6.8 vs 6.4; P=0.67), while EQ-5D-5L scores changed minimally from baseline (0.006 vs 0.007; P=0.50)."		-	1219 (2 RCTs) [1]	⨁⨁⨁⨁ **HIGH**	Azelaic acid does not result in an important reduction in health related quality of life when compared with vehicle
Participant-assessed improvement in rosacea severity Assessed with: Likert scales, marked improvement to complete remission Follow up: mean 3 months	Study population		**RR 1.40** (1.28 to 1.53)	2223 (6 RCTs) [2]	⨁⨁⨁⨁ **HIGH**	Azelaic acid improves rosacea severity according to the participants
	402 per 1.000	**563 per 1.000** (515 to 616)				
Proportion of participants with adverse event Follow up: mean 3 months	Study population		**RR 1.29** (0.92 to 1.81)	1559 (4 RCTs) [3]	⨁⨁⨁⊖ **MODERATE** [4]	Azelaic acid probably results in little to no difference in number of participants experiencing an adverse event when compared with vehicle. Adverse events were transient and of mild to moderate intensity, with burning, stinging or irritation being the most commonly reported
	188 per 1.000	**243 per 1.000** (173 to 341)				

Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment Follow up: mean 3 months	Study population		**RR 1.30** (1.19 to 1.43)	2080 (6 RCTs) [2]	⨁⨁⨁⨁ **HIGH**	Azelaic acid improves rosacea severity according to the physicians
	393 per 1.000	**511 per 1.000** (468 to 562)				
Assessment of erythema or telangiectasia Follow up: mean 3 months	Decrease in erythema in groups treated with azelaic acid ranged from 44-47.9% and for placebo from 28-37.9%, telangiectasia minimal changes. SDs missing. Only the study of Draelos 2015 showed that 258/420 (61.5%) of the participants in the azelaic acid foam group had an improvement of the erythema compared with 204/398 (51.3%) in the vehicle foam group (RR 1.20, 95% CI 1.06 to 1.35; P = 0.004; NNTB = 10, 95% CI 6 to 29).		-	2113 (7 RCTs) [5]	⨁⨁⨁⨁ **HIGH**	Azelaic acid reduces erythema slightly and has minimal to no effect on telangiectasia
Lesion count Follow up: mean 3 months	The mean lesion count ranged from **-10.8 to -9.8 inflammatory lesions**	MD **3 inflammatory lesions fewer** (4.13 fewer to 1.86 fewer)	-	1302 (3 RCTs) [6]	⨁⨁⨁⨁ **HIGH**	Azelaic acid results in a small effect that may not be an important difference in reduction in lesion counts when compared with vehicle
Time needed until improvement Follow up: mean 3 months	This was not a prespecified outcome in any of the studies, but all studies showed clear improvement after three to six weeks.		-	1245 (5 RCTs) [7]	⨁⨁⨁⨁ **HIGH**	Effect of azelaic acid starts between 3 to 6 weeks after start treatment
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of azelaic acid on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Draelos 2013a, Draelos 2015

[2] Bjerke 1999, Draelos 2013a, Draelos 2015, NCT00617903, Thiboutot 2003a, Thiboutot 2003b

[3] Bjerke 1999, Draelos 2013a, Draelos 20155, NCT00617903

[4] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1) , whilst the upper boundary of the CI indicates appreciable harm (1.25)

[5] Bjerke 1999, Carmichael 1993, Draelos 2013a, Draelos 2015, NCT00617903, Thiboutot 2003a, Thiboutot 2003b

[6] Draelos 2013a, Draelos 2015, NCT00617903

[7] Bjerke 1999, Carmichael 1993, Draelos 2013a, Thiboutot 2003a, Thiboutot 2003b

5 Topical ivermectin compared to vehicle for rosacea

Topical ivermectin compared to vehicle for rosacea						
Patient or population: participants with rosacea **Intervention:** topical ivermectin **Comparison:** vehicle						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with vehicle	**Risk with topical ivermectin**				
HRQoL (Number of participants experiencing their rosacea had no effect on QoL) Assessed with: DLQI and RosaQoL Follow up: mean 12 weeks	Study population **332 per 1.000**	**514 per 1.000** (445 to 594)	**RR 1.55** (1.34 to 1.79)	1371 (2 RCTs) [1]	⨁⨁⨁⨁ **HIGH**	Topical ivermectin increases the number of participants experiencing their rosacea had no effect on quality of life. Although data were statistically significant in favour of ivermectin, MID in reduction of DLQI score was not reached and is unknown for RosaQoL [2]
Participant-assessed improvement in rosacea severity Assessed with: Likert scale, good to excellent improvement Follow up: mean 12 weeks	Study population **367 per 1.000**	**675 per 1.000** (594 to 766)	**RR 1.84** (1.62 to 2.09)	1371 (2 RCTs) [1]	⨁⨁⨁⨁ **HIGH**	Topical ivermectin improves rosacea severity according to the participants
Proportion of participants with adverse event Follow up: mean 12 weeks	Study population **79 per 1.000**	**66 per 1.000** (43 to 102)	**RR 0.83** (0.54 to 1.28)	1581 (3 RCTs) [3]	⨁⨁⨁⊖ **MODERATE** [4]	Topical ivermectin likely results in little to no difference in number of participants experiencing an adverse event when compared with vehicle. Reported side effects that were reported more often in the ivermectin group were skin burning, pruritus and dry skin
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment of clear or almost clear	RR 1.64, 95% CI 1.20 to 2.25 (EUCTR2010-018319-13-DE), RR 3.30, 95% CI 2.27 to 4.79 (Stein 2014a), RR 2.10, 95% CI 1.57 to 2.81 (Stein 2014b). The results are in concordance with the assessments of the participants		-	1581 (3 RCTs) [3]	⨁⨁⨁⊖ **MODERATE** [5]	Topical ivermectin likely improves rosacea severity according to the physicians

Follow up: mean 12 weeks						
Assessment of erythema or telangiectasia - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of topical ivermectin on erythema and telangiectasia
Lesion count Follow up: mean 12 weeks	The mean lesion count ranged from **-12 to -22 inflammatory lesions**	MD **8.09 inflammatory lesions fewer** (9.82 fewer to 6.35 fewer)	-	1581 (3 RCTs) [3]	⨁⨁⨁⨁ **HIGH**	Topical ivermectin reduces inflammatory lesions
Time needed until improvement Follow up: mean 12 weeks	Based on interim data improvement started around 4 weeks		-	1581 (3 RCTs) [3]	⨁⨁⨁⨁ **HIGH**	Effect of topical ivermectin starts at 4 weeks after start treatment
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of ivermectin on duration of remission
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference						
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

Footnotes

[1] Stein 2014a, Stein 2014b

[2] MID is minimal important difference

[3] EUCTR2010-018319-13-DE, Stein 2014a, Stein 2014b

[4] Downgraded one level for serious imprecision, the lower boundary of the CI indicates appreciable benefit, whilst the upper boundary of the CI indicates appreciable harm

[5] Downgraded one level for serious inconsistency (I^2 = 76%)

6 Topical azelaic acid compared to topical metronidazole for rosacea

Topical azelaic acid compared to topical metronidazole for rosacea						
Patient or population: participants with rosacea **Intervention:** topical azelaic acid **Comparison:** topical metronidazole						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with topical metronidazole	**Risk with topical azelaic acid**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of topical azelaic acid compared with topical metronidazole on quality of life
Participant-assessed improvement in rosacea severity Follow up: mean 15 weeks	RR 1.23, CI 95% 1.04 to 1.44 (Elewski 2003), RR 1.00, 95% CI 0.83 to 1.21 (Wolf 2006), Maddin 1999, within-participant design authors report P = 0.02 in favour of azelaic acid		-	451 (3 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [2] [3]	Topical azelaic acid likely results in a small beneficial effect on rosacea severity according to the participants that may not be important when compared with topical metronidazole
Proportion of participants with adverse event Follow up: mean 15 weeks	RR 3.64, 95% CI 1.81 to 7.31 (Elewski 2003), RR 0.74, 95% CI 0.52 to 1.07 (Wolf 2006). In Maddin 1999 1 participant reported stinging on azelaic acid treated site		-	451 (3 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [2] [4]	Topical azelaic acid likely results in a small possible unimportant increase of adverse events when compared with topical metronidazole
Physician-assessed improvement in rosacea severity Follow up: mean 15 weeks	Study population		**RR 1.18** (1.00 to 1.40	411 (2 RCTs) [5]	⨁⨁⨁⊖ **MODERATE** [6] [7]	Topical azelaic acid likely results in a small beneficial effect on rosacea severity according to the physicians that may not be important when compared with topical metronidazole. Maddin 1999 (within-patient design) score 2.7 (SD 1.0) for azelaic acid treated side versus 3.1 (SD 1.0) for topical metronidazole treated side (higher is worse)
	545 per 1.000	**644 per 1.000** (545 to 764)				
Assessment of erythema or telangiectasia Follow up: mean 15 weeks	Study population		RR 1.19 (0.88 to 1.61)	411 (2 RCTs) [5]	⨁⨁⨁⊖ **MODERATE** [6] [7]	Azelaic acid likely results in little to no difference in reducing erythema when compared with metronidazole. Furthermore, in Maddin 1999 (within-patient design) the participants and physicians had contradictive judgements
	421 per 1.000	**501 per 1.000** (371 to 678)				
Lesion counts Follow up: mean 15 weeks	No SD's were reported, all 3 studies demonstrated important reductions in lesion count in both treatment arms but differences were small. In		-	451 (3 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [8.9]	Both azelaic acid and metronidazole likely reduce lesion counts

	Elewski 2003 -12.9 vs -10.7, in Maddin 1999 -78.5% vs -69.4% and in Wolf 2006 -80% vs -77%				
Time needed until improvement Follow up: mean 15 weeks	Based on interim data improvement started around 4 to 6 weeks in both treatment arms	-	451 (3 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [8] [9]	Effect of both topical azelaic acid and topical metronidazole likely starts between 4 and 6 weeks after start treatment
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of azelaic acid compared with metronidazole on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Elewski 2003, Maddin 1999, Wolf 2006

[2] Although all three studies were at unclear risk of bias, they were stated to be double-blind and we decided to downgrade only for inconsistency

[3] Downgraded one level due to serious inconsistency (Elewski 2003 and Wolf 2006 no statistically significant difference (severe heterogeneity unexplained (I^2 >62%), and the 95% CIs do overlap but lead to different interpretation of the effect estimate, but in Maddin 1999 azelaic was more effective)

[4] Downgraded one level due to serious inconsistency (statistically significant difference in participants reporting adverse events in Elewski 2003 (in favour of metronidazole), not confirmed in Wolf 2006 (severe heterogeneity unexplained (I^2>94% and the 95% CI did not overlap))

[5] Elewski 2003, Wolf 2006

[6] Although both studies were at unclear risk of bias, we decided only to downgrade for imprecision

[7] Downgraded one level for serious imprecision, lower boundary of CI includes the line of no difference (1) whilst the upper boundary indicates appreciable benefit (1.25)

[8] Although all three studies were at unclear risk of bias, they were stated to be double-blind and we decided to downgrade only for imprecision

[9] Downgraded one level for serious imprecision, the optimal sample size is not met

7 Topical ivermectin compared to topical metronidazole for rosacea

Topical ivermectin compared to topical metronidazole for rosacea						
Patient or population: participants with rosacea **Intervention:** topical ivermectin **Comparison:** topical metronidazole						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with topical metronidazole	**Risk with topical ivermectin**				
HRQoL Assessed with: DLQI, proportion of participants that reported at end of study that rosacea had no impact on QoL Follow up: mean 16 weeks	Study population **640 per 1.000**	**711 per 1.000** (647 to 775)	**RR 1.11** (1.01 to 1.21)	962 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Topical ivermectin likely improves quality of life slightly more than topical metronidazole. Reduction in DLQI was 5.18 in the topical ivermectin group and 3.92 in the topical metronidazole group (both meeting minimal important difference)
Participant-assessed improvement in rosacea severity Assessed with: Likert scale - good to excellent improvement Follow up: mean 16 weeks	Study population **748 per 1.000**	**853 per 1.000** (800 to 912)	**RR 1.14** (1.07 to 1.22)	962 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Topical ivermectin likely results in slightly more participants experiencing a good to excellent improvement when compared with topical metronidazole
Proportion of participants with adverse event Follow up: range 12 weeks to 16 weeks	Study population **13 per 1.000**	**23 per 1.000** (9 to 58)	**RR 1.78** (0.72 to 4.43)	1062 (2 RCTs) [3]	⨁⨁⨁⨀ **MODERATE** [4]	Topical ivermectin probably results in little to no difference in number of participants experiencing adverse events when compared with topical metronidazole
Physician-assessed improvement in rosacea severity Follow up: range 12 weeks to 16 weeks	Study population **742 per 1.000**	**832 per 1.000** (787 to 884)	**RR 1.12** (1.06 to 1.19)	1062 (2 RCTs) [3]	⨁⨁⨁⨀ **MODERATE** [2]	Topical ivermectin probably results in slightly more participants being clear/almost clear or having treatment success according to the physicians compared with topical metronidazole
Assessment of erythema or telangiectasia Follow up: mean 12 weeks	Investigators reported "Decrease in erythema score were not statistically significant between any of CD5024 concentrations (ivermectin) and vehicle or metro. Telangiectasia remained unchanged in all groups"		-	100 [5] (1 RCT)	⨁⨁⨁⨀ **MODERATE** [6]	Topical ivermectin probably results in little to no difference in reduction of erythema and telangiectasia when compared with metronidazole

Lesion count Follow up: mean 16 weeks	The mean lesion count was **-23.60 inflammatory lesions**	MD **4.1 inflammatory lesions fewer** (5.18 fewer to 3.02 fewer)	-	962 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH**	Topical ivermectin results in a small effect that may not be an important difference in reduction in lesion counts when compared with topical metronidazole. Both treatments showed important reductions in lesion counts. Reduction in EUCTR2006-001999-20-HU was 70% and 59.9% (P = 0.26)
Time needed until improvement Follow up: mean 16 weeks	This was not a predefined outcome, but clear improvement could be seen for both treatment arms around 6 weeks		-	962 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH**	Effect of topical ivermectin and topical metronidazole starts within 6 weeks after start treatment
Duration of remission Follow up: mean 52 weeks	Study population		**RR 0.92** (0.83 to 1.02)	757 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH**	Topical ivermectin results in little to no difference in number of participants experiencing a relapse when compared with metronidazole. The mean time to relapse was 147 days (SD 4.66) in the topical ivermectin group and 133.6 days (5.13) in the topical metronidazole group
	684 per 1.000	**630 per 1.000** (568 to 698)				
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference						
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

Footnotes

[1] Taieb 2015

[2] Downgraded one level for serious imprecision, lower boundary close to the line of no difference (1), whilst upper boundary is closer to appreciable benefit (1.25)

[3] Taieb 2015, EUCTR2006-001999-20-HU

[4] Downgraded one level due to serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable harm (1.25)

[5] EUCTR2006-001999-20-HU

[6] Downgraded one level for serious imprecision, low sample size

8 Clindamycin compared to vehicle for rosacea

Clindamycin compared to vehicle for rosacea						
Patient or population: participants with rosacea **Intervention:** clindamycin **Comparison:** vehicle						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with vehicle	**Risk with clindamycin**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of clindamycin on quality of life
Participant-assessed changes in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of clindamycin on participant-assessed changes in rosacea severity
Proportion of participants with adverse event Follow up: mean 12 weeks	The authors reported "Overall, 12 participants had AEs considered by the investigator as possibly or probably related to the study treatment: 4.9% in the clindamycin cream 1% twice daily group, 4.6% in the clindamycin cream 1% once daily group, 3.7% in the vehicle cream twice daily group, 1.2% in the clindamycin cream 0.3% once daily group, and 0% in the vehicle cream once daily group". No mentioning of adverse events on Martel 2017b		-	375 (2 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Clindamycin probably results in little to no difference in participants reporting an adverse event when compared with vehicle
Physician-assessed changes in rosacea severity Assessed with: Rosacea severity score - treatment success (score 0 or 1) Follow up: mean 12 weeks	Study population		**RR 1.17** (0.85 to 1.61)	213 (1 RCT) [5]	⨁⨁⊖⊖ **LOW** [3 4]	Clindamycin appears to not improve physician-assessed rosacea severity when compared with vehicle. The results were confirmed by Martel 2017a where the rosacea severity score reduced by 0.6 in the clindamycin group vs 0.7 in the vehicle group
	385 per 1.000	**450 per 1.000** (327 to 619)				
Assessment of erythema or telangiectasia, or both Assessed with: Erythema Severity Score	In Martel 2017a the score reduced by 1.8 in the clindamycin group and by 1.7 in the vehicle group. In the study of Martel 2017b the reductions were 1.5 and 1.9 respectively.		-	375 (2 RCTs) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Clindamycin probably results in little to no difference in reduction of erythema when compared with vehicle

Follow up: mean 12 weeks					
Lesion count Follow up: mean 12 weeks	In Martel 2017a lesion count was reduced by 30% in the clindamycin group and by 35% in the vehicle group and in Martel 2017b 32% in the clindamycin group and 29% in the vehicle group	-	375 (2 RCTs) [2]	⨁⨁⨁⊖ **MODERATE** [2]	Clindamycin probably results in little to no difference in reduction of lesion counts when compared with vehicle
Time needed until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of clindamycin on time needed until improvement
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of clindamycin on duration of remission
***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes

[1] Martel 2017a, Martel 2017b

[2] Downgraded one level for serious risk of bias, for both studies 6/7 domains were assessed as unclear risk of bias

[3] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable benefit (1.25)

[4] Downgraded one level for serious risk of bias, 6/7 domains were assessed as unclear risk of bias

[5] Martel 2017b

9 Clindamycin phosphate 1.2% + tretinoin 0.025% gel compared to placebo for rosacea

Clindamycin phosphate 1.2% + tretinoin 0.025% gel compared to placebo for rosacea						
Patient or population: participants with rosacea **Intervention:** clindamycin phosphate 1.2% + tretinoin 0.025% gel **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with clindamycin phosphate 1.2% + tretinoin 0.025% gel**				
HRQoL Assessed with: RosaQoL Follow up: mean 12 weeks	No mean scores were provided, only percentages of participants that had improved per item on the 21 survey items, no statistically significant difference for any item		-	83 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Clindamycin phosphate 1.2% + tretinoin 0.025% gel probably results in little to no difference in quality of life when compared with placebo
Participant-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of clindamycin phosphate 1.2% + tretinoin 0.025% gel on participant-assessed improvement of rosacea severity
Proportion of participants with adverse event Follow up: mean 12 weeks	Study population		**RR 2.45** (1.42 to 4.23)	83 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [3]	Clindamycin phosphate 1.2% + tretinoin 0.025% gel likely results in more participants experiencing adverse events. Worsening of rosacea, facial scaling, as well as dry skin were reported most often in the active treatment group
	275 per 1.000	**674 per 1.000** (391 to 1.000)				
Physician-assessed improvement in rosacea severity Assessed with: Physician's Global Assessment as defined by Wilkin 2004 Follow up: mean 12 weeks	None of the primary features of the PGA showed statistically significant differences between the treatment groups except for edema in favour of placebo		-	83 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Clindamycin phosphate 1.2% + tretinoin 0.025% gel probably results in little to no difference in physician-assessed improvement in rosacea severity when compared with placebo
Assessment of erythema or telangiectasia Follow up: mean 12 weeks	Study population		**RR 1.71** (0.70 to 4.18)	83 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [3]	Clindamycin phosphate 1.2% + tretinoin 0.025% gel probably results in little to no difference in reduction of erythema when compared with placebo. There was also probably no difference in improvement of telangiectasia (RR 2.42, 95% CI 0.95 to 6.17)
	150 per 1.000	**257 per 1.000** (105 to 627)				

Lesion count Follow up: mean 12 weeks	The mean lesion count was **-3.13 inflammatory lesions**	MD **3.96 inflammatory lesions more** (1.28 fewer to 9.2 more)	-	83 (1 RCT)	⨁⨁⨁⊖ **MODERATE** [3]	Clindamycin phosphate 1.2% + tretinoin 0.025% gel probably results in little to no difference in lesion counts when compared with placebo
Time needed until improvement - not measured	There was no improvement during study period		-	-	-	We are uncertain about the effect of clindamycin phosphate 1.2% + tretinoin 0.025% gel on time needed to improvement
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of clindamycin phosphate 1.2% + tretinoin 0.025% gel on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Chang 2012

[2] Downgraded one level for serious imprecision (low sample size)

[3] Downgraded one level for serious imprecision (wide confidence interval due to low sample size)

10 Minocycline foam compared to vehicle foam for rosacea

Minocycline foam compared to vehicle foam for rosacea						
Patient or population: participants with rosacea **Intervention:** minocycline foam **Comparison:** vehicle foam						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with vehicle foam	**Risk with minocycline foam**				
HRQoL Assessed with: RosaQoL Follow up: mean 12 weeks	The overall score reduced 0.4 in the minocycline group versus a reduction of 0.2 in the vehicle group. Investigators report P = 0.003 but as MID is not established of RosaQoL data are difficult to interpret		-	157 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Minocycline likely results in a small effect that may not be an important improvement in quality of life
Participant-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of minocycline foam on participant-assessed improvement in rosacea severity
Proportion of participants with adverse event Follow up: mean 12 weeks	Study population		**RR 1.47** (1.05 to 2.04)	157 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [3]	Minocycline foam likely results in a small effect that may not be an important increase in number of participants experiencing an adverse event when compared with vehicle foam
	397 per 1.000	**584 per 1.000** (417 to 811)				
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment - 2 grade improvement Follow up: mean 12 weeks	Study population		**RR 2.33** (1.35 to 4.00)	157 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Minocycline foam likely improves rosacea severity according to the physicians
	179 per 1.000	**418 per 1.000** (242 to 718)				
Assessment of erythema or telangiectasia Assessed with: Clinician's Erythema Assessment - clear to mild	Study population		**RR 1.12** (0.92 to 1.36)	157 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [4]	Minocycline foam likely results in little to no difference in reduction of erythema when compared with vehicle foam
	679 per 1.000	**761 per 1.000** (625 to 924)				

Follow up: mean 12 weeks						
Lesion count Follow up: mean 12 weeks	The mean lesion count was **-7.8 inflammatory lesions**	MD **13.3 inflammatory lesions fewer** (15.82 fewer to 10.78 fewer)	-	157 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Minocycline foam likely results in a large reduction in lesion counts
Time needed until improvement Follow up: mean 12 weeks	This was not a predefined outcome, but clear improvement could be seen for minocycline foam between 4 and 6 weeks		-	157 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Effect of minocycline foam likely starts between 4 and 6 weeks after start of treatment
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of minocycline foam on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).__CI:__ Confidence interval; __RR:__ Risk ratio; __MD:__ Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Mrowietz 2018

[2] Downgraded one level for serious imprecision (low sample size)

[3] Downgraded one level for serious imprecision, the lower boundary of the CI almost crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable harm (1.25), and small sample size

[4] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable benefit (1.25)

11 Ciclosporin ophthalmic emulsion 0.05% compared to artificial tears for ocular rosacea

Ciclosporin ophthalmic emulsion 0.05% compared to artificial tears for ocular rosacea						
Patient or population: participants with ocular rosacea **Intervention:** ciclosporin ophthalmic emulsion 0.05% **Comparison:** artificial tears						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with artificial tears	**Risk with ciclosporin ophthalmic emulsion 0.05%**				
HRQoL Assessed with: Ocular Surface Disease Index (scale 0-100, 100 worst) Follow up: mean 3 months	The mean HRQoL was **16.9**	MD **8.6 lower** (15.42 lower to 1.78 lower)	-	37 (1 RCT) [1]	⨁⨁⊖⊖ **LOW** [2]	Ciclosporin ophthalmic emulsion appears to improve quality of life
Participant-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of ciclosporin ophthalmic emulsion on participants-assessed improvement in ocular rosacea
Proportion of participants with adverse event Follow up: mean 3 months	Study population		**RR 2.32** (0.10 to 53.42)	37 (1 RCT) [1]	⨁⨁⊖⊖ **LOW** [2]	Ciclosporin ophthalmic emulsion may result in little to no difference in number of participants reporting an adverse events when compared with artificial tears
	31 per 1.000	**73 per 1.000** (3 to 1.000)				
Physician-assessed improvement in rosacea severity Assessed with: Schirmer score Follow up: mean 3 months	The mean improvement in Schirmer score was **-1.4**	MD **4.1 higher** (1.66 higher to 6.54 higher)	-	37 (1 RCT) [1]	⨁⨁⊖⊖ **LOW** [2]	Ciclosporin ophthalmic emulsion appears to improve Schirmer score when compared with artificial tears
Assessment of erythema or telangiectasia - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of ciclosporin ophthalmic emulsion on erythema or telangiectasia
Lesion count - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of ciclosporin ophthalmic emulsion on lesion counts
Time needed until improvement - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of ciclosporin ophthalmic emulsion on time needed to improvement

Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of ciclosporin ophthalmic emulsion on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Schechter 2009

[2] Downgraded two levels for very serious imprecision (very wide confidence interval due to very low sample size)

12 Tetracycline compared to placebo for rosacea

Tetracycline compared to placebo for rosacea						
Patient or population: participants with rosacea **Intervention:** tetracycline **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with tetracycline**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of tetracycline on quality of life
Participant-assessed improvement in rosacea severity Assessed with: Number of participants that considered themselves to be better or much better Follow up: mean 6 weeks	Study population **474 per 1.000**	**701 per 1.000** (403 to 1.000)	**RR 1.48** (0.85 to 2.57)	39 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2]	Tetracycline may result in little to no difference in improving participant assessment of rosacea severity
Proportion of participants with adverse event Follow up: mean 6 weeks	Study population **53 per 1.000**	**50 per 1.000** (3 to 744)	**RR 0.95** (0.06 to 14.13)	39 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [3]	Tetracycline may result in little to no difference in number of participants experiencing an adverse event. Only one adverse event was reported in each group, diarrhoea in the tetracycline group, maculopapular rash in the placebo group
Physician-assessed improvement in rosacea severity Follow up: range 4 weeks to 6 weeks	RR 4.04 (95% CI 1.66 to 9.83)(Marks 1971) and RR 1.72 (95% CI 1.18 to 2.50)(Sneddon 1966). Data were not pooled (I^2 = 70%)		-	107 (2 RCTs) [5]	⨁⨁⨀⨀ **LOW** [4 6]	Tetracycline appears to improve physician-assessed rosacea severity
Assessment of erythema or telangiectasia Follow up: mean 6 weeks	There were no significant changes in erythema (Marks 1971)		-	39 (1 RCT)[1]	⨁⨁⨀⨀ **LOW** [7]	Tetracycline may not reduce erythema
Lesion count Follow up: mean 6 weeks	The mean lesion count was **1.41 inflammatory lesions**	MD **14.64 inflammatory lesions fewer**	-	39 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [8]	Tetracycline may result in a large reduction of lesion counts

Time needed until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of tetracycline on time needed until improvement
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of tetracycline on duration of remission
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes

[1] Marks 1971

[2] Downgraded two levels for very serious imprecision (wide confidence interval, due to very low sample size)

[3] Downgraded two levels for very serious imprecision, the lower boundary crosses the line of no difference (1), whilst the upper boundary indicates serious harm (1.25). Very low sample size

[4] Downgraded one level for serious imprecision (low sample size). We decided not to downgrade twice as we already downgraded for inconsistency

[5] Marks 1971 and Sneddon 1966

[6] We downgraded once for serious inconsistency (I^2 = 70%)

[7] Downgraded two levels for very serious imprecision (very low sample size)

[8] Downgraded two levels for very serious imprecision (skewed data and very low sample size)

13 Doxycycline 40 mg compared to placebo for rosacea

Doxycycline 40 mg compared to placebo for rosacea						
Patient or population: participants with rosacea **Intervention:** doxycycline 40 mg **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with doxycycline 40 mg**				
HRQoL Assessed with: Ocular Surface Disease Index Scale from: 0 to 100 (higher is worse) Follow up: mean 12 weeks	The mean HRQoL was **-8.7**	MD **3.55 higher** (4.61 lower to 11.71 higher)	-	70 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2]	Doxycycline 40 mg may result in little to no difference in improving quality of life of participants with ocular rosacea
Participant-assessed improvement in rosacea severity - not measured	No study assessed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg on participants-assessed improvement in rosacea severity
Proportion of participants with adverse event Follow up: range 12 weeks to 16 weeks	Study population		**RR 1.27** (1.08 to 1.49)	777 (4 RCTs) [3]	⨁⨁⨁⨀ **MODERATE** [4]	Doxycycline 40 mg probably increases the number of participants reporting an adverse event slightly. The majority of these adverse events were considered to be mild or moderate in severity
	368 per 1.000	**467 per 1.000** (397 to 548)				
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment, clear or near clear Follow up: range 12 weeks to 16 weeks	Study population		**RR 1.69** (1.26 to 2.28)	707 (3 RCTs) [5]	⨁⨁⨁⨁ **HIGH**	Doxycycline 40 mg increases the number of participants reaching IGA of clear or almost clear
	150 per 1.000	**253 per 1.000** (189 to 341)				
Assessment of erythema or telangiectasia Assessed with: Clinician's Erythema Assessments scale 0-4	The mean assessment of erythema ranged from **-1.8 to -0.8**	MD **0.48 lower** (0.97 lower to 0)	-	707 (3 RCTs) [5]	⨁⨁⨁⨀ **MODERATE** [6]	Doxycycline 40 mg probably reduces erythema slightly

Follow up: range 12 weeks to 16 weeks						
Lesions count Follow up: mean 16 weeks	The mean lesions count ranged from **-4.3 to -5.9 inflammatory lesions**	MD **5.51 inflammatory lesions fewer** (7.81 fewer to 3.21 fewer)	-	537 (2 RCTs) [7]	⨁⨁⨁⊖ **MODERATE** [8]	Doxycycline 40 mg probably reduces lesion counts
Time needed until improvement Follow up: mean 16 weeks	Based on interim data improvement started around 3 weeks		-	537 (2 RCTs) [7]	⨁⨁⨁⨁ **HIGH**	Effect of doxycycline starts within 3 weeks after start treatment
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] NCT00560703

[2] Downgraded two levels for very serious imprecision (very wide CI)

[3] Del Rosso 2007a, Del Rosso 2007b, Di Nardo 2016, NCT00560703

[4] Downgraded one level for serious imprecision, lower boundary of CI close to line of no difference (1), whilst upper boundary indicates appreciable harm (1.25)

[5] Del Rosso 2007a, Del Rosso 2007b, Di Nardo 2016

[6] Downgraded one level for serious imprecision, low boundary of CI indicates appreciable benefit, whilst upper boundary indicates no difference (0)

[7] Del Rosso 2007a, Del Rosso 2007b

[8] Downgraded one level for serious imprecision (wide confidence interval)

14 Minocycline 100 mg compared to doxycycline 40 mg for rosacea

Minocycline 100 mg compared to doxycycline 40 mg for rosacea						
Patient or population: participants with rosacea **Intervention:** minocycline 100 mg **Comparison:** doxycycline 40 mg						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with doxycycline 40 mg	**Risk with minocycline 100 mg**				
HRQoL Assessed with: RosaQoL (scale 1 to 5, higher = worse) Follow up: mean 16 weeks	The mean HRQoL was **-0.62**	MD **0.24 lower** (0.3 lower to 0.18 lower)	-	80 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 100 mg may result in a small possibly unimportant effect on quality of life when compared with doxycycline 40 mg
Participant-assessed improvement in rosacea severity Assessed with: Patient's Global Assessment - Excellent or good improvement Follow up: mean 16 weeks	Study population **500 per 1.000**	**550 per 1.000** (360 to 835)	**RR 1.10** (0.72 to 1.67)	80 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 100 mg may result in little to no difference in participant-assessed improvement (good or excellent) in rosacea severity when compared with doxycycline 40 mg
Proportion of participants with adverse event Follow up: mean 16 weeks	Study population **575 per 1.000**	**673 per 1.000** (477 to 949)	**RR 1.17** (0.83 to 1.65)	80 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 4]	Minocycline 100 mg may result in little to no difference in number of participants experiencing an adverse event when compared with doxycycline 40 mg
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment scale - clear or near clear Follow up: mean 16 weeks	Study population **175 per 1.000**	**600 per 1.000** (292 to 1.000)	**RR 3.43** (1.67 to 7.04)	80 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [3]	Minocycline 100 mg likely results in a large increase of physician-assessed improvement (clear or near clear) when compared with doxycycline 40 mg
Assessment of erythema or telangiectasia Assessed with: Clinician's Erythema Assessment - at	Study population **325 per 1.000**	**400 per 1.000** (221 to 718)	**RR 1.23** (0.68 to 2.21)	80 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [5]	Minocycline 100 mg probably results in little to no difference in number of participants experiencing a 1 point decrease of erythema on the CEA scale when compared with doxycycline 40 mg

least 1 point decrease Follow up: mean 16 weeks						
Lesion count Follow up: mean 16 weeks	The mean lesion count was **-13 inflammatory lesions**	MD **1 inflammatory lesions fewer** (7.96 fewer to 5.96 more)	-	80 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [6]	Minocycline 100 mg probably results in little to no difference in reduction in lesion counts when compared with doxycycline 40 mg. Both treatments showed important reductions in lesion count
Time needed until improvement - not measured	No study assessed this outcome		-	-	-	We are uncertain about the effect of minocycline 100 mg on time needed until improvement when compared with doxycycline 40 mg
Duration of remission Follow up: mean 28 weeks	Study population		**RR 0.95** (0.45 to 1.99)	31 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [7]	Minocycline 100 mg may result in little to no difference in number of participants experiencing an IGA of 0 or 1 (clear or near clear) 12 weeks after stopping treatment when compared with doxycycline 40 mg
	571 per 1.000	**543 per 1.000** (257 to 1.000)				

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] van der Linden 2017

[2] Downgraded one level for serious risk of bias (participants were not blinded)

[3] Downgraded one level for serious imprecision (low sample size)

[4] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary of the CI indicates appreciable harm (1.25)

[5] Downgraded one level for serious imprecision, the lower boundary indicates appreciable harm (0.75), whilst the upper boundary of the CI indicates appreciable benefit (1.25)

[6] Downgraded one level for serious imprecision (wide confidence interval)

[7] Downgraded two levels for very serious imprecision (very low sample size and wide confidence interval)

15 Azithromycin compared to doxycycline 100 mg for rosacea

Azithromycin compared to doxycycline 100 mg for rosacea						
Patient or population: participants with rosacea **Intervention:** azithromycin **Comparison:** doxycycline 100 mg						
Outcomes	**Anticipated absolute effects*** **(95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with doxycycline 100 mg	**Risk with azithromycin**				
HRQoL - not measured	No study assessed this outcome		-	-	-	We are uncertain about the effect of azithromycin on quality of life when compared with doxycycline
Participant-assessed improvement in rosacea severity Follow up: mean 3 months	Study population		**RR 0.98** (0.77 to 1.25)	67 (1 RCT) [1]	⨁⊖⊖⊖ **VERY LOW** [2 3]	We are uncertain about the effect of azithromycin on participant-assessed improvement in rosacea severity when compared with doxycycline. In both treatment arms the majority of participants considered themselves improved
	800 per 1.000	**784 per 1.000** (616 to 1.000)				
Proportion of participants with adverse event Follow up: mean 3 months	Study population		**RR 1.62** (0.32 to 8.26)	67 (1 RCT) [1]	⨁⊖⊖⊖ **VERY LOW** [2 4]	We are uncertain about the effect of azithromycin on number of participants reporting an adverse event when compared with doxycycline
	67 per 1.000	**108 per 1.000** (21 to 551)				
Physician-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of azithromycin on physician-assessed improvement in rosacea severity when compared with doxycycline
Assessment of erythema or telangiectasia - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of azithromycin and doxycycline on erythema and telangiectasia
Lesions count Follow up: mean 3 months	Lesion count decreased in azithromycin group from 19.24 (9.67) to 1.90 (3.28) at 3 months and for doxycycline from 18.86 (8.95) to 2.34 (3.47). Skewed data		-	67 (1 RCT) [1]	⨁⊖⊖⊖ **VERY LOW** [2 5]	We are uncertain about the effect of azithromycin on lesion counts when compared with doxycycline. Both treatments showed important reductions in lesion counts
Time needed until improvement - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of azithromycin on time needed until improvement when compared with doxycycline

Duration of remission Follow up: mean 5 months	No data on duration of remission, but both groups showed no statistically significant change between the third month of treatment and the second month post-treatment	-	67 (1 RCT) [1]	⨁⊖⊖⊖ **VERY LOW** [2] [6]	We are very uncertain about the effect of azithromycin on duration of remission when compared with doxycycline. The effect in both treatment arms sustained at least for two months after discontinuation

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Akhyani 2008

[2] Downgraded two levels for very serious risk of bias (allocation concealment was at high risk of bias, no blinding)

[3] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1) whilst the upper boundary indicates appreciable benefit (1.25) and low sample size

[4] Downgraded one level for serious imprecision (wide confidence interval due to low sample size)

[5] Downgraded one level for serious imprecision (large SDs and skewed data, low sample size)

[6] Downgraded one level for serious imprecision (low sample size)

16 Doxycycline 40 mg + metronidazole 1% gel compared to doxycycline 100 mg + metronidazole 1% gel for rosacea

Doxycycline 40 mg + metronidazole 1% gel compared to doxycycline 100 mg + metronidazole 1% gel for rosacea						
Patient or population: participants with rosacea **Intervention:** doxycycline 40 mg + metronidazole 1% gel **Comparison:** doxycycline 100 mg + metronidazole 1% gel						
Outcomes	**Anticipated absolute effects[*] (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with doxycycline 100 mg + metronidazole 1% gel	**Risk with doxycycline 40 mg + metronidazole 1% gel**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg + metronidazole 1% gel on quality of life when compared with doxycycline 100 mg + metronidazole gel
Participant-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg + metronidazole 1% gel on participant-assessed improvement in rosacea severity when compared with doxycycline 100 mg + metronidazole gel
Proportion of participants with adverse event Follow up: mean 16 weeks	Study population		**RR 0.25** (0.11 to 0.54)	91 (1 RCT) [1]	⨁⨁⊖⊖ **LOW** [2 3]	Doxycycline 40 mg + metronidazole 1% gel appears to result in a large reduction of participants reporting an adverse event when compared with doxycycline 100 mg + metronidazole 1% gel. The majority of these adverse events were gastro-intestinal complaints
	553 per 1.000	**138 per 1.000** (61 to 299)				
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment Follow up: mean 16 weeks	The mean reduction in IGA was **-1.6**	**MD 0** (0.11 lower to 0.11 higher)	-	91 (1 RCT) [1]	⨁⨁⊖⊖ **LOW** [2 3]	Doxycycline 40 mg + metronidazole 1% gel may result in little to no difference in physician-assessed improvement of rosacea severity when compared with doxycycline 100 mg + metronidazole 1% gel
Assessment of erythema or telangiectasia Assessed with: Clinician's Erythema Assessment	Reduction in CEA 4.2 in doxycycline 40 mg and 4.0 in doxycycline 100 mg group, investigator's state P = 0.50		-	91 (1 RCT)	⨁⨁⊖⊖ **LOW** [2 3]	Doxycycline 40 mg + metronidazole 1% gel may result in little to no difference in reduction of erythema when compared with doxycycline 100 mg + metronidazole 1% gel. Both treatments showed a large reduction of erythema

Follow up: mean 16 weeks						
Lesion count Follow up: mean 16 weeks	The mean lesion count was **-12.2 inflammatory lesions**	**MD 0.3 inflammatory lesions fewer** (3.03 fewer to 2.43 more)	-	91 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Doxycycline 40 mg + metronidazole 1% gel may result in little to no difference in reduction of lesion counts when compared with doxycycline 100 mg + metronidazole 1% gel. Both treatments showed an important reduction of lesion counts
Time needed until improvement Follow up: mean 16 weeks	Not reported as per the methods section, a clear improvement was seen from week four for both groups		-	91 (1 RCT)	⨁⨁⨀⨀ **LOW** [2 3]	Both treatment arms may show improvements 4 weeks after start of treatment
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg + 1% metronidazole gel on duration of remission when compared with doxycycline 100 mg + metronidazole gel
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference						
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

Footnotes

[1] Del Rosso 2008

[2] Downgraded one level for serious risk of selection bias and attrition bias (sequence generation and allocation concealment at unclear risk of bias, high drop-out rate and although ITT analysis judged at unclear risk of bias)

[3] Downgraded one level for serious imprecision (low sample size)

17 Doxycycline 40 mg + azelaic acid gel compared to doxycycline 40 mg + metronidazole gel for rosacea

Doxycycline 40 mg + azelaic acid gel compared to doxycycline 40 mg + metronidazole gel for rosacea						
Patient or population: participants with rosacea **Intervention:** doxycycline 40 mg + azelaic acid gel **Comparison:** doxycycline 40 mg + metronidazole gel						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with doxycycline 40 mg + metronidazole gel	**Risk with doxycycline 40 mg + azelaic acid gel**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg + azelaic acid gel on quality of life when compared with doxycycline 100 mg + metronidazole gel
Participant-assessed improvement in rosacea severity Assessed with: Excellent improvement on a four point Likert scale Follow up: mean 12 weeks	Study population		**RR 1.05** (0.79 to 1.40)	207 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Doxycycline 40 mg + azelaic acid probably results in little to no difference in participant-assessed improvement in rosacea severity when compared with doxycycline 40 mg + metronidazole. Excellent improvement was reported in approximately half of each intervention group
	465 per 1.000	**489 per 1.000** (368 to 651)				
Proportion of participants with adverse event Follow up: mean 12 weeks	Study population		**RR 0.27** (0.06 to 1.28)	207 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [3]	Doxycycline 40 mg + azelaic acid may result in little to no difference in number of participants reporting an adverse event when compared with doxycycline 40 mg + metronidazole. In both groups there were few adverse events
	69 per 1.000	**19 per 1.000** (4 to 89)				
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment of 0, 1 or 2 (clear to mild) Follow up: mean 12 weeks	Study population		**RR 1.08** (0.93 to 1.27)	207 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Doxycycline 40 mg + azelaic acid probably results in little to no difference in physician-assessed improvement in rosacea severity when compared with doxycycline 40 mg + metronidazole
	723 per 1.000	**781 per 1.000** (672 to 918)				
Assessment of erythema or	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg + azelaic acid gel on erythema and telangiectasia when compared with doxycycline 100 mg + metronidazole gel

telangiectasia - not measured						
Lesion count Follow up: mean 12 weeks	The mean lesion count was **-9.4 inflammatory lesions**	MD **1.1 inflammatory lesions fewer** (3.62 fewer to 1.42 more)	-	207 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [4]	Doxycycline 40 mg + azelaic acid probably results in little to no difference in reduction of lesion counts when compared with doxycycline 40 mg + metronidazole. Both treatment arms showed an important reduction in lesion counts
Time needed until improvement Follow up: mean 12 weeks	Not reported as per the methods section but from 4 weeks on improvement could be seen for both treatment arms		-	207 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH**	Improvement starts 4 weeks after start treatment for both treatment arms
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of doxycycline 40 mg + azelaic acid gel on duration of remission when compared with doxycycline 100 mg + metronidazole gel

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Del Rosso 2010

[2] Downgraded one level for serious imprecision, the lower boundary of the CI crosses the line of no difference (1), whilst the upper boundary indicates appreciable benefit (1.25)

[3] Downgraded two levels for very serious imprecision, the lower boundary crosses the line of appreciable benefit (0.75), whilst the upper boundary crosses the line of appreciable harm (1.25), low occurrence of events

[4] Downgraded one level for serious imprecision (wide confidence interval)

18 Minocycline 45 mg compared to minocycline 45 mg + azelaic acid gel for rosacea

Minocycline 45 mg compared to minocycline 45 mg + azelaic acid gel for rosacea						
Patient or population: rosacea **Intervention:** minocycline 45 mg **Comparison:** minocycline 45 mg + azelaic acid gel						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with minocycline 45 mg + azelaic acid gel	**Risk with minocycline 45 mg**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of minocycline on quality of life when compared with minocycline + azelaic acid
Participant-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of minocycline on participant-assessed improvement in rosacea severity when compared with minocycline + azelaic acid
Proportion of participants with adverse event Follow up: mean 12 weeks	Study population **533 per 1.000**	**368 per 1.000** (208 to 651)	**RR 0.69** (0.39 to 1.22)	60 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 45 mg may result in little to no difference in number of participants experiencing an adverse event when compared with minocycline 45 mg + azelaic acid gel
Physician-assessed improvement in rosacea severity Assessed with: Investigator's Global Assessment (Likert scale 0-5) Follow up: mean 12 weeks	The mean physician-assessed improvement in rosacea severity was **-2 IGA** scale	MD **0 IGA scale** (0.32 lower to 0.32 higher)	-	60 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 45 mg may result in little to no difference in reduction of IGA score when compared with minocycline 45 mg + azelaic acid gel. Both treatment arms showed a reduction of 2 on the IGA scale
Assessment of erythema or telangiectasia Assessed with: CEA scale (Likert scale 0-4) Follow up: mean 12 weeks	The mean assessment of erythema or telangiectasia was **-4 CEA** scale	MD **1 CEA scale higher** (0.18 lower to 2.18 higher)	-	60 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 45 mg may result in little to no difference in reduction of CEA score when compared with minocycline 45 mg + azelaic acid gel. Both treatment arms showed important reductions in erythema
Lesion count Follow up: mean 12 weeks	The mean lesion count was **-12.2 inflammatory lesions**	MD **1 inflammatory lesions more** (0.93 fewer to 2.93 more)	-	60 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 45 mg may result in little to no difference in reduction lesion counts when compared with minocycline 45 mg + azelaic acid gel. Both treatment arms showed an important reduction in lesion counts

Time needed until improvement Follow up: mean 12 weeks	Improvement was seen in both arms at four weeks	-	60 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Minocycline 45 mg as well as minocycline 45 mg + azelaic acid gel may result in improvement after 4 weeks of treatment
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of minocycline 45 mg on duration of remission when compared with minocycline 45 mg + azelaic acid gel
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes

[1] Jackson 2013

[2] Downgraded one level for serious risk of performance and detection bias (blinding was assessed as at unclear risk of bias)

[3] Downgraded one level for serious imprecision (small sample size), as we already downgraded for risk of bias we decided not to downgrade twice for imprecision

19 Topical metronidazole compared to oral (oxy) tetracycline for rosacea

Topical metronidazole compared to oral (oxy) tetracycline for rosacea

Patient or population: participants with rosacea
Intervention: topical metronidazole
Comparison: oral (oxy) tetracycline

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with oral (oxy) tetracycline	Risk with topical metronidazole				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of topical metronidazole on quality of life when compared to (oxy) tetracycline
Participant-assessed improvement in rosacea severity Follow up: range 8 weeks to 9 weeks	Study population		**RR 0.90** (0.66 to 1.23)	81 (2 RCTs) [1]	⨁⨁◯◯ **LOW** [2 3]	Topical metronidazole may result in little to no difference in the number of participant-assessed improvements of rosacea severity when compared with oral (oxy) tetracycline. In Schachter 1991 no exact data were provided other than that "both groups considered their condition much improved"
	825 per 1.000	**660 per 1.000** (330 to 1.000)				
Proportion of participants with adverse event Follow up: range 8 weeks to 9 weeks	Study population		**RR 0.80** (0.40 to 1.62)	206 (3 RCTs) [4]	⨁⨁◯◯ **LOW** [3 5]	Topical metronidazole may result in little to no difference in number of participants reporting an adverse event when compared to oral (oxy) tetracycline. In Schachter 1991 12 adverse events reported in metronidazole group and 9 in tetracycline group but number randomised to each group unclear
	175 per 1.000	**140 per 1.000** (70 to 284)				
Physician-assessed improvement in rosacea severity Follow up: range 8 weeks to 9 weeks	Study population		**RR 0.95** (0.70 to 1.29)	81 (2 RCTs) [1]	⨁⨁◯◯ **LOW** [3 5]	Topical metronidazole may result in little to no difference in physician-assessed improvement of rosacea severity when compared with oral (oxy) tetracycline
	850 per 1.000	**808 per 1.000** (595 to 1.000)				
Assessment of erythema or telangiectasia Follow up: range 8 weeks to 9 weeks	Erythema score -1.4 vs -1.3 (Monk 1991), "the reduction of erythema was the same in both groups, and the number and extent of telangiectases were unchanged" (Nielsen 1983b). In Schachter 1991 no differences in erythema nor telangiectasia were seen in either group. In Veien 1986 11.1% in the metronidazole group versus 12.5% in the tetracycline group showed no improvement of erythema		-	258 (4 RCTs) [6]	⨁⨁◯◯ **LOW** [7 8]	Topical metronidazole may result in little to no difference in reduction of erythema when compared with oral (oxy) tetracycline

Lesion count Follow up: range 8 weeks to 9 weeks	100% clearing in 75% (topical metronidazole) vs 66% (oxy) tetracycline (Monk 1991), "the reduction of papules and pustules was the same in both groups"(Nielsen 1983b), decrease of 68% vs 77% in papule count and of 53% and 61% in pustule count (Schachter 1991). In Veien 1986 the median lesion count at end of study was 11.1 vs 0	-	258 (4 RCTs) [6]	⨁⨁⊖⊖ **LOW** [7 9]	Topical metronidazole may result in little to no difference in reduction of lesion counts when compared with oral (oxy) tetracycline
Time needed until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of topical metronidazole on time needed until improvement when compared with oral (oxy) tetracycline
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of topical metronidazole on duration of remission when compared with oral (oxy) tetracycline

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Monk 1991, Nielsen 1983b

[2] Downgraded two levels for very serious imprecision, lower boundary of CI indicates appreciable harm (0.75), whilst the upper boundary crosses the line of no difference (1)(very low sample size)

[3] Not downgraded for risk of bias, blinding was ensured

[4] Monk 1991, Nielsen 1983b, Veien 1986

[5] Downgraded two levels for very serious imprecision (wide confidence intervals including appreciable harm and appreciable benefit)

[6] Monk 1991, Nielsen 1983b, Schachter 1991, Veien 1986

[7] Downgraded one level for serious imprecision (low sample size)

[8] Downgraded one level for serious inconsistency (in contrast to the other 3 studies, Schachter 1991 did not show any improvement in erythema and telangiectasia)

[9] Downgraded for serious inconsistency (in Monk 1991 topical metronidazole performed better, In Schachter 1991 en Veien 1986 oral (oxy) tetracycline and in Nielsen 1983b there was no difference

20 Topical ciclosporin emulsion 0.05% compared to oral doxycycline 200 mg, after 1 month 100 mg for ocular rosacea

Topical ciclosporin emulsion compared to oral doxycycline for ocular rosacea

Patient or population: patients with ocular rosacea
Intervention: topical ciclosporin emulsion
Comparison: oral doxycycline

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with oral doxycycline 200 mg, after 1 month 100 mg	Risk with topical ciclosporin emulsion 0.05%				
HRQoL Assessed with: Ocular Surface Disease Index (OSDI) (scale 0 to 100, 100 = worst) Follow up: mean 3 months	The mean HRQoL was **-11.22**	MD **8.82 lower** (14.32 lower to 3.32 lower)	-	38 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Topical ciclosporin may improve quality of life slightly when compared with oral doxycycline
Participant-assessed improvement in rosacea severity Assessed with: Symptom score (0 to 9, higher is worse) Follow up: mean 3 months	The mean participant-assessed improvement in rosacea severity was **-3.47**	MD **1.85 lower** (2.6 lower to 1.1 lower)	-	38 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Topical ciclosporin appears to increase participant-assessed improvement in rosacea severity slightly when compared with oral doxycycline
Proportion of participants with adverse event - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of topical ciclosporin on the number of participants experiencing an adverse event when compared with oral doxycycline
Physician-assessed improvement in rosacea severity Assessed with: Eyelid score and cornea/conjunctival score (0-9, higher is worse), Schirmer's test and TBUT (for both higher is better) Follow up: mean 3 months	Eyelid score ciclosporin vs doxycycline MD -1.10 (95% CI -1.67 to -0.53), cornea/conjunctival sign score ciclosporin vs doxycycline MD -0.53 (95% CI -0.92 to -0.14), Schirmer test ciclosporin vs doxycycline MD 2.11 (95% CI 0.82 to 3.40), TBUT ciclosporin vs doxycycline MD 2.32 (95% CI 0.81 to 3.83)		-	38 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Topical ciclosporin appears to increase physician-assessed improvement in rosacea severity slightly when compared with oral doxycycline

Assessment of erythema or telangiectasia - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of topical ciclosporin on erythema and telangiectasia when compared with oral doxycycline
Lesion count - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of topical ciclosporin on lesion counts when compared with oral doxycycline
Time needed until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of topical ciclosporin on time needed until improvement when compared with oral doxycycline
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of topical ciclosporin on duration of remission when compared with oral doxycycline

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI). __CI:__ Confidence interval; __RR:__ Risk ratio; __MD:__ Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Arman 2015

[2] Downgraded one level for serious risk of bias (study was not blinded)

[3] Downgraded one level for serious imprecision (low sample size). As we also downgraded for risk of bias we decided not to downgrade twice for imprecision

21 Low dose isotretinoin 0.3 mg/kg compared to doxycycline 100 mg for rosacea for 14 days and then tapered to 50 mg

Low dose isotretinoin 0.3 mg/kg compared to doxycycline 100 mg for rosacea

Patient or population: participants with rosacea
Intervention: low dose isotretinoin 0.3 mg/kg
Comparison: doxycycline 100 mg for 14 days and then tapered to 50 mg

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with doxycycline 100 mg for 14 days and then tapered to 50 mg	Risk with low dose isotretinoin 0.3 mg/kg				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of low dose isotretinoin 0.3 mg/kg on quality of life when compared with doxycycline 100 mg for 14 days and then tapered to 50 mg
Participant-assessed improvement in rosacea severity Assessed with: Good to excellent improvement on 5 point Likert scale Follow up: mean 12 weeks	Study population		**RR 1.23** (1.05 to 1.43)	261 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Low dose isotretinoin 0.3 mg/kg probably increases participant-assessed improvement in rosacea severity slightly when compared with doxycycline 100 mg for 14 days and then tapered to 50 mg
	644 per 1.000	**792 per 1.000** (676 to 921)				
Proportion of participants with adverse event Follow up: mean 12 weeks	Study population		**RR 1.19** (0.74 to 1.92)	299 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [3]	Low dose isotretinoin 0.3 mg/kg probably results in little to no difference in number of participants experiencing an adverse event when compared to doxycycline 100 mg for 14 days and then tapered to 50 mg. There were more gastrointestinal and respiratory complaints reported in the doxycycline group; and cheilitis, dry mouth and lips were more frequent occurrences in the isotretinoin group
	171 per 1.000	**204 per 1.000** (127 to 328)				
Physician-assessed improvement in rosacea severity Assessed with: Complete remission or marked improvement on a 6 point Likert	Study population		**RR 1.18** (1.03 to 1.36)	261 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Low dose isotretinoin 0.3 mg/kg probably increases physician-assessed improvement of rosacea severity slightly when compared with doxycycline 100 mg for 14 days and then tapered to 50 mg
	689 per 1.000	**813 per 1.000** (710 to 938)				

scale) Follow up: mean 12 weeks						
Assessment of erythema or telangiectasia Assessed with: Improved or healed follow up: mean 12 weeks	Study population **783 per 1.000**	**736 per 1.000** (667 to 869)	**RR 0.94** (0.83 to 1.08)	285 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH** [4]	Low dose isotretinoin results in little to no difference in number of participants with improvement or clearing of erythema when compared to doxycycline 100 mg for 14 days and then tapered to 50 mg. Telangiectasia were improved or healed RR 1.03 (95% CI 0.77 to 1.37)
Lesion count Follow up: mean 12 weeks	The mean lesion count was **-13 inflammatory lesions**	MD **3 inflammatory lesions fewer** (5.18 fewer to 0.82 fewer)	-	261 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [5]	Low dose isotretinoin 0.3 mg/kg probably results in a small effect that may not be an important difference in reduction in lesion counts when compared to doxycycline 100 mg for 14 days and then tapered to 50 mg. Both treatments showed important reductions in lesion count
Time needed until improvement - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of low dose isotretinoin 0.3 mg/kg on time needed until improvement when compared with doxycycline 100 mg for 14 days and then tapered to 50 mg
Duration of remission - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of low dose isotretinoin 0.3 mg/kg on duration of remission when compared with doxycycline 100 mg for 14 days and then tapered to 50 mg
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference						
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect						

Footnotes

[1] Gollnick 2010

[2] Downgraded one level for serious imprecision, lower boundary of CI close to line of no difference (1), whilst upper boundary indicates appreciable benefit (1.25)

[3] Downgraded one level for serious imprecision, lower boundary of CI indicates appreciable benefit, whilst upper boundary indicates appreciable harm, low occurrence of events

[4] We did not downgrade for imprecision as the CI effect estimate is not near appreciable benefit or appreciable harm and therefore rather precise

[5] Downgraded one level for imprecision, the upper boundary of the CI is close to the line of no difference (0)

22 Low dose isotretinoin 0.25 mg/kg compared to placebo for rosacea

Low dose isotretinoin 0.25 mg/kg compared to placebo for rosacea						
Patient or population: participants with rosacea **Intervention:** low dose isotretinoin 0.25 mg/kg **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with low dose isotretinoin 0.25 mg/kg**				
HRQoL Assessed with: Skindex-29 Follow up: mean 4 months	Skindex scores showed median relative variations of -49.4% in the isotretinoin-treated group compared with -18.0% in the placebo group (investigators reported "P = 0.002").		-	156 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Low dose isotretinoin 0.25 mg/kg likely improves quality of life
Participant-assessed improvement in rosacea severity Assessed with: VAS 0-100 (higher = better) Follow up: mean 4 months	Rosacea severity was not assessed, but satisfaction was assessed; median values of 80 in the isotretinoin group versus 9 in the placebo group.		-	156 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 3]	Low dose isotretinoin 0.25 mg/kg appears to result in a large improvement of participants' satisfaction
Proportion of participants with adverse event Follow up: mean 4 months	Study population		**RR 1.59** (1.12 to 2.24)	156 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Low dose isotretinoin 0.25 mg/kg probably increases the number of participants experiencing an adverse event. Reported adverse events included eczema, cheilitis, dry skin and abdominal pain, myalgias/arthralgias and dry eyes
	438 per 1.000	**696 per 1.000** (490 to 980)				
Physician-assessed improvement in rosacea severity Assessed with: Dermatologist's assessment scale 0 or 1 Follow up: mean 4 months	Study population		**RR 4.89** (2.28 to 10.49)	156 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH** [4]	Based on physician assessments low dose isotretinoin 0.25 mg/kg results in far more participants with no or few inflammatory lesions, no to moderate erythema and no to moderate telangiectasia, when compared with placebo
	125 per 1.000	**611 per 1.000** (285 to 1.000)				

Assessment of erythema or telangiectasia Follow up: mean 4 months	Investigators reported "No difference between the 2 groups (isotretinoin vs. placebo group) was observed for the associated symptoms (telangiectasia and erythema)"	-	156 (1 RCT) [1]	⨁⨁⨁⊖ **MODERATE** [2]	Low dose isotretinoin 0.25 mg/kg likely results in little to no difference in reduction of erythema and telangiectasia when compared with placebo
Lesion count Assessed with: number of participants with 90% reduction Follow up: mean 4 months	Study population **104 per 1.000** / **574 per 1.000** (247 to 1.000)	**RR 5.51** (2.37 to 12.83)	156 (1 RCT) [1]	⨁⨁⨁⨁ **HIGH** [4]	Low dose isotretinoin 0.25 mg/kg results in far more participants with at least a 90% reduction in lesion counts when compared with placebo
Time needed until improvement - not measured	No study assessed this outcome	-	-	-	We are uncertain about the effect of low dose isotretinoin 0.25 mg/kg on time needed until improvement when compared with placebo
Duration of remission Follow up: mean 8 months	Of the 62 participants in the isotretinoin-treated group which achieved at least a 90% reduction of inflammatory lesions 51 (82.3%) agreed to a four month follow-up. In 27/51 rosacea relapsed with a median of 15 weeks to recurrence	-	51 (1 RCT) [1]	⨁⊖⊖⊖ **VERY LOW** [5 6]	Low dose isotretinoin 0.25 mg/kg may increase duration of remission but we are very uncertain

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Sbidian 2016

[2] Downgraded one level for serious imprecision (low sample size)

[3] Downgraded one level for serious indirectness as measuring satisfaction is not the same as measuring rosacea severity

[4] Not downgraded for imprecision as the lower boundary of the CI still indicates large effect, therefore the effect estimate is rather precise

[5] Downgraded two levels for very serious imprecision (very low sample size)

[6] Downgraded one level for serious risk of bias (no control group)

23 Omega 3 fatty acids compared to placebo for dry eyes in rosacea

Omega 3 fatty acids compared to placebo for dry eyes in rosacea						
Patient or population: participants with rosacea and dry eyes **Intervention:** omega 3 fatty acids **Comparison:** placebo						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with placebo	**Risk with omega 3 fatty acids**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of omega 3 fatty acids on quality of life
Participant-assessed improvement in rosacea severity Assessed with: Dry Eye questionnaire and Scoring System (0-18, higher = worse) Follow up: mean 6 months	The mean participant-assessed improvement in rosacea severity was **-0.20**	MD **5.1 lower** (5.63 lower to 4.57 lower)	-	130 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Omega 3 fatty acids likely reduce dry eyes according to the participants (based on Dry Eye questionnaire and Scoring System)
Proportion of participants who reported an adverse event - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of omega 3 fatty acids on participants experiencing an adverse event when compared with placebo
Physician-assessed improvement in rosacea severity Assessed with: Meibom gland score (lower = better), Tear Break Up Time, Schirmer's Score (last two higher is better) Follow up: mean 6 months	Omega 3 fatty acids versus placebo Meibom gland score: MD -1.28, 95% CI -1.53 to -1.03; Tear Break Up Time (TBUT): MD 3.30, 95% CI 2.86 to 3.74; Schirmer's score: 1.70 95% CI 0.62 to 2.78; all favouring omega 3 fatty acids		-	130 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [2]	Omega 3 fatty acids likely improve Meibom gland function, Tear Break Up Time and Schirmer's score as measure by the physicians in participants with rosacea suffering from dry eyes
Assessment of erythema or telangiectasia - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of omega 3 fatty acids on erythema and telangiectasia
Lesion count - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of omega 3 fatty acids on lesion counts

Time needed until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of omega 3 fatty acids on time needed until improvement
Duration of remission - not measured		-	-	-	We are uncertain about the effect of omega 3 fatty acids on duration of remission

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). **CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Bhargava 2016

[2] Downgraded one level for serious imprecision (small sample size)

24 Pulsed dye laser compared to Nd:YAG laser for rosacea

Pulsed dye laser compared to Nd: YAG laser for rosacea						
Patient or population: patients with rosacea **Intervention:** pulsed dye laser **Comparison:** Nd: YAG laser						
Outcomes	**Anticipated absolute effects[*] (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with Nd:YAG laser	**Risk with pulsed dye laser**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of PDL on quality of life when compared with Nd:YAG laser
Participant-assessed improvement in rosacea severity Assessed with: Improvement in erythema (percentage) Follow up: mean 6 months [3]	The mean participant-assessed improvement in rosacea severity was **34 %**	MD **18 % higher** (1.94 higher to 34.6 higher)	-	14 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2]	PDL may improve participant-assessed rosacea severity slightly based on improvement in facial redness (percentage) when compared with Nd:YAG laser
Proportion of participants with adverse event Assessed with: Pain as assessed by VAS (0-10; higher score is worse) Follow up: mean 6 months [3]	Pain was assessed on the PDL treated side 3.87, whilst it was 3.07 on the Nd:YAG side, according to the investigators P = 0.0028		-	14 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [4]	PDL may be slightly more painful when compared with Nd:YAG laser
Physician-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of PDL on physician-assessed rosacea severity when compared with Nd:YAG laser
Assessment of erythema or telangiectasia Assessed with: Spectrophotometer to assess facial redness (percentage) Follow up: mean 6 months [3]	The mean assessment of erythema or telangiectasia was **-2.5 %**	**MD 6.4 % lower** (11.6 lower to 1.2 lower)	-	14 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2]	PDL may reduce erythema and telangiectasia slightly based on assessments with spectrophotometer (percentage) when compared with Nd:YAG laser
Lesion count - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of PDL on lesion counts when compared with Nd:YAG laser

Time until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of PDL on time until improvement when compared with Nd: YAG laser
Duration of remission - not reported	No study addressed this outcome	-	-	-	We are uncertain about the effect of PDL on duration of remission when compared with Nd:YAG laser
*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).**CI:** Confidence interval; **RR:** Risk ratio; **MD:** Mean difference					
GRADE Working Group grades of evidence **High certainty:** We are very confident that the true effect lies close to that of the estimate of the effect **Moderate certainty:** We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different **Low certainty:** Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect **Very low certainty:** We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect					

Footnotes

[1] Alam 2013

[2] Downgraded two levels for very serious imprecision (very wide confidence interval due to very low sample size)

[3] Within-participant design

[4] Downgraded two levels for very serious imprecision (very small sample size)

25 Long pulsed dye laser compared to intense pulsed light therapy for rosacea

Long pulsed dye laser compared to intense pulsed light therapy for rosacea						
Patient or population: participants with rosacea **Intervention:** long pulsed dye laser **Comparison:** intense pulsed light therapy						
Outcomes	**Anticipated absolute effects* (95% CI)**		**Relative effect (95% CI)**	**№ of participants (studies)**	**Certainty of the evidence (GRADE)**	**Comments**
	Risk with intense pulsed light therapy	**Risk with long pulsed dye laser**				
HRQoL - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of LPDL on quality of life when compared with IPL
Participant-assessed improvement in rosacea severity Assessed with: VAS (0 being a poor and 10 an excellent result) Follow up: mean 18 weeks [3]	Median was 8 (2-10) for LPDL group and 7 (2-10) for IPL group (10 and 90% percentiles)(investigators reported P = 0.05)		-	40 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 4]	LPDL may may result in a small effect that may not be an important improvement of participant-assessed rosacea severity when compared with IPL
Proportion of participants with adverse event Assessed with: Pain with VAS scale Follow up: mean 18 weeks [3]	Median was 4 (2-6) for LPDL group and 7 (2-10) for IPL group (10 and 90% percentiles) (investigators reported P < 0.001)		-	40 (1 RCT) [1]	⨁⨁⨀⨀ **LOW** [2 4]	LPDL appears slightly less painful when compared with IPL
Physician-assessed improvement in rosacea severity - not measured	No study addressed this outcome		-	-	-	We are uncertain about the effect of LPDL on physician-assessed improvement of rosacea severity when compared with IPL
Assessment of erythema or telangiectasia Assessed with: 5 point Likert scale Follow up: mean 18 weeks [3]	At the LPDL treated side 18 had an excellent (75-100% vessel clearance) response and 12 a good response (50-74% clearance) and at the IPL treated sides 11 had an excellent response and 19 a good response		-	40 (1 RCT) [1]	⨁⨁⨁⨀ **MODERATE** [4 5]	LPDL likely results in a small effect that may not be an important reduction in erythema when compared with IPL

Lesion count - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of LPDL on lesion counts when compared with IPL
Time until improvement - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of LPDL on time until improvement when compared with IPL
Duration of remission - not measured	No study addressed this outcome	-	-	-	We are uncertain about the effect of LPDL on duration of remission when compared with IPL

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Footnotes

[1] Nymann 2010

[2] Downgraded one level for serious risk of bias (participants were not blinded)

[3] Within-participant design

[4] Downgraded one level for serious imprecision (small sample size)

[5] Not downgraded for risk of bias as "Clinical efficacy was evaluated by one blinded trained physician"

Additional tables

1 Glossary of unfamiliar terms

Term	Definition
Acne	A skin condition characterised by the inflammation or infection of sebaceous glands (usually attached to hair follicles) resulting in comedones (whiteheads and blackheads) and inflammatory lesions such as papules (pimples), pustules, and nodules
Bacillus oleronius	A bacteria found in Demodex mites
Bacterial resistance	Resistance of a micro-organism to an antimicrobial drug that was originally effective for treatment of infections caused by this micro-organism
Body dysmorphic disorder	An anxiety disorder surrounding perceived flaws in one's own appearance
Cytokine	A small protein released by cells, and having a specific effect on the behavior of other cells, or on the interactions or communications between cells
Demodex folliculorum	A species of face mite found in human hair follicles
Down-regulation	Process of reducing or suppressing a response to a stimulus
Epidermal barrier	The skin's front line of defence in the upper layer of the skin (the epidermis) against environmental factors such as UV light, chemicals, bacteria and other organisms and limits water loss from the body
Innate immune response	The first line generic defence of the immune system against infection and other organisms
Keratinocyte	A predominant cell type in the outermost layer of skin (epidermis), and when found in the basal layer, are referred to as 'basal cells' or 'basal keratinocytes'. Their main function is the formation of a barrier against environmental damage
Matrix-Metalloproteinases	Zinc dependent enzymes that promote break down of proteins like collagen. They regulate various inflammatory and repair processes
Neurovascular dysregulation	A failure of the vascular response, vasodilation, and neurosensory symptoms to regulate properly Dysfunction of both nerves and vascular elements, controlling the calibre of blood vessels
Nodule	Solid, raised area in or under the skin
Nodularities	An increased density of tissues
Pathophysiology	The functional changes that accompany a particular syndrome or disease (combined terms of ‘patho’ (path, related to disease) and ‘physiology’ (a branch of biology that

	specialises in the study of the functions of living organisms and their parts)
Phototype	A classification of skin type based on a person's sensitivity to sunlight
Pustule	A small bump on the skin containing purulent material (pus) in the top layer (epidermis) or beneath it (dermis)
Reactive oxygen species (ROS)	Chemically reactive molecules containing oxygen, or oxygen-derived radicals, having important roles in cell signalling (communication and interaction) and homeostasis (the maintenance of a steady state)
Retinoids	Chemical compounds related chemically to Vitamin A
Stratum corneum	The outermost layer of the epidermis
Stye	A bacterial infection of a gland at the base of any eyelash, causing painful swelling on the inner or outer eyelid
Toll-like receptors	A class of proteins that play a key role in the innate immune system, activating immune cell responses

Footnotes

2 Pharmaceutical companies contacted

Name	Response	Additional	Comment
Bayer	Yes	Yes	Added information on Del Rosso 2010 Christopher Billis <christopher.billis@bayer.com> and that ongoing studies were not yet published
Roche	Yes	No	-
ASTA Medica	Yes	No	-
Merck	Yes	No	-
Dumex-Alpharma	Yes	No	-
Galderma	Yes	Yes	Patricia.VanLith@galderma.com, michael.graeber@galderma.com August 2014 several times contact with Galderma NL, France and US, provided lots of extra information regarding brimonidine and ivermectin 2016 Galderma, Gregor Schaefer about study Berlin 2015, no additional info received
AHP Pharma	No	No	-
Yamanouchi	No	No	-
Dermik Laboratories	No	No	-
CollaGenex	No	No	Taken over by Galderma

Footnotes

3 Investigators contacted

Name	Response	Additional	Comment
Akhyani 2008	Yes	Yes	mghiasi@sina.tums.ac.ir. (sequence generation and allocation concealment) "In efficacy of azithromycin vs. doxycycline in the treatment of rosacea: a randomised open clinical trial" Patients were allocated to the trial using a randomised numbers table. Unfortunately this trial was not blinded" "The randomised number table generated by computer. The list was only in access of physician, and patients could not see that
Altinyazar 2005	Yes	Yes	After email contact with the primary investigator and following on from discussion between the review authors, this was judged to be quasi-randomised, i.e. a CCT
Arman 2015	Yes	Yes	ddemirseren@yahoo.com (sequence generation and allocation concealment) Replies 6-3-2018 We used “Restricted Randomisation Technique “ to divide the patients into two treatment groups. For this we used two letters; A meaned first patient will be in group 1; following patient will be in group 2. B meaned first patient will be in group 2; following patient will be in group 1. We always drew a lot for the first patient whether A or B to determine the group type and the following patient got the other group. This method enabled us to assign patients into treatment groups randomly and prevent selection bias. Group 1 was the topical Cyclosporine treatment ; group 2 was oral doxycycline treatment group. Patients were informed about their treatment methods and durations.
Baumann 2018	No	No	23-5-2018 lsb@derm.net (allocation concealment and blinding). 14-6-2018 sent again
Benkali 2014	Yes	Yes	nathalie.wagner@galderma.com, 1-8-2014 (sequence generation and allocation concealment) 1) Regarding the allocation sequence generated for the 4 subsequent groups consisting of different doses or regimen for topical applications, the randomisation list was

			created before the study started, with a 1:1:1:1 ratio and block size of 4. This randomisation list was generated by a designated biostatistician and was distributed to the clinical supply team in a sealed envelope (see the attached pdf file for the randomisation memo) 2) As explained above, only the 4 arms treated with topical products were to be randomised. The block size of 4 was not known by the sites, so foreseeing the next allocation was possible but unlikely. Since the study had 2 treatment groups for QD regimen and 2 treatment groups for BID regimen, subjects and the personnel who distributed the medication necessarily knew this information Of note, the primary objective of this study was PK assessment (and not efficacy), an objective measure, and the primary comparison was topical versus eye drop which was in no way planned to be randomised or blinded 3) This study was not posted on CT.gov since it was classified as a phase 1 study
Berardesca 2008	Yes	Yes	Berardesca@berardesca.it. After email communication with the investigators to clarify aspects of trial conduct, the criterion for sequence generation was changed from UNCLEAR to High risk, i.e. the study was not a RCT and participants appear to have been allocated to the intervention by alternation
Berardesca 2012	Yes	Yes	18-8-2014 maurizio.caserini@polichem.com (sequence generation and allocation concealment and blinding) 29-9-2013 replies 1. This was a randomised, double-blind, parallel-group, placebo-controlled study Patients, having signed their informed consent and who satisfied all inclusion and exclusion criteria at inclusion visit were randomly assigned to one of two treatment groups (P-3075 cream, placebo), according to a computer-generated randomisation list Patients were sequentially assigned to the next available randomisation number, starting from the lowest number provided to each investigational site Furthermore, for ethical reason, in order to minimise the exposure to placebo, randomisation was unbalanced between the P-

			3075 and placebo groups with a 2:1 ratio using blocks of 3 treatments 2/3. The double blind study design was guaranteed by the use of placebo cream units, which were identical to the active product in terms of size, shape, volume, colour. The tubes (P-3075 and placebo) were identically labelled for clinical use as it is in a double-blind procedure 4. Thank you for this observation (you are the first). We confirm that the correct value is -167.00 and not 167.00, as reported in our database. It was a typing error that was not detected when the manuscript was transformed in draft paper by the editor 5. As described in the paper, a 4-point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) was used by the investigators at each visit for the clinical evaluation of erythema The results at Day 28 (end of treatment) showed that, in the P-3075 group, erythema was absent in 27 patients (96.4%) and mild in 1 (3.6%), while in the placebo group, erythema was absent in 9 patients (64.3%) and mild in 5 (35.7%). There were no cases of moderate or severe intensity at Day 28 in both groups. The statistically significance values were reported in the paper as you underlined. For completeness the baseline clinical assessment for erythema was as follows: for P-3075 absent in 7 patients, mild in 14, moderate in 6 and severe in 1 and for placebo absent in 3 patients, mild in 6 and moderate in 5
Berlin 2015	Yes	No	To Dr Winkelman and Galderma for more data, they are working on it
Beutner 2005	Yes	Yes	kbeutner@anacor.com and bcalvarese@dowpharmsci.com, LAmdahl@dowpharmsci.com. Useful additional information provided by primary investigator, on randomisation, allocation concealment and characteristics of patients
Braithwaite 2015	Yes	Yes	Irene Braithwaite Irene.Braithwaite@mrinz.ac.nz 3-4-2018 (sequence generation, allocation concealment and blinding and baseline data DLQI) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details:

			1. the method used to generate the allocation sequence 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 3. How were outcome assessors blinded? 4. Can you provide us with DLQI data at baseline per group and at the prespecified follow-up data?(especially at 8 weeks) 5. Can you provide us with VAS-S and VAS-CS data at baseline per group and at the prespecified follow-up data?(especially at 8 weeks) 17-4-2018 sent again 19-4-2018 response "I am just ensuring there are no organizational limitations to sending you the data, and hope to be responding to you formally shortly." 30-4-2018, received data
Bribeche 2015	Yes	Yes	'ridha.bribech@gmail.com' 30-8-2014 Dear professor Bribeche (allocation concealment and blinding) reply 7-9-2014: 1- During enrolment we used an allocation randomiser programme: http://www.randomizer.org/ 2- Only the participants were blinded to treatment, praziquantel ointment and the placebo had the same colour (white), and ointment were given to participants in identical boxes for both groups (white box with a blue cover) Next mail 7-9-2014: The reply to our first question is more on sequence generation, and not concealment of the allocation. Who was responsible for using that programme and who had access to the generated list? Reply 10-9-2014: Me and professor Fedotov VP, were responsible for using this programme, both of us had access to the generated list and a doctor from our department (Dr Makurina); who was fully unaware of the aims of the study and overseen the enrolment
Buendia-Bordera 2013			Can't find mail address, sent invite on LinkedIn

Cunliffe 1977	No	No	-
Dahl 2001	Yes	Yes	Dahl.MarkV@mayo.edu."Subjects will be randomised to 1 of the 2 treatment groups at a ratio of 1:1. The randomisation process will be done in blocks of 4, stratified by investigators. The randomisation will be carried out using SAS PROC PLAN"
Dayan 2017	No	No	sdayan@drdayan.com 4-4-2018 ((allocation concealment and blinding baseline data patient satisfaction, patient global assessment and physicians global assessment) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 2. How were patients and outcome assessors blinded? 3. Can you provide us with patients satisfaction data at baseline per group (as data start one week after treatment) 4. Can you provide us with patients global assessment data at baseline per group and at the prespecified follow-up data for saline group?(now only for the 3 persons on active treatment provided in Table 2) 5. Can you provide us with physicians global assessment data at baseline per group and at the prespecified follow-up data for saline group?(now only for the 3 persons on active treatment provided in Table 2) 17-4-2018 sent again
Del Rosso 2010	Yes	Yes	jqdelrosso@yahoo.com, 1-8-2014 (sequence generation, allocation concealment) Chris Billis [Christopher.billis@bayer.com]; Keith Flanders [keith.flanders@bayer.com] 15-8-2014 Randomisation was done centrally by the generation of a randomisation list using the randomisation program RANCODE (version 3.6). Randomisation used blocks. Whole randomisation blocks were allocated to each site. In each study site, each newly enrolled patient was allocated to study

			medication with the lowest randomisation number available in that particular site at the subjects baseline visit. The patient randomisation number was entered into the CRF immediately after allocation. Each patient retained the randomisation number originally allocated at Baseline for the duration of the study Six drug tubes (tubes with a blinded label to cover the trademarks) and 3 bottles were packaged by a CMO in individual numbered kit boxes. Each patient was issued an individual numbered kit box containing 6 tubes and 3 bottles of study materials. The study drug was not to be dispensed by the investigator, but was dispensed by and returned to qualified study personnel (e.g., practice or clinic nurses) not involved with the selection and the assessment of the patients. At the control visits after Weeks 4, 8 and 12, patients returned empty, partially used, and unused containers to qualified study personnel before being examined by the investigator. Study drug compliance was assessed by the qualified study personnel. The patient was advised not to discuss the treatment schedule with the investigator 19-8-2014 sent additional mail regarding SD of lesions 3-9-2014, resent, received 4-9-2014
Di Nardo 2016	Yes	No	adinardo@ucsd.edu 4-4-2018 (sequence generation, allocation concealment and blinding and number of inflammatory lesions at baseline) To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1.. the method used to generate the allocation sequence 2. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!) 3.How were patients and outcome assessors

			blinded? 4. Can you provide us with number of inflammatory lesions at baseline per group and at 12 weeks? 17-4-2018 sent again Reply 17-4-2018 "Thank you for your email.But I was not involved in the clinical sample collection, my lab did the bio marker evaluations" We asked to forward to someone who does have the info
Dreno 1998	Yes	No	Old study, no further data available
Draelos 2005b; Draelos 2006	Yes	Yes	zdraelos@northstate.net. On 2006. Sequence generation? "Subjects were randomised based on the order in which they presented to the office". Allocation concealment? "The research coordinator maintained the blind which was not shared with anyone, including the investigator." 5 dropouts but in which group? The dropouts were for personal reasons, not related to product. They were random between the groups On 2005 Sequence generation? "Subjects were randomised based on severity of disease and the order in which they presented to the office". Allocation concealment? 'The research coordinator maintained the double blind." Dropouts? "The drop outs were one in each group."
Draelos 2009	No	No	zdraelos@northstate.net, 2-8-2014 (sequence generation and allocation concealment and blinding, how many randomised to each group, separate data for participants with rosacea? losses to follow-up?) 9-8-2014 sent again. No reaction
Draelos 2013a	Yes	Yes	zdraelos@northstate.net, 2-8-2014 (blinding and details on RosaQoL data) Reply 2-8-2014 This was the pivotal trial for FDA approval. The blind was maintained by dispensing the vehicle and the vehicle plus the active in identical containers. I do not have more detail on the QOL scores
Draelos 2013b	Yes	Yes	zdraelos@northstate.net (sequence generation, stratification and allocation concealment and blinding) Reply 2-8-2014 I will answer your questions below: 1. the method used to generate the allocation

			sequence as “were divided equally into two groups” does not seem at random. Subjects were randomised in two balanced populations based on a computer generated randomisation sequence 2. How was stratification done during the sequence generation? That is, can you describe the method used to generate the allocation sequence in sufficient detail to allow us an assessment of whether it should produce comparable groups stratified for demographics and presence and severity of acne, eczema, rosacea and atopic dermatitis? The data for each person was entered into a database and then the computer randomisation balanced the two groups for all of the characteristics you have mentioned 3. the method used to conceal the allocation sequence to ensure that intervention allocations could not have been foreseen in advance of, or during, enrolment i.e. participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). I realize that randomisation and blinding are not the same. The products were identically packaged 4. How were the investigators and participants blinded to the treatment the participants received? Yes, both the investigator and the participant did not know the product identity which was concealed through identically appearing products packaged identically 5. Are there separate data for women on rosacea? No, the data was not analysed in this fashion. follow-up mail that allocation concealment is not yet satisfactorily answered 9-8: sent again, no reply
Draelos 2015	No	No	Bayer, mailed via website 22-7-2014 15-8-2014: Christopher Billis <christopher.billis@bayer.com>, resent 15-8-2014, not published and no additional info
Ertl 1994	Yes	No	Dr Levine, study 17 years old, no further data available
Fabi 2011	No	No	sfabi@gbkderm.com 2-8-2014 (sequence generation and allocation concealment and dropouts?)

			Follow-up mail 11-8-2014 and 17-8-2014, no reply
Faghihi 2015	No	No	23-9-2014 G_faghihi@med.mui.ac.ir, p_khosravani@resident.mui.ac.ir My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already completed or submitted for publication. IRCT2014010516079N1 “Comparison of dapsone 5% Topical gel with metronidazole 0.75% efficacy in combination with oral doxycycline in papulopustular rosacea”. Can you tell us if IRCT2014010516079N1 is already completed? Or submitted for publication? 25-5-2018 G_faghihi@med.mui.ac.ir; p_khosravani@resident.mui.ac.ir (allocation concealment)
Fowler 2007	Yes	Yes	fowlerjoe@msn.com and christian.loesche@galderma.com. "Randomisation was done by using a computer generated table provided by the sponsor. Neither subjects nor investigators and study staff had any control over this"
Fowler 2012a; Fowler 2012b; Fowler 2013a; Fowler 2013b	Yes	Yes	fowlerjoe@msn.com and Jean Jacovella (Jean.JACOVELLA@galderma.com) 22-8-2014, 27-8 Asked for separate exact data of PSA and CEA at different time points, wash-out period and details on AE Received replies 25-9-2014
Fowler 2013a	Yes	Yes	20-7-2014 asked Galderma if it is published (Patricia van Lith) is this Fowler 2013? 28-7-2014 confirmed (NCT01355471 and NCT01789775 are the same studies) Received replies 25-9-2014
Freeman 2012	Yes	Yes	'summer.moon@med.lecom.edu' 3-8-2014 (sequence generation and allocation concealment and blinding) Follow-up mail 11-8-2014 reply 12-8-2014 1) Random selection by study coordinator 2) Medication and placebo allocation was the responsibility of the study coordinator who randomly selected which product to provide each subject (2:1 ratio). The investigators were

			unaware of the selection process and the study coordinator was not privy, prior to selection of product, of the type or severity of disease of any subject 3) Investigators were not privy to the medication/placebo selection process. No medication tubes were shown to the investigators. No questions were asked about the topical product (i.e. Odor, color or feel). There was no communication between the study coordinator and the investigators regarding the medication/placebo selection follow-up mail 12-8-2014 Regarding 1) this answer still does not inform us the method, so what method did the study coordinator used? Regarding 2) You describe that the investigators were unaware of selection process, but if the study coordinator was aware who received what, then the allocation was NOT concealed, even if he was not privy Regarding 3) if the patients knew what they received they could tell the investigators, as slip of the tongue. So it might be that study coordinator did not say anything, the patients could say something to the investigator. So was there any possibility that patients knew what they received? And if not why not? Why did they not know what they received (as stated as double-blinded) Response: 12-8-2014: Randomisation: every third patient was given placebo to create a 2:1 ratio Follow-up mail: then it is not truly randomised but quasi-randomised as you know every third patient gets placebo it is no longer at random and we have to exclude the study
Frucht-Pery 1993	No	No	-
Gollnick 2010	Yes	Yes	3-8-2014 harald.gollnick@med.ovgu.de christoph.willers@almirall.com (sequence generation and allocation concealment clarification of N) 5-9-2014 follow-up, and received replies with clear information
Heitz 2014	Yes	No	19-3-2018 response <Bernard.Cribier@chru-strasbourg.fr> "I had the answer from Pr Sauer: this study has not been published."

Huang 2012	No	No	18-7-2014 lglzsj@163.com (sequence generation and allocation concealment) 9-8-2014 follow-up mail and 17-8-2014, no reply
Jackson 2007	No	No	-
Jackson 2013	Yes	Yes	jacksonjmark@gmail.com 9-8-2014 1. The dropouts are noted below: 5 total Two adverse events were classified as possibly related to the study medication – an upset stomach and generalized urticaria in separate patients both receiving ER minocycline + azelaic acid 15%. Four adverse events in three patients (all receiving ER minocycline + azelaic acid 15%) were severe but not suspected to be related to the study medication (bilateral oophorectomy with dermoid cyst removal, gastric erosion after lap band surgery, a severe respiratory infection, and cholecystitis) 2. The CEA was a scale of 0 to 4 so there was a typo on 295. The IGA went from 0 to 5. As for the total CEA it was a combined number of the CEA for each location of the face as per the table below APPENDIX B Clinician's Erythema Assessment Scale ERYTHEMA Definition 0 None No redness present 1 Mild Slight pinkness 2 Moderate Definite redness 3 Significant Marked erythema 4 Severe Fiery redness ERYTHEMA Score • Check one box for each area of the face based upon the definitions given above • Enter the Erythema Score for each area of the face • Sum all of the individual Erythema Scores to obtain the Total Erythema Score Erythema Score Forehead Chin Nose Right Cheek Left Cheek none (0) none (0) none (0) none (0) none (0) mild (1) mild (1) mild (1) mild (1) mild (1) moderate (2) moderate (2) moderate (2) moderate (2) moderate (2) significant (3) significant (3) significant (3) significant (3) significant (3) severe (4) severe (4) severe (4) severe (4) severe (4)
Jansen 1997	No	No	-
Jorizzo 1998	Yes	No	-

Karabulut 2008	Yes	Yes	dr.aa.karabulut@gmail.com. After email contact with the primary investigator this study was excluded
Karsai 2008	No	No	-
Kendall 2014	Yes	Yes	james.kendall@galderma.com 6-8-2014 (sequence generation and allocation concealment and blinding and dropouts) 9-9-2014 reply: I did not receive your previous e-mails as my address is jim.kendall@galderma.com 70 patients were enrolled in the study. Two subjects withdrew from the study and they were both in the brimonidine tartrate gel 0.5% treatment group in phase 1 and did not enter phase 2. One for an adverse event and one for a protocol deviation
Kim 2017	No	No	im1177@hanmail.net 29-4-2018 (sequence generation, allocation concealment and blinding) We are conducting an update of our review on interventions for rosacea. Your study published in Dermatologic Surgery 2017 “Comparative Efficacy of Radiofrequency and Pulsed Dye Laser in the Treatment of Rosacea” might be eligible. To enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to generate the allocation sequence 2. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 3. How were outcome assessors blinded? resent 28-5-2018
Kircik 2018	No	No	29-4-2018, dr Kircik wedoderm@yahoo.com (allocation concealment and blinding) We are conducting an update of our review on interventions for rosacea. Your study published in JDD 2018 “Pivotal Trial of the Efficacy and Safety of Oxymetazoline Cream 1.0% for the Treatment of Persistent Facial Erythema Associated With Rosacea: Findings from the First REVEAL Trial.” might be eligible. To

			enable us to further assess this trial for inclusion I would be obliged if you could you kindly provide us with the following missing trial details: 1. the method used to conceal the allocation sequence to ensure that **intervention allocations could not have been foreseen in advance of, or during, enrolment** ie participants and investigators enrolling participants could not foresee the upcoming assignment (this is not the same as blinding!!). 2. How were patients and outcome assessors blinded? (it states double-blind but method not described) Resent 23-5-2018
Koch 1999	Yes	No	Appeared to be wrong R Koch
Koçak-Altintas 2005	Yes	Yes	After extensive email contact, clarified as a CCT
Krishna 2015	No	No	rajesh_krishna@merck.com 1-5-2018 (sequence generation, allocation concealment and blinding) Resent 23-5-2018
Kuang 2018	Yes	Yes	kuang_amy@allergan.com 1-5-2018 (sequence generation, allocation concealment and blinding) The method used to generate the allocation sequence • The randomization scheme was prepared by Allergan's Biostatistics group • Patients were then randomized via automated interactive voice response system/interactive web response system (IVRS/IWRS), which was used to manage the randomization and treatment assignment The method used to conceal the allocation sequence to ensure that intervention allocations could not have been forseen in advance of, or during, enrollment ie, participants and investigators enrolling participants could not forsee the upcoming assignments (this is not the same as blinding). • The IVRS/IWRS was used to manage the randomization and treatment assignment • At the time of randomization, the IVRS/IWRS provided the site with specific

			study medication kit number(s) for each randomized patient, corresponding to the treatment How were the patients and outcome assessors blinded? • Prior to initiation, each patient who provided informed consent was assigned a patient number; the patient identifier was used on all subsequent study documents • The investigator, investigator staff, and patients were masked to study medication • Study medication was provided in identical tubes and cartons and labeled with medication kit numbers • At time of randomization, the IVRS/IWRS provided the site with specific study medication kit number(s) for each randomized patient, corresponding to the treatment group assigned via central randomization Sites dispense study medication according to IVRS/IWRS instructions
Laquieze 2007	No	No	-
Layton 2015	Yes	Yes	21-7-2014 asked Galderma if it is published (Patricia van Lith) several follow-up mails also to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 august with several people of Galderma including Maria-Jose Rueda and Jean Jacovella 19-8-2014 received poster abstracts Layton 2014
Lebwohl 1995	Yes	No	Old study, no further data available
Leyden 2011	Yes	No	jjleyden@mindspring.com 7-8-2014 (sequence generation and allocation concealment) Reply 12-8-2014: I am now Emeritus and mostly out of the loop and my clinical research nurse has retired. Nobody in the clinical trials unit was there when that study was done and I can't get the details you are asking for Sorry! Jim Leyden
Leyden 2014	Yes	Yes	19-7-2014, info@sol-gel.com Ofer.Toledano@sol-gel.com My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure

			if it is already published? NCT00940992 “A Study of DER 45-EV Gel to Treat Rosacea (SGTDER45EV)”. Can you tell us if the NCT00940992 is published and if so give us a pdf of the publication? Reply 19-7-2014 Ofer.Toledano@sol-gel.com, Gaby.Peleg@sol-gel.com . The study results were published by James Leyden in the JDD (journal of drugs in dermatology) in June 2014, volume 13, issue 6, p.685
Luger 2015	Yes	Yes	Mderma@uni-muenster.de (allocation concealment and blinding) Reply 18-8-2014 The generation of the random code list was performed in a validated environment by an independent CRO not involved in study conduct and monitoring using the software RANCODE Version 3.6. Central randomisation was performed by this CRO. For eligible subjects, investigators called the randomisation centre and provided the patient’s identification number and gender. Patients were subsequently randomised and the study centre was notified of the treatment number of the patient via telefax by the randomisation centre. Treatment allocation provided by the central randomisation service was documented in the CRF and monitored. ad 2) The investigational product and its matching vehicle had a similar appearance and all subject kits were packaged in the same way. The randomisation list was kept strictly confidential. It was accessible only to authorized persons who were not involved in the conduct, monitoring and analysis of the study, until time of unblinding. Based on the randomisation list, sets of sealed individual code envelopes were prepared for emergency procedures. No emergency unblinding occurred during the study
Lupin 2014	No	No	Ulthera, Inc. Mark Lupin, M.D 23-7-2014 info @cosmedica.ca office@cosmedica.com, sent several mails no reply (sequence generation and allocation concealment, dropouts)
Martel 2017a	No	No	philippe.martel@galderma.com 2-5-2018 (sequence generation, allocation concealment and blinding and drop-outs in study A) Resent 23-5-2018

Mostafa 2009	No	No	S Mokadem no response
Neuhaus 2009	No	No	-
Powell 2005	Yes	No	-
Raoufinejad 2016	Yes	No	23-9-2014 kosaraoofi@yahoo.com; kosaraoofi@gmail.com; mehdirj@aol.co.uk My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already submitted for publication. IRCT2014030416837N1 “Effects of permethrin 5% topical gel in comparison with placebo on Demodex density in rosacea patients: a double-blind, randomised clinical trial”. Can you tell us if IRCT2014030416837N1 is already submitted for publication? Reply: 23-9-2014 Dear Dr Zuuren Many thanks for your query, We are in the process of completing and submitting the article. Regards, Mehdi
Rigopoulos 2005	No	No	-
Sainthillier 2005	No	No	-
Salem 2013	No	No	dr_doaasalem@yahoo.com 10-08-2014 Resent 17-8-2014 and 3-9-2014 (sequence generation and allocation concealment and blinding), no replies
Sbidian 2016	Yes	Yes	olivier.chosidow@hmn.aphp.fr and emilie.sbidian@hmn.aphp.fr,18-7-2014 Is the NCT00882531 published and if so give us a pdf of the publication? Reply 18-7-2014 "Hi Esther, we are still in processing the manuscript and hope submitting the paper before the end of 2014" and "We could send your our submitted manuscript?" 2016: "isotretinoin and placebo capsules looked similar, and had similar packages"
Seité 2013	Yes	Yes	sophie.seite@loreal.com 16-7-2014 (sequence generation and allocation concealment and blinding, dropouts) Reply 12-8-2014: 1. The allocation sequence was generated by a statistician using a specific software

			2. As soon as they have been recruited (because they answered to the inclusion criteria) by the investigating dermatologist (only one = Dr Zelenkova) a number given chronologically, as indicated in the allocation sequence purchase to the investigator, was attributed to the patient (the first was the N°1, the 2nd the N° 2…) 3. After enrolment and at the end of the 1st visit, a nurse (in the absence of the investigating dermatologist) give the products allocated to the patient's number. Both products was in the same packaging (blind white packaging) without any indication about formula reference (only reference of study and number of patient) and some information about use (topical use only…) 4. None dropped out between the stop of metronidazole treatment (Week 8) and the end of the study (week 16). 67 patients were included before metronidazole treatment, 1 dropped out due to irritative dermatitis at day 53 (before the end of the 8-week Metronidazole treatment); So 66 patients remained after 8 weeks, 32 received the test formula and 34 the vehicle 5. More detail about the 66 patients included in this study are available (see below (printscreens)) 25-8-2014, received additional info on Investigator's assessments
Seo 2016	No	No	12-5-2018 susini@naver.com (sequence generation and allocation concealment and blinding) Resent 25-5-2018
Sharquie 2006	No	No	-
Stein 2014b	Yes	Yes	19-7-2014 asked Galderma if NCT01493687 it is published and looks the same as NCT01494467 (Patricia van Lith), confirmed 28-7 are the same and are Stein Gold MLSTEIN1@hfhs.org and Jean.JACOVELLA@galderma.com on details DLQI and SDs 3-9-2014, received data
Stein-Gold 2017	Yes		15-5-2018 STEIN1@hfhs.org; Nabil.kerrouche@galderma.com; Gregor.SCHAEFER@galderma.com

			(sequence generation and allocation concealment and blinding) Resent 22-5-2017
Stein-Gold 2018 withdrawn	No	No	Allergan clinicaltrials@allergan.com seems the same as NCT02131636 which I did NOT add? **NCT02131636** Efficacy and Safety of AGN-199201 in Patients With Persistent Erythema Associated With Rosacea **NCT02132117** Safety and Efficacy of AGN-199201 in Patients With Persistent Erythema Associated With Rosacea Also **NCT02095158** Longterm and efficacy and safety clinicaltrials@allergan.com sent several mails, to ask if these are same studies, no replies
Taieb 2015	Yes	Yes	19-7-2014 asked Galderma if NCT01493947 is published (Patricia van Lith), confirmation 28-7-2014, EADV abstract 2014 alain.taieb@chu-bordeaux.fr (sequence generation and allocation concealment and blinding, dropouts) Response 19-8-2014 The study was a parallel group study of 960 subjects; however 1800 kit numbers are randomised in blocks of 6. The RANUNI routine of the SAS system was used to randomly assign, in balanced blocks, kit to a treatment (Ivermectin 1% cream, Metronidazole 0.75% cream). Prior to the start of the study, a randomisation list was generated by the statistician and was secured with restricted access. Treatment assignment was balanced into consecutive blocks in a 1:1 ratio and kit numbers were assigned sequentially in chronological order. The study design was investigator-blinded. The integrity of the blinding was ensured by packaging the products in identical tubes, not allowing the investigator and subject to discuss study treatments, and requiring a third party other than the investigator to dispense the medication. Study population and causes for withdrawal are summarised in the figure below
Thiboutot 2003a; Thiboutot 2003b; Thiboutot 2008; Thiboutot 2009	No	No	19-7-2014 Alan Fleischer <afleisch@wakehealth.edu>My colleagues and I are updating our Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially

			eligible for inclusion, but not sure if it is already included in our review? NCT00417937 “A Multicenter Trial of a Topical Medication for Papulopustular Rosacea Applied Twice Daily Versus Once Daily”. Is this the same study as published in Thiboutot DM, Fleisher AB, Del Rosso JQ, Graupe K. Azelaic acid 15% gel once daily versus twice daily in papulopustular rosacea. Journal of Drugs in Dermatology 2008;7(6):541-6.? Or is it another one? Reply 19-7-2014: I do believe that this is the exact same study. Sorry that my name appears in lots of clinical trials settings (Thiboutot 2008)
Tirnaksiz 2012	No	No	figentirnaksiz@gmail.com 17-8-2014 ((sequence generation and allocation concealment) resent 3-9-2014 no reply
Torok 2005	Yes	Yes	helenmtorok@aol.com. "The patients were not cognizant nor were they aware of the different formulations Nor their unique characteristics so they were easily utilized and dispensed in unmarked tubes". "Central randomisation that was computer generated"
Two 2014	Yes	Yes	rgallo@ucsd.edu 17-8-2014 (sequence generation and allocation concealment and blinding) resent 3-9-2014, received reply 4-9-2014 1. The allocation sequence was generated by an unblinded member of the study team who worked off-site in a separate laboratory to group in a 2-to-1 fashion, so that 8 of those numbers were assigned to the treatment group, and 4 to the control group. As subjects were enrolled in the study, they were sequentially assigned a unique study identification number from 1-12 by the blinded study coordinator, with the first subject to enrol in the study being assigned the study identification number of 1. The list matching study identification numbers to their corresponding treatment group was only accessible by this unblinded member of the study team 2. The allocation sequence was created prior to enrolling any subjects in the study, therefore ensuring that intervention allocations could not

			be foreseen in advance of, or during, enrolment 3. This study was conducted in a double-blind fashion so that both participants and investigators were blinded as to which intervention group participants were assigned. As stated previously, randomisation was completed by an unblinded member of the study team who worked off-site and had no contact with enrolled subjects. The list of treatment group assignments was stored on a password-protected computer accessible only to this unblinded study team member. This same unblinded member of the study team was also responsible for preparing all study medication. Once prepared, the study medication was placed into a bottle labelled with the participant's unique study identification number that was assigned to the participant at the time of enrolment in the trial. The unblinded study team member dispensed the bottles of prepared medication to the study's clinical coordinator, who was also blinded, for distribution to subjects. Both the treatment and the control creams were identical in appearance and viscosity so that the two drugs could not be distinguished by look or feel Resent regarding exact data IGE and CEA 12-9-2013 Received 12-9-2013 exact data + SD
Waibel 2016	No	No	'jwaibelmd@miamidermlaser.com' 21-5-2018, asked for more study data, published in full? other report? 4-6-2018 sent again
Wilkin 1989; Wilkin 1993	No	No	-
Wittpenn 2005	Yes	Yes	Additional information could not be used
Wittpenn 2005	Yes	No	jrwittpenn@aol.com, jwittpenn@ocli.net 16-7-2014 My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion (NCT00348335 "Efficacy of topical cyclosporin 0.05% for the treatment of ocular rosacea") Has this study ever been published as I could not find it? (I do have the 2005 one)

			Follow-up mail 11-8-2014 Reply: 12-8-2014 The study was discontinued when early results showed that we did not have a reproducible method of quantifying injection. It was far too variable and did not appear to correspond at all to patients reporting symptomatic improvement. John Wittpenn
Wolf 2006	No	No	-
Yoo 2011	No	No	ellen.marmur@mountsinai.org 18-8-2014 (sequence generation and allocation concealment and blinding) Resent 3-9-2014
Zhang 2017	No	No	wzx2003@163.com 22-5-2018 (sequence generation and allocation concealment and blinding) 5-6-2018 sent again
Zhong 2015	No	No	adelewu@medmail.com.cn 23-5-2018 (sequence generation and allocation concealment and more precise erythema data) 5-6-2018 sent again
EUCTR2006-001999-20-HU	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2006-003707-40-DE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2009-013111-35-DE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2010-018319-13-DE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2010-023566-43-DE	Yes	No	23-9-2014 Dr. Bertil Wachall, studien@infectopharm.com 2-10-2014 Thank you for your request concerning our permethrin rosacea trial (permethrin 5% and 2.5% vs metronidazole cream). Unfortunately, the data are not published or submitted up to now. We hope this will be done in the next months, but the principal investigator who is responsible for the publication seems to be very busy. In addition, please be informed that we are currently conducting another permethrin trial (permethrin 5% vs placebo cream) in PPR-patients. We expect the results of this trial in spring 2015 (we discussed with PI, study does

			NOT appear in EUCTR (EUDRACT-Nr. 2013-000979-32) Sent another mail 16-3-2018 Sent again 17-4-2018 Reply 18-4-2018 Unfortunately, we still don't have any news in direction of the publication of our permethrin rosacea studies. The results of the metronidazole controlled study ("PAROP" stopped after pilot phase) as well as the placebo controlled study ("PROPER") did not show clear results and are difficult to interpret. In addition, we don't believe that the corresponding principle investigator is still interested in a publication. Moreover, at Infectopharm the project was cancelled in the meantime.
EUCTR2011-002057-65-DE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2011-002058-30-DE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2012-001044-22-SE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
EUCTR2013-005083-26-DE	Yes	No	23-9-2014, sent e-mail to Galderma NL and several more to Galderma International, no reply
JPRN-UMIN000008315			Mari Wataya-Kaneda mkaneda@derma.med.osaka-u.ac.jp not sent mail as they are still recruiting
NCT00041977	Yes	No	Info@pariserderm.com 16-7-2014 My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion (NCT00041977 "A Multicentre, randomised, Double-Blind, Placebo-Controlled, Clinical Trial to Determine the Effects of Doxycycline Hyclate 20 Mg Tablets [Periostat(R)] Administered Twice Daily for the Treatment of Acne Rosacea") Has this study ever been published as I could not find it? If not, do you have a contact at CollaGenex Pharmaceuticals, as on the web site of clinicaltrials.gov this is not provided, but

			we found your name on it, also asked Galderma (Patricia van Lith) Follow up mail to Dr Pariser 11-8-2014 Reply 13-8: They sent me a study, but is not correct one, but on acne, so sent again request
NCT00249782	No	No	Allergan, results published on the Internet, as word doc and pdf we made several, but unsuccessful, attempts to contact Allergan
NCT00436527	Yes	No	19-7-2014, asked Galderma if it is published (Patricia van Lith), several follow-up mails also to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 august with several people of Galderma including Maria-Jose Rueda and Jean Jacovella
NCT00495313	Yes	No	Sent 16-7-2014 message via LinkedIn, and Galderma (Patricia van Lith) several follow-up mails also to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 august with several people of Galderma including Maria-Jose Rueda and Jean Jacovella
NCT00560703	Yes	No	16-7-2014, asked Galderma if it is published (Patricia van Lith) several follow-up mails also to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 august with several people of Galderma including Maria-Jose Rueda and Jean Jacovella
NCT00617903	Yes	No	18-7-2014 clinical-trials-contact@bayerhealthcare.com My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT00617903 “Exploration of Safety and Efficacy of AzA 15% Foam Twice a Day in Rosacea”. I found a study of Draelos published in 2013 in CUTIS, but that one included far more participants than the 84 mentioned in the NCT00617903 study. Can you tell us if the NCT00617903 is published and if so give us a pdf of the publication? 11-8-2014 follow-up mail 15-8-2014: Christopher Billis

			<christopher.billis@bayer.com>, resent 15-8-2014, not published and no additional info 13-3-2018 Never published
NCT00621218	No	No	18-7-2014 via website Valeant Pharmaceuticals who took over Coria Laboratories, asked if it is published
NCT00667173	No	No	18-7-2014 via website Valeant Pharmaceuticals who took over Dow Pharmaceutical Sciences, Inc, asked if it is published
NCT00697541	Yes	No	18-7-2014 asked Galderma if it is published (Patricia van Lith) several follow-up mails also to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 august with several people of Galderma including Maria-Jose Rueda and Jean Jacovella
NCT01016782	No	No	19-7-2014, mail though website Sandoz. My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT01016782 “Study of 0444 Gel in the Treatment of Inflammatory Lesions of Rosacea)”. Can you tell us if the NCT01016782 is published and if so give us a pdf of the publication?
NCT01125930	Yes	No	19-7-2014, maierl@med.umich.edu. My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT01125930 “Atralin Gel for the Treatment of Rosacea”. Can you tell us if NCT01125930 is published and if so give us a pdf of the publication? Reply 29-7-2014: Dear Dr. van Zuuren, The study has not yet been published yet. When it has been accepted for publication, I can notify you. Thank you, Lisa Maier 15-3-2018 sent again request for pdf of published study. mail address no longer correct!
NCT01134991	Yes	No	19-7-2014 dov@foamix.co.il. My colleagues and I are conducting a Cochrane review

			(Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT01134991 “Study to Evaluate the Safety and Efficacy of Topical Minocycline FXFM244 in Rosacea Patients”. Can you tell us if NCT01134991 is published and if so give us a pdf of the publication? Reply 21-7 Dov Tamarkin, Ph.D. dov.tamarkin@foamixpharma.com, study is still ongoing
NCT01186068	Yes	No	19-7-2014 fowlerjoe@msn.com My colleagues and I are updating our Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT01186068 “A randomised, double-blind, vehicle-controlled, parallel-group study of the dose-response profile of V-101 cream in subjects with erythematous rosacea” Can you tell us if the NCT01186068 is published and if so give us a pdf of the publication? (By the way we will include your dose-finding studies and phase III studies on brimonidine, and might need to contact you later about these. Follow-up 11-8-2014 beyer@sambrown.com Reply 12-8-2014 Dr Fowler: not published
NCT01257919	Yes	No	22-7-2014. Bayer sent though website, Novum, info@novumprs.com My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? The study was supported by Bayer and Novum are listed as "locations" on clinicaltrials.gov NCT01257919 “ Safety and Pharmacokinetics of Azelaic Acid Foam, 15% in Papulopustular Rosacea Can you tell us if the study has been published if so could I request a pdf of the publication? If not could we please access the data? 15-8-2014: Christopher Billis <christopher.billis@bayer.com>, resent 15-8-2014, not published and no additional info
NCT01426269	Yes	Yes	21-7-2014 asked Galderma if it is published (Patricia van Lith) several follow-up mails also

			to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 August with several people of Galderma including Maria-Jose Rueda and Jean Jacovella 5-9-2014: Warren.WINKELMAN@galderma.com. 22-9-2014, received all we needed
NCT01449591	Yes	Yes	Novartis Pharmaceuticals, no contact details, sent mail through Dutch website 12-8-2014 reply pieter.ekkel@novartis.com U vraagt om informatie over de studie NCT01449591 (CBFH772A2203) met als compound BFH772. De enige informatie die we nu kunnen delen over deze studie zijn gepubliceerd op 'Novartis clinical trial database', onder 'Novartis Institute for Biomedical Research', Dermatology/Skin, CBFH772 http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public 22-8-2014: What was the rationale behind study, are they going to proceed with further studies? will it be published? Reply 9-9-2014: BFH772 is currently under investigation and has not been approved for use other than for use as part of a clinical trial. Therefore, at this present time, no further information can be provided other than what is publicly available at the previously indicated location (http://www.novctrd.com/ctrdWebApp/clinicaltrialrepository/public) Whether or not results of trial NCT01449591 "Safety, Tolerability and Efficacy of BFH77s in Rosacea Patients" will be published in medical journals in the future cannot be anticipated at this stage. Please do not hesitate to reach out to us again in six months' time to inquire about potential updates, if of interest."
NCT01513863	Yes	No	19-7-2014 GDGongas@novumprs.com. My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT01513863 "A Therapeutic Equivalence Study of Two Metronidazole 1%Topical Gel Treatments for Patients With

			Rosacea (MTZG)". Can you tell us if NCT01513863 is published and if so give us a pdf of the publication? 21-7-2014 reply Aimee Brown, ABrown@novumprs.com. "Thank you Dr. Zuuren for your inquiry, however this study has not yet been published."
NCT01579084	No	No	Allergan, sent mail 22-07-2014 through website no response
NCT01631656	Yes	Yes	Amy McMichael, Wake Forest School of Medicine 23-7-2014 amcmicha@wakehealth.edu, amcmicha@wfubmc.edu (sequence generation, allocation concealment), several e-mail exchanges, no replies to this. They explained that they did not manage to get the paper published
NCT01659853	Yes	No	20-7-2014 asked Galderma if it is published (Patricia van Lith), 28-7-2014, not yet published, but I thought already submitted so sent another mail. several follow-up mails also to Maria-Jose Rueda marie-jose.rueda@galderma.com last 11-8-2014 Follow-up mails 14 August with several people of Galderma including Maria-Jose Rueda and Jean Jacovella
NCT01735201	No	No	Allergan, results posted on clinicaltrials.gov clinicaltrials@allergan.com, 23-7-2014 My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published, we saw results published on clinicaltrials.gov? NCT01735201 "AGN-199201 for the Treatment of Erythema With Rosacea". Can you tell us if NCT01735201 is published and if so give us a pdf of the publication? Follow-up 11-8-2014 and 17-8-2014 no replies Follow-up 15-3-2018
NCT01740934	Yes	No	Rock Creek Pharmaceuticals, Inc. M Varga, 23-7-2014 health@rockcreekpharma.com response 1-8-2014: Thanks very much for your interest in our just concluded clinical trial, we are in the process of writing the clinical study report. We will make it available to you. If you have additional question, please do not

			hesitate to contact me.Dr Ernest Okorie,MD gddssconsultant@gmail.com 15-3-2018 sent mail again 17-4-2018 again
NCT01784133	No	No	Cutanea Life Sciences, Inc 23-7-2014, info@cutanealife.com This study has been completed. My colleagues and I are conducting a Cochrane review (Interventions for rosacea) this study has been identified as potentially eligible for inclusion. Can you please indicate if the study has been published and if so could I request a pdf or the citation? If not are the data available? 10-8-2014 Resent e-mail
NCT01828177			PreCision Dermatology, Inc.Syd Dromgoole, as study is still ongoing not sent mail
NCT01933464			Anna Di Nardo, MD, PhD, University of California, San Diego. As study is still recruiting not sent mail
NCT01993446	No	No	Dermira, Inc. Beth Zib, info@dermira.com 23-7-2014 Follow-up 11-8-2014 no replies
NCT02036229			Rina Segal, Rabin Medical Center, rinas3@clalit.org.il not sent mail as not yet open to recruitment
NCT02052999	No	No	Amorepacific Corporation BeomJoon Kim, Professor Department of Dermatology, Chungang University Hospital, sent mail through website 23-7-2014 My colleagues and I are conducting a Cochrane review (Interventions for rosacea) and one of your studies have been identified as potentially eligible for inclusion, but not sure if it is already published? NCT02052999 “Study to evaluate the efficacy and safety of PAC-14028 cream in rosacea patients”. Can you tell us if NCT02052999 is published and if so give us a pdf of the publication? Study is performed by BeomJoon Kim
NCT02075671			George Washington University, Jack Short, jshort@mfa.gwu.edu as they are still recruiting, not sent mail
NCT02120924			Actavis Inc. John Capicchioni Akesis, LLC As they are still recruiting, not sent mail

NCT02144181 Evaluation of the Safety and Efficacy of the Ulthera® System for the Treatment of Signs and Symptoms of Erythematotelangiectatic Rosacea	No	No	Ulthera, Inc. Mark Lupin, MD is LUPIN 2014 part of this? As they are still recruiting, not sent mail e-mail sent 29-7-2014 to confirm, office@cosmedica.com Dear Colleagues I have received no further response could you please confirm with Dr Lupin?There appears to be a poster in JAAD 2014 vol17 Iss 5 referring to this trial? **NCT01756027** Evaluation of the safety and effectiveness of microfocused ultrasound with visualization (MFU-V) for the treatment of erythematotelangiectatic rosacea Mark Lupin, MD, The Department of Dermatology and Skin Science, University of British Columbia, Vancouver, Canada I also have this trial NCT02144181 which appears to be still recruiting and the contact person is Dr Mark Lupin Resent 22-8-2014 no replies
NCT02147691			Leon Kircik, M.D., Derm Research, PLLC wedoderm@yahoo.com As they are still recruiting, not sent mail
NCT02204254			Florence Le Duff, leduff.f2@chu-nice.fr, not sent e-mail as they are still recruiting

Footnotes

RCT = randomised controlled trial
CCT = controlled clinical trial (quasi-randomised)

4 Newly included studies for this update

	Newly included studies
1	Arman 2015
2	Baumann 2018
3	Berlin 2015
4	Bhargava 2016
5	Braithwaite 2015
6	Dayan 2017
7	Di Nardo 2016
8	Draelos 2015
9	EUCTR2006-001999-20-HU
10	EUCTR2006-003707-40-DE
11	EUCTR2009-013111-35-DE
12	EUCTR2010-018319-13-DE

13	EUCTR2011-002057-65-DE
14	EUCTR2011-002058-30-DE
15	EUCTR2012-001044-22-SE
16	EUCTR2013-005083-26-DE
17	Faghihi 2015
18	Han 2014
19	Heitz 2014
20	Jaque 2012
21	Kim 2017
22	Kircik 2018
23	Krishna 2015
24	Kuang 2018
25	Martel 2017a
26	Martel 2017b
27	Mrowietz 2018
28	NCT00560703
29	NCT00617903
30	NCT00697541
31	NCT01579084
32	NCT01735201
33	NCT02147691
34	NCT02300129
35	NCT03035955
36	Park 2016
37	Raoufinejad 2016
38	Sbidian 2016
39	Seo 2016
40	Stein Gold 2014c
41	Stein Gold 2014d
42	Stein-Gold 2017
43	van der Linden 2017
44	Waibel 2016
45	Zhang 2017
46	Zhong 2015

Footnotes

5 Checklist for describing and assessing patient-reported outcomes (PROs) in clinical trials

1. What were PROs measuring? a. What concepts were the PROs used in the study measuring? b. What rationale (if any) for selection of concepts or constructs did the authors provide? c. Were patients involved in the selection of outcomes measured by the PROs?
2. Omissions a. Were there any important aspects of health (e.g. symptoms, function, perceptions) or quality of life (e.g. overall evaluation, satisfaction with life) that were omitted in this study from the perspectives of the patient, clinician, significant others, payers, or other administrators and decision-makers?
3. If randomised trials and other studies measured PROs, what were the instruments' measurement strategies? a. Did investigators use instruments that yield a single indicator or index number, a profile, or a battery of instruments? b. If investigators measure PROs, did they use specific or generic measures, or both? c. Who exactly completed the instruments?
4. Did the instruments work in the way they were supposed to work - validity? a. Had the instruments used been validated previously (provide reference)? Was evidence of prior validation for use in this population presented? b. Were the instruments re-validated in this study?
5. Did the instruments work in the way they were supposed to work - ability to measure change? a. Are the PROs able to detect change in patient status, even if those changes are small?
6. Can you make the magnitude of effect (if any) understandable to readers? a. Can you provide an estimate of the difference in patients achieving a threshold of function or improvement, and the associated number needed to treat (NNT)?
Table 17.6.a Patrick D, Guyatt GH, Acquadro C. Chapter 17: Patient-reported outcomes. In: Higgins JPT, Green S (editors), *Cochrane Handbook for Systematic Reviews of Interventions* Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011.

Footnotes

6 Included studies with no usable or irretrievable data

Study ID	Interventions and comparisons	N	Comments
Benkali 2014	Four different concentrations brimonidine tartrate gel	102	None of our outcomes were addressed
Berlin 2015	Doxycycline 40 mg modified release versus placebo	?	Unclear how many were randomised. Poster, very limited data reported
Blom 1984	Sulphur 10% cream versus lymecycline	40	Unclear how many were randomised to each group,

			minimal reporting of outcomes. Participants who failed to respond or got worse were switched to the alternative treatment, unclear who and how many
Buendia-Bordera 2013	PDL + post-laser serum versus PDL + placebo gel	31	Poster, very limited data reported, not able to contact PI
Draelos 2006	Azelaic acid 15% gel + habitual self-selected skin cleanser and moisturizer versus azelaic acid 15% gel + standardised PHA (polyhydroxy acid) containing cleanser, and anti-aging moisturizer	67	None of our primary outcomes were addressed combined with that it was unclear how many participants were randomised to each intervention. Because very limited outcomes data were reported no reliable conclusions could be drawn
Draelos 2009	Facial foundation with niacinamide and N-acetylglucosamine, cleanser and moisturizer versus marketed foundation + cleanser and moisturizer	146	Poster, lot of data missing, PI did not reply to e-mail. Also included patients with sensitive skin, no separate data reported for participants with rosacea
Draelos 2013b	Gentle foaming cleanser containing hydrophobically modified polymers versus commercial gentle liquid non-foaming facial cleanser	40	Participants with other skin diseases (atopic dermatitis, eczema, acne) were included and no separate data reported for participants with rosacea
Ertl 1994	Isotretinoin + topical tretinoin versus topical tretinoin versus isotretinoin	22	Data unreliable, its re-analysis using the individual participant data confirmed its flawed analysis by the investigators
Espagne 1993	Metronidazole gel versus placebo gel	51	Allocation to intervention was based on up to four participants in each of 18 clinics but not all clinics enrolled four participants. The report did not provide any reassurance that the allocation sequence was adequately generated and no evidence that any form of central randomisation had been employed for the 18 clinics involved in this study
EUCTR2011-002058-30-DE	Diclofenac sodium 3% gel versus metronidazole 0.75% gel versus placebo	58	No precise data are provided only generic comments. Unlikely it will be published with more data

EUCTR2013-005083-26-DE	Brimonidine tartrate 0.5% gel versus placebo	34	Very limited and confusing data only on adverse events
Fabi 2011	IPL + azelaic acid versus IPL	20	Poster, very limited data reported, PI failed to respond to several e-mails
Guillet 1999	Metronidazole 75% gel versus metronidazole 0.75% lotion	114	Poster, very limited data reported, old study, not able to contact PI
Han 2014	PDL versus diode laser	25	Poster, very limited data reported, no separate data for rosacea
Heitz 2014	Azithromycin 500 mg three times a week versus doxycycline 100 mg/day	95	Poster, very limited data reported
Huang 2014	Doxycycline 40 mg versus placebo	170	Poster abstract, limited data, unclear how many were randomised to each group, PI failed to respond to several e-mails
Jorizzo 1998	Metronidazole versus placebo	277	Unclear how many participants were initially recruited. Unclear how many participants started in each group, no SDs, dropout rate unclear. Data seem very skewed
Kuang 2018	Various concentrations and dosages oxymetazoline versus vehicle	356	Pharmacokinetic study on plasma concentration. Only reporting on adverse events met our inclusion criteria, but adverse events of all active treatment arms were combined and no fair comparison between different concentrations and dosages could be made
Lupin 2014	MFU-V one treatment versus MFU-V two treatments	12	Poster abstract, limited data, unclear how many were randomised to each group, PI failed to respond to several e-mails
NCT00249782	Dapsone 5% gel QD vs dapsone 5% BID, versus metronidazole gel versus dapsone + metronidazole gel versus vehicle	400	Unclear how many were randomised to each group, Allergan failed to respond to several e-mails requesting further data
NCT00697541	Brimonidine facial gel versus brimonidine eyedrops	20	None of our outcomes were assessed

NCT01579084	Various concentrations AGN-199201 versus vehicle	64	AGN-199201 concentrations were unclear, no response received of Allergan
NCT01735201	Various concentrations AGN-199201 versus vehicle	356	AGN-199201 concentrations were unclear, no response received of Allergan
NCT02300129	Brimonidine facial gel versus placebo gel	34	None of our outcomes were assessed
NCT03035955	Azelaic acid versus no treatment	20	None of our outcomes were assessed
Rehmus 2006	Antiinflammatory cream versus placebo	40	Poster, no results provided, very limited data reported
Thiboutot 2005	Doxycycline versus placebo	134	Poster, lot of data are missing, PI did not reply to e-mail
Utaş 1997	Ketoconazole oral versus ketoconazole cream versus ketoconazole oral + cream versus placebo cream versus placebo pills	53	Letter, limited and no exact data
Van Landuyt 1997	Clonidine versus placebo	60	Interim report only on first 30 participants, incomplete and very limited data
Waibel 2016	KTP laser vs PDL laser	22	Poster, with incomplete and missing data
Wilkin 1989	Nadolol versus placebo, four arms, crossover, 3 periods	15	Small groups, unclear what dropout rate was. No separate data for period A
Wilkin 1993	Topical clindamycin versus tetracycline	43	Unclear how many participants were assigned to each group, dropouts not mentioned, no exact data provided
Wittpenn 2005	Topical ciclosporin A versus artificial tears	20	Unclear how many randomised to each group, poster with very limited data see also Table 3
Yoo 2011	PDL + calcium dobesilate versus PDL	6	Poster, with incomplete and missing data

Footnotes

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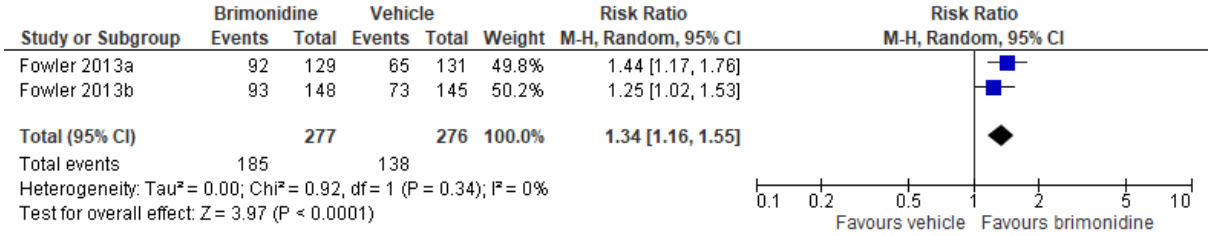
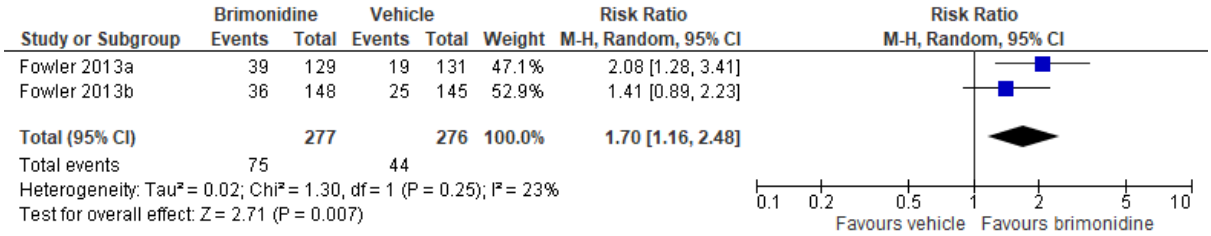
Data and analyses

1 Topical brimonidine versus vehicle

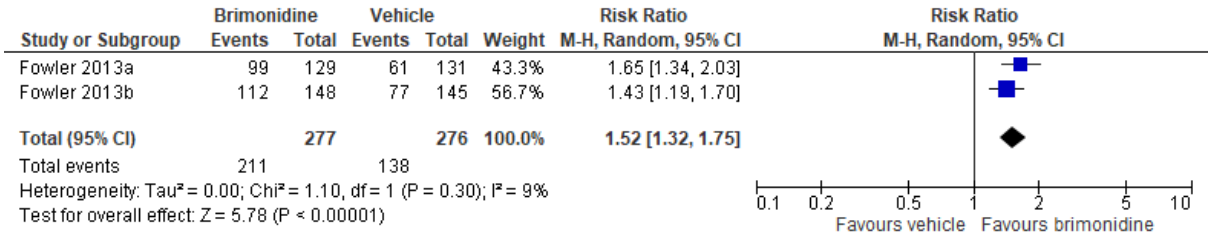
1.1 Patient's Self Assessment 1 grade improvement at 30 min



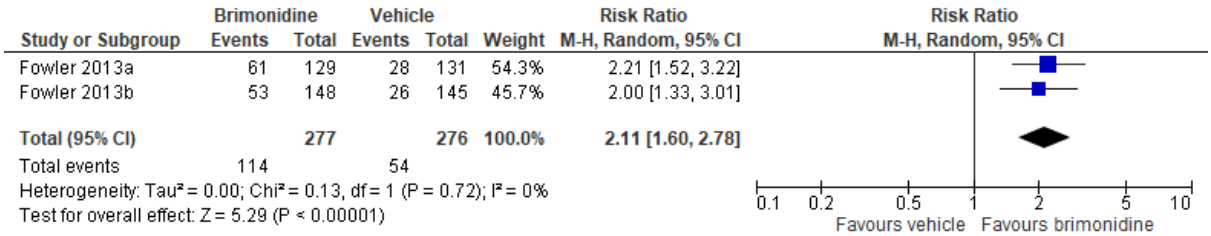
1.2 Patient's Self Assessment 2 grade improvement at 30 min



1.3 Patient's Self Assessment 1 grade improvement at 3 hours



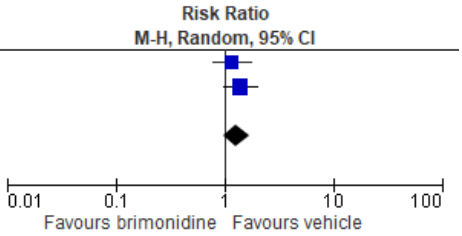
1.4 Patient's Self Assessment 2 grade improvement at 3 hours



1.5 Number of participants experiencing an adverse event

Study or Subgroup	Brimonidine Events	Brimonidine Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Fowler 2013a	38	129	33	131	45.9%	1.17 [0.79, 1.74]
Fowler 2013b	50	148	35	145	54.1%	1.40 [0.97, 2.02]
Total (95% CI)		**277**		**276**	**100.0%**	**1.29 [0.98, 1.69]**
Total events	88		68			

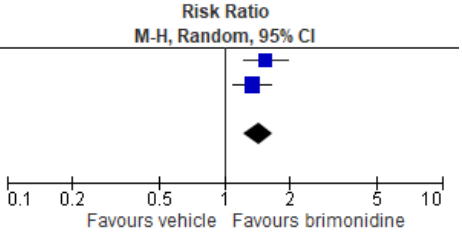
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.51); I² = 0%
Test for overall effect: Z = 1.85 (P = 0.06)



1.6 Clinican's Erythema Assessment 1 grade improvement at 30 min

Study or Subgroup	Brimonidine Events	Brimonidine Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Fowler 2013a	87	129	57	131	44.7%	1.55 [1.23, 1.95]
Fowler 2013b	96	148	70	145	55.3%	1.34 [1.09, 1.65]
Total (95% CI)		**277**		**276**	**100.0%**	**1.43 [1.23, 1.67]**
Total events	183		127			

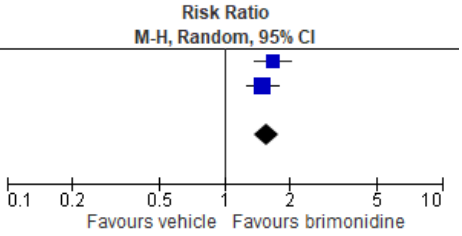
Heterogeneity: Tau² = 0.00; Chi² = 0.83, df = 1 (P = 0.36); I² = 0%
Test for overall effect: Z = 4.60 (P < 0.00001)



1.7 Clinican's Erythema Assessment 1 grade improvement at 3 hours

Study or Subgroup	Brimonidine Events	Brimonidine Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Fowler 2013a	105	129	64	131	43.7%	1.67 [1.37, 2.02]
Fowler 2013b	119	148	78	145	56.3%	1.49 [1.26, 1.77]
Total (95% CI)		**277**		**276**	**100.0%**	**1.57 [1.38, 1.78]**
Total events	224		142			

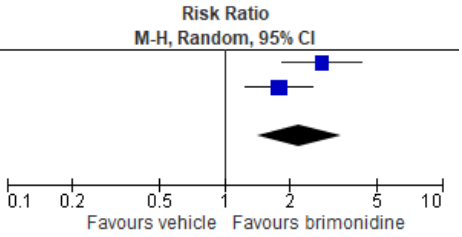
Heterogeneity: Tau² = 0.00; Chi² = 0.68, df = 1 (P = 0.41); I² = 0%
Test for overall effect: Z = 6.88 (P < 0.00001)



1.8 Clinican's Erythema Assessment 2 grade improvement at 3 hours

Study or Subgroup	Brimonidine Events	Brimonidine Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Fowler 2013a	61	129	22	131	46.9%	2.82 [1.85, 4.30]
Fowler 2013b	60	148	33	145	53.1%	1.78 [1.25, 2.55]
Total (95% CI)		**277**		**276**	**100.0%**	**2.21 [1.41, 3.46]**
Total events	121		55			

Heterogeneity: Tau² = 0.07; Chi² = 2.64, df = 1 (P = 0.10); I² = 62%
Test for overall effect: Z = 3.46 (P = 0.0005)

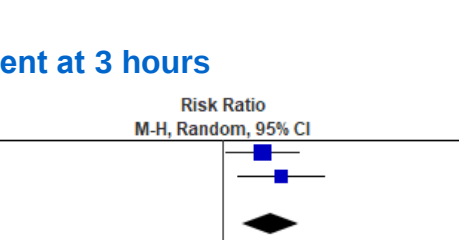


2 Topical oxymetazoline versus vehicle

2.1 Subject's Self Assessment 2 grade improvement at 3 hours

Study or Subgroup	Oxymetazoline Events	Oxymetazoline Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Baumann 2018	54	224	35	221	59.0%	1.52 [1.04, 2.23]
Kircik 2018	45	222	24	218	41.0%	1.84 [1.16, 2.91]
Total (95% CI)		**446**		**439**	**100.0%**	**1.65 [1.23, 2.21]**
Total events	99		59			

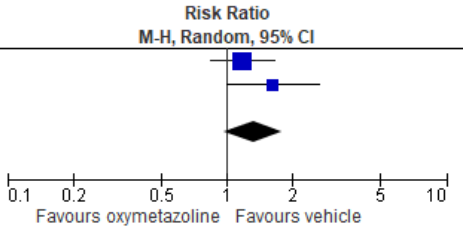
Heterogeneity: Tau² = 0.00; Chi² = 0.39, df = 1 (P = 0.53); I² = 0%
Test for overall effect: Z = 3.32 (P = 0.0009)



2.2 Number of participants experiencing an adverse event

Study or Subgroup	Oxymetazoline Events	Oxymetazoline Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Baumann 2018	56	224	47	221	64.6%	1.18 [0.84, 1.65]
Kircik 2018	38	222	23	218	35.4%	1.62 [1.00, 2.63]
Total (95% CI)		**446**		**439**	**100.0%**	**1.32 [0.97, 1.78]**
Total events	94		70			

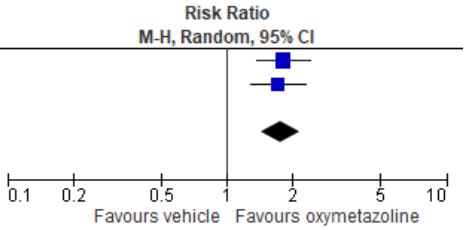
Heterogeneity: Tau² = 0.01; Chi² = 1.15, df = 1 (P = 0.28); I² = 13%
Test for overall effect: Z = 1.78 (P = 0.07)



2.3 Clinician's Erythema Assessment 2 grade improvement at 3 hours

Study or Subgroup	Oxymetazoline Events	Oxymetazoline Total	Vehicle Events	Vehicle Total	Weight	Risk Ratio M-H, Random, 95% CI
Baumann 2018	99	224	54	221	53.3%	1.81 [1.37, 2.38]
Kircik 2018	87	222	50	218	46.7%	1.71 [1.27, 2.29]
Total (95% CI)		**446**		**439**	**100.0%**	**1.76 [1.44, 2.15]**
Total events	186		104			

Heterogeneity: Tau² = 0.00; Chi² = 0.08, df = 1 (P = 0.78); I² = 0%
Test for overall effect: Z = 5.53 (P < 0.00001)

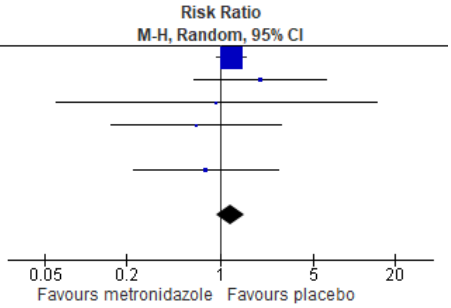


3 Topical metronidazole versus placebo

3.1 Number of participants experiencing an adverse event

Study or Subgroup	Topical metronidazole Events	Topical metronidazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Beutner 2005	362	1110	51	189	88.8%	1.21 [0.94, 1.55]
Bitar 1990	8	50	4	50	4.3%	2.00 [0.64, 6.22]
Bjerke 1989	1	50	1	47	0.7%	0.94 [0.06, 14.60]
Breneman 1998	4	104	3	52	2.6%	0.67 [0.15, 2.87]
Koçak 2002	0	20	0	20		Not estimable
Nielsen 1983a	4	41	5	40	3.6%	0.78 [0.23, 2.70]
Total (95% CI)		**1375**		**398**	**100.0%**	**1.19 [0.94, 1.51]**
Total events	379		64			

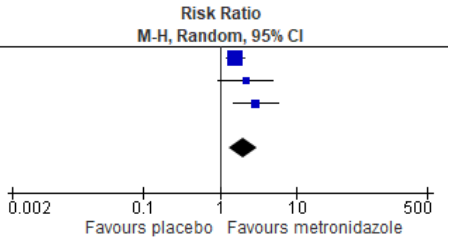
Heterogeneity: Tau² = 0.00; Chi² = 1.90, df = 4 (P = 0.75); I² = 0%
Test for overall effect: Z = 1.49 (P = 0.14)



3.2 Physician-assessed improvement

Study or Subgroup	Topical metronidazole Events	Topical metronidazole Total	Placebo Events	Placebo Total	Weight	Risk Ratio M-H, Random, 95% CI
Bjerke 1989	44	50	26	47	54.9%	1.59 [1.21, 2.10]
Breneman 1998	26	104	6	52	19.4%	2.17 [0.95, 4.93]
Nielsen 1983a	24	41	8	40	25.7%	2.93 [1.50, 5.73]
Total (95% CI)		**195**		**139**	**100.0%**	**1.98 [1.29, 3.02]**
Total events	94		40			

Heterogeneity: Tau² = 0.07; Chi² = 3.55, df = 2 (P = 0.17); I² = 44%
Test for overall effect: Z = 3.14 (P = 0.002)



3.3 Incomplete data on which further analysis is not possible

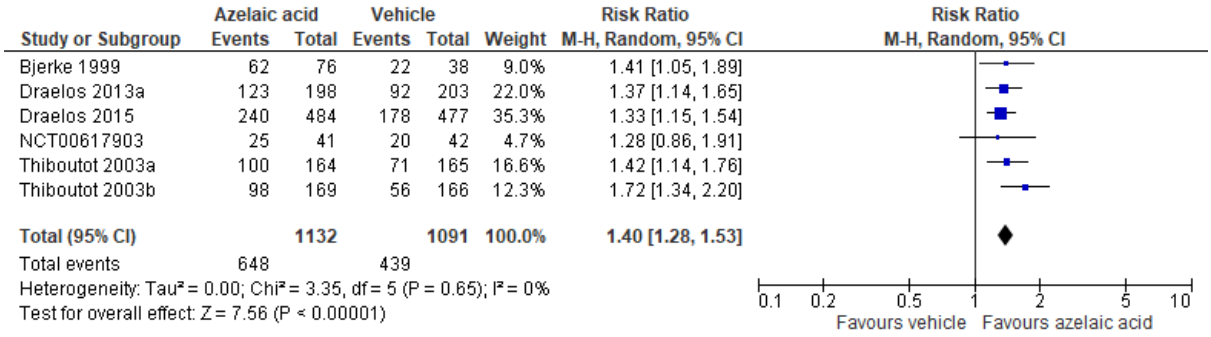
Study ID	Interventions	Summary Outcomes	Comment	Notes
Barnhorst 1996	13 participants were treated with lid hygiene plus warm compresses plus metronidazole 0.75% gel in one eye BID, versus lid hygiene plus warm compresses in the other eye. Within-patient comparison.	No adverse events reported. Eye and eyelid grading pre-post mean (SD) -1.5 (1.7) versus -1.0 (1.7). Authors report significant improvement in treatment group but not in control group, P = 0.022 versus P = 0.10 [inappropriate analysis]. No direct comparison reported. Eye pre-post mean (SD) -0.4 (1.0) versus -0.3 (0.9). Eyelid pre-post mean (SD) -1.1 (0.9) versus -0.7 (0.8)	Small group (13 participants), within-patient comparison. Not much data. Participant not blinded. Data skewed.	BID = twice a day SD = standard deviation

Beutner 2005	557 were treated with metronidazole gel 1% QD versus 553 with metronidazole 1% cream QD versus 189 with metronidazole gel vehicle.	Adverse events 186/557 versus 176/553 versus 51/189. Subjects rated as success according to physicians 38.4% versus 35.4% versus 27.5%. Reduction in lesion count 66.7% versus 58.3% vs. 46.2%	Large vehicle effect.	QD = once daily
Bitar 1990	50 were treated with metronidazole cream 1% BID versus 50 with placebo cream BID.	Erythema and telangiectasia, no statistical difference. Number of papules (SD) after a month 4.5 (4.24) versus 6.5 (4.96). Number of pustules 1.5 (1.41) versus 3.4 (4.94)	Data on papules and pustules are skewed.	BID = twice a day
Bjerke 1989	50 were treated with metronidazole cream 1% BID versus 47 with placebo cream BID.	Erythema: 3 score reduction 2% versus 5%, 2 score reduction 26% versus 5% and 1 score reduction 46% versus 45%, unchanged 26% versus 41%, worse 0% versus 5%. Lesion count reduction 78% versus 48%, reduction of papules 75% versus 43%, reduction of pustules 100% versus 81%.	No SDs were reported.	BID = twice a day N = number SD = standard deviation
Bleicher 1987	40 were treated with metronidazole 0.75% BID versus 40 with placebo BID.	Adverse events, one complained of tearing when gel came to close to the eyes. Reduction in erythema, 0.8 versus 0.3 (erythema rating 0 to 3, higher is worse). Increase in telangiectasia of 0.3 at both sides (rating 0-3) Decrease in lesion counts, 65.1% versus 14.9%.	No SDs were reported. Within-patient comparison.	BID = twice a day SD = standard deviation
Breneman 1998	104 were treated with metronidazole 1% QD versus 52 with placebo QD.	Mean decrease in erythema score of 0.9 in metronidazole group versus 0.5 in placebo group. Decrease in lesion count 8 versus 3.	No SDs were reported.	SD = standard deviation QD = once daily
Dahl 1998	44 were treated with metronidazole 0.75% BID versus 44 with placebo BID.	At baseline 35/44 had no or mild erythema versus 32/44. At end of study this was 32/43 versus 24/44. Telangiectasia (no significant difference or effect) Lesion count 3.3 versus 5.8, relapse rate 23% versus 42%, free of lesions 53% versus 32%.	No SDs reported. N of adverse events unclear.	BID = twice a day SD = standard deviation
Koçak 2002	20 patients were treated with metronidazole 0.75% gel BID versus 20 with placebo BID.	No local adverse events in any group Mean change from baseline in papules (SD) -5.10 (23.36) versus 0.25 (11.25) with a MD of -5.35 (95% CI -16.71 to 6.01). Mean change from baseline in pustules -2.50 (13.65) versus -0.20 (9.20) with a MD of -2.30 (95% CI -9.51 to 4.91). No effects on rhinophyma and telangiectasia.	Most data are skewed.	BID = twice a day SD = standard deviation

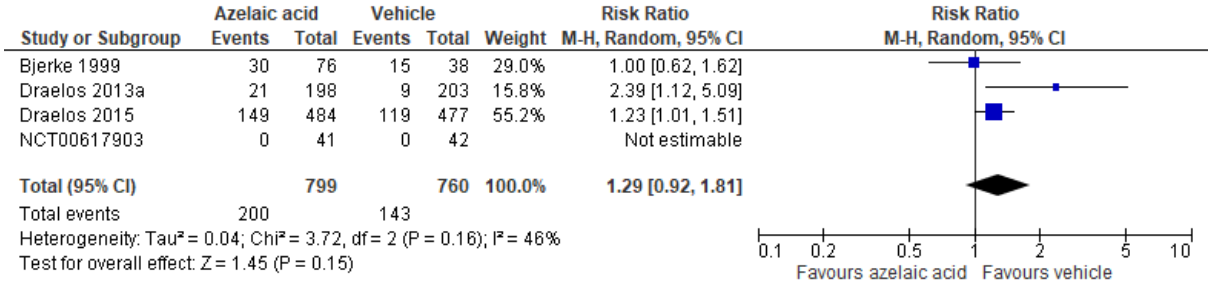
Nielsen 1983a	41 were treated with metronidazole 1% QD versus 40 with placebo QD.	Reduction on erythema from 3.8 to 2.5 for metronidazole group and from 3.7 to 3.1 in placebo group. Authors state P < 0.05. There were no effects on telangiectasia. Papules count 8.6 versus 16.6, and pustules count 0.3 versus 0.8.	No SDs were reported.	SD = standard deviation QD = once daily

4 Topical azelaic acid versus vehicle

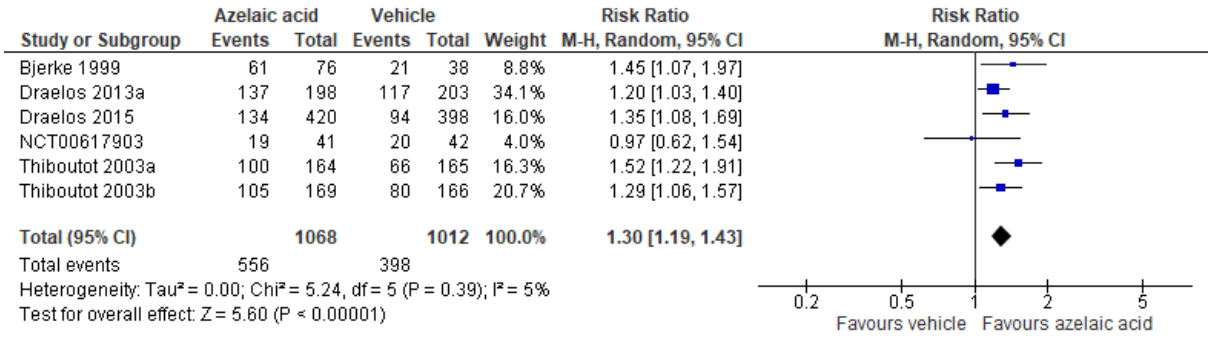
4.1 Participant-assessed improvement



4.2 Number of participants experiencing an adverse event



4.3 Physician-assessed improvement



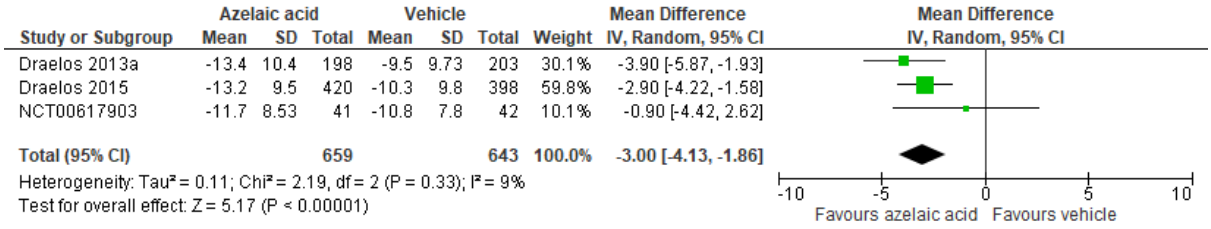
4.4 Incomplete data on which further analysis is not possible

Study ID	Intervention	Summary Outcomes	Comment	Notes
Bjerke 1999	76 were treated with azelaic cream 20% BID versus 38 with placebo BID.	Decrease in erythema 47.9% versus 37.9%, in telangiectasia 22.3% versus 23.5%. Decrease in lesions 73.4% versus 50.6%.	No SDs were reported.	BID = twice a day

				SD = standard deviation
Carmichael 1993	Azelaic cream 20% BID versus placebo BID. Within-patient comparison in 33 patients.	VAS scale of improvement 6.9 (1.15) to 2.6 (1.72) for azelaic acid treated side versus 7.0 (1.15) to 4.5 (2.30) for placebo treated side Erythema index decreased from 539.6 (76.98) to 500.6 (84.45) at the azelaic acid treated side and from 533.5 (82.15) to 518.3 (95.36) at the placebo treated side Telangiectasia (VAS scores) decreased from 4.3 (2.30) to 4.2 (1.71) at the azelaic acid treated side and from 4.4 (2.30) to 4.5 (2.30) at the placebo side Papule count 2.5 (2.87) versus 6.3 (4.6), pustule count 0.0 (0.17) versus 0.4 (0.57).	Data are skewed.	BID = twice a day
Draelos 2013a	198 were treated with azelaic acid 15% foam BID versus 203 vehicle foam BID	There were no statistically significant differences between the 2 groups in end-of-treatment or end-of-study erythema and telangiectasia		BID = twice a day
NCT00617903	41 were treated with azelaic acid 15% foam BID versus 42 with vehicle foam BID	Erythema intensity score: 1 - Clear or almost clear; 2 - Mild; 3 - Moderate; 4 - Severe In the azelaic acid foam group the reduction in erythema was 0.8 (SD 0.8) and in the vehicle foam group 0.6 (0.9)		BID = twice a day
Thiboutot 2003a	164 were treated with azelaic acid 15% BID versus 165 with vehicle BID.	Marked improvement or complete remission according to investigator: 51% versus 27% (investigators reported P < 0.001). Overall improvement in erythema : 44% versus 29% (investigators reported P = 0.0017). Overall improvement in telangiectasia: Unchanged in 77% versus 80% (investigators reported 'not statistically significant'). Change in number of inflammatory lesions from 17.5 to 6.8 versus 17.6 to 10.5.	No SDs were reported, can only be estimated from figures	BID = twice a day SD = standard deviation
Thiboutot 2003b	169 were treated with azelaic acid 15% BID versus 166 with vehicle BID Same reference describes 2 studies.	Marked improvement or complete remission according to investigator: 46% versus 31% (investigators reported P < 0.0048). Overall improvement in erythema : 46% versus 28% (investigators reported P = 0.0005). Overall improvement in telangiectasia: Unchanged in 73% versus 78% (investigators reported 'not statistically significant').	No SDs were reported, can only be estimated from figures	BID = twice a day SD = standard deviation

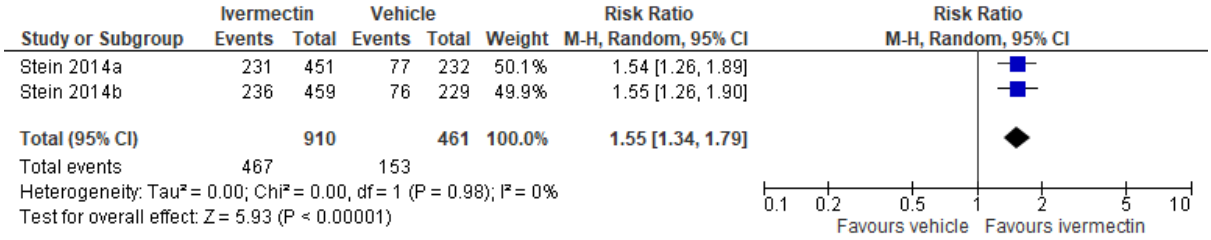
		Change in number of inflammatory lesions from 17.8 to 8.9 versus 18.5 to 12.1.		

4.5 Lesion count

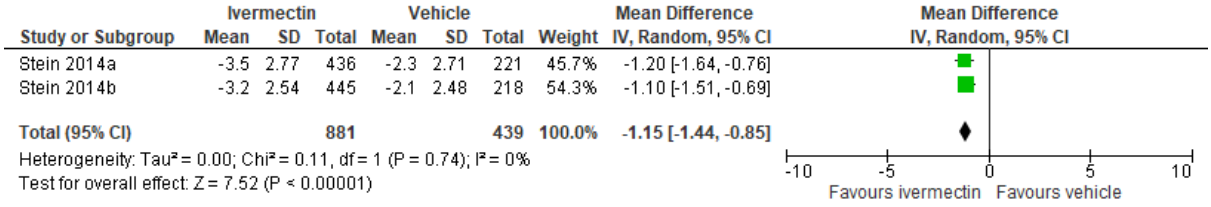


5 Topical ivermectin versus vehicle

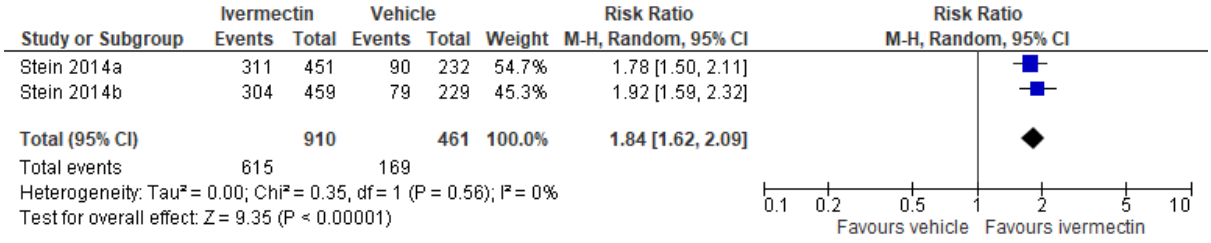
5.1 Number of participants experiencing no effect of disease on quality of life (anymore)



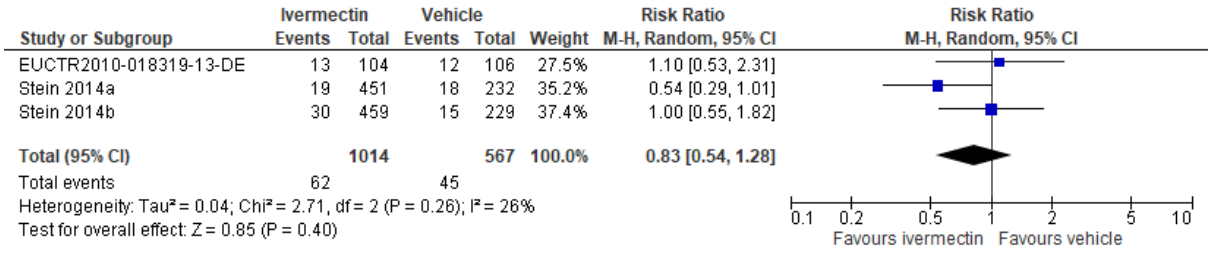
5.2 Mean change in DLQI



5.3 Participant-assessed improvement (good, excellent)



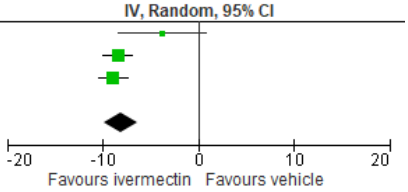
5.4 Number of participants experiencing an adverse event



5.5 Lesion count

Study or Subgroup	Ivermectin Mean	SD	Total	Vehicle Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
EUCTR2010-018319-13-DE	-26.6	15.9	104	-22.8	18.4	106	11.6%	-3.80 [-8.45, 0.85]
Stein 2014a	-20.4	8.72	451	-12	10.1	232	44.5%	-8.40 [-9.93, -6.87]
Stein 2014b	-22.3	8.21	459	-13.4	10.5	229	44.0%	-8.90 [-10.45, -7.35]
Total (95% CI)			**1014**			**567**	**100.0%**	**-8.09 [-9.82, -6.35]**

Heterogeneity: Tau² = 1.15; Chi² = 4.16, df = 2 (P = 0.12); I² = 52%
Test for overall effect: Z = 9.13 (P < 0.00001)

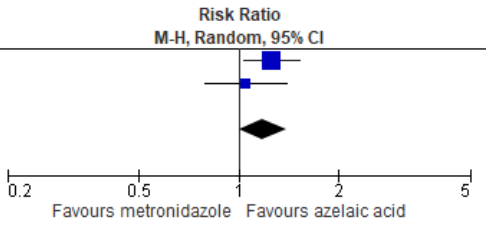


6 Topical azelaic acid versus topical metronidazole

6.1 Physician-assessed improvement (clear, nearly clear)

Study or Subgroup	Azelaic acid Events	Total	Metronidazole Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Elewski 2003	86	124	70	127	66.1%	1.26 [1.03, 1.53]
Wolf 2006	44	78	44	82	33.9%	1.05 [0.79, 1.39]
Total (95% CI)		**202**		**209**	**100.0%**	**1.18 [1.00, 1.40]**
Total events	130		114			

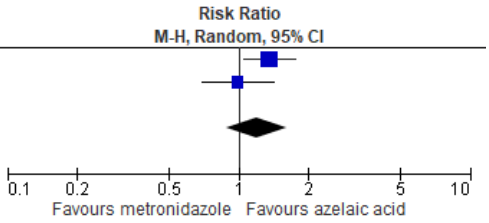
Heterogeneity: Tau² = 0.00; Chi² = 1.07, df = 1 (P = 0.30); I² = 6%
Test for overall effect: Z = 1.98 (P = 0.05)



6.2 Improvement in erythema

Study or Subgroup	Azelaic acid Events	Total	Metronidazole Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Elewski 2003	70	124	53	127	58.6%	1.35 [1.05, 1.75]
Wolf 2006	33	78	35	82	41.4%	0.99 [0.69, 1.42]
Total (95% CI)		**202**		**209**	**100.0%**	**1.19 [0.88, 1.61]**
Total events	103		88			

Heterogeneity: Tau² = 0.02; Chi² = 1.90, df = 1 (P = 0.17); I² = 47%
Test for overall effect: Z = 1.13 (P = 0.26)

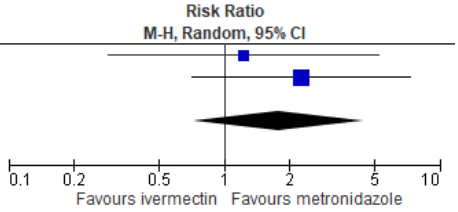


7 Topical ivermectin versus topical metronidazole

7.1 Number of participants experiencing an adverse event

Study or Subgroup	Ivermectin Events	Total	Metronidazole Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
EUCTR2006-001999-20-HU	4	52	3	48	39.7%	1.23 [0.29, 5.22]
Taieb 2015	9	478	4	484	60.3%	2.28 [0.71, 7.35]
Total (95% CI)		**530**		**532**	**100.0%**	**1.78 [0.72, 4.43]**
Total events	13		7			

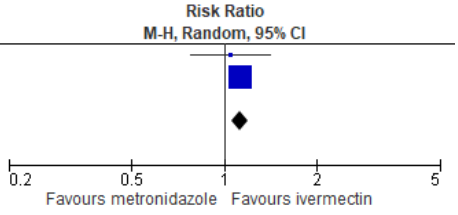
Heterogeneity: Tau² = 0.00; Chi² = 0.42, df = 1 (P = 0.52); I² = 0%
Test for overall effect: Z = 1.25 (P = 0.21)



7.2 Physician-assessed improvement

Study or Subgroup	Ivermectin Events	Total	Metronidazole Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
EUCTR2006-001999-20-HU	34	52	30	48	4.4%	1.05 [0.78, 1.41]
Taieb 2015	406	478	365	484	95.6%	1.13 [1.06, 1.20]
Total (95% CI)		**530**		**532**	**100.0%**	**1.12 [1.06, 1.19]**
Total events	440		395			

Heterogeneity: Tau² = 0.00; Chi² = 0.24, df = 1 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.66 (P = 0.0003)

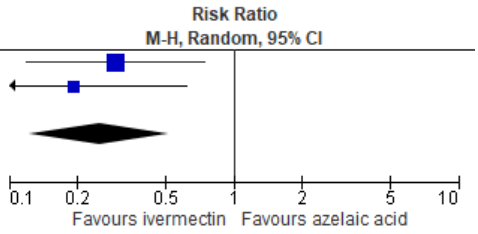


8 Topical ivermectin versus topical azelaic acid

8.1 Number of participants experiencing an adverse event

Study or Subgroup	Ivermectin Events	Total	Azelaic acid Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Stein Gold 2014c	7	412	12	210	61.0%	0.30 [0.12, 0.74]
Stein Gold 2014d	4	428	10	208	39.0%	0.19 [0.06, 0.61]
Total (95% CI)		**840**		**418**	**100.0%**	**0.25 [0.12, 0.52]**
Total events	11		22			

Heterogeneity: Tau² = 0.00; Chi² = 0.32, df = 1 (P = 0.57); I² = 0%
Test for overall effect: Z = 3.77 (P = 0.0002)

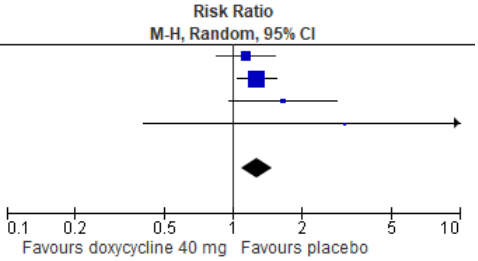


9 Doxycycline 40 mg versus placebo

9.1 Number of participants experiencing an adverse event

Study or Subgroup	Doxycycline 40 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Del Rosso 2007a	56	127	48	124	28.3%	1.14 [0.85, 1.53]
Del Rosso 2007b	93	142	74	144	62.7%	1.27 [1.04, 1.55]
Di Nardo 2016	26	84	16	86	8.3%	1.66 [0.96, 2.87]
NCT00560703	6	46	1	24	0.6%	3.13 [0.40, 24.53]
Total (95% CI)		**399**		**378**	**100.0%**	**1.27 [1.08, 1.49]**
Total events	181		139			

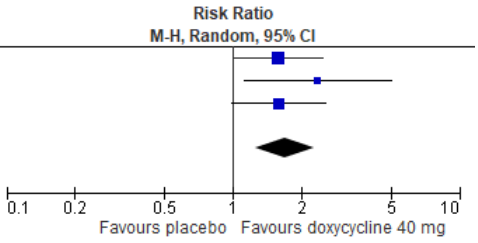
Heterogeneity: Tau² = 0.00; Chi² = 2.24, df = 3 (P = 0.52); I² = 0%
Test for overall effect: Z = 2.97 (P = 0.003)



9.2 Physician-assessed improvement (clear, nearly clear)

Study or Subgroup	Doxycycline 40 mg Events	Total	Placebo Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Del Rosso 2007a	39	127	24	124	44.9%	1.59 [1.02, 2.47]
Del Rosso 2007b	21	142	9	144	15.9%	2.37 [1.12, 4.99]
Di Nardo 2016	31	84	20	86	39.2%	1.59 [0.99, 2.55]
Total (95% CI)		**353**		**354**	**100.0%**	**1.69 [1.26, 2.28]**
Total events	91		53			

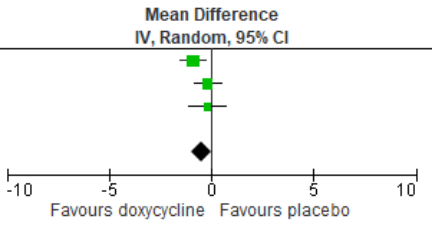
Heterogeneity: Tau² = 0.00; Chi² = 0.94, df = 2 (P = 0.63); I² = 0%
Test for overall effect: Z = 3.46 (P = 0.0005)



9.3 Clinician's Erythema Assessment

Study or Subgroup	Doxycycline 40 mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Del Rosso 2007a	-2.7	2.4	127	-1.8	2.6	124	40.4%	-0.90 [-1.52, -0.28]
Del Rosso 2007b	-1.4	2.8	142	-1.2	3	144	36.2%	-0.20 [-0.87, 0.47]
Di Nardo 2016	-1	2.9	84	-0.8	3.1	86	23.4%	-0.20 [-1.10, 0.70]
Total (95% CI)			**353**			**354**	**100.0%**	**-0.48 [-0.97, 0.00]**

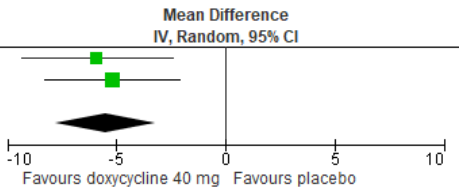
Heterogeneity: Tau² = 0.05; Chi² = 2.79, df = 2 (P = 0.25); I² = 28%
Test for overall effect: Z = 1.94 (P = 0.05)



9.4 Lesion count

Study or Subgroup	Doxycycline 40 mg Mean	SD	Total	Placebo Mean	SD	Total	Weight	Mean Difference IV, Random, 95% CI
Del Rosso 2007a	-11.8	14.04	127	-5.9	14.04	124	43.8%	-5.90 [-9.37, -2.43]
Del Rosso 2007b	-9.5	13.23	142	-4.3	13.23	144	56.2%	-5.20 [-8.27, -2.13]
Total (95% CI)			**269**			**268**	**100.0%**	**-5.51 [-7.81, -3.21]**

Heterogeneity: Tau² = 0.00; Chi² = 0.09, df = 1 (P = 0.77); I² = 0%
Test for overall effect: Z = 4.69 (P < 0.00001)

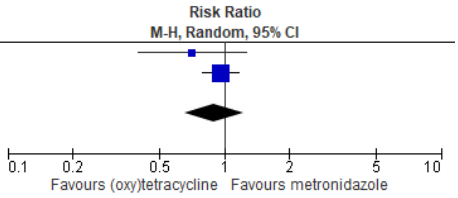


10 Topical metronidazole versus oral (oxy) tetracycline

10.1 Participant-assessed improvement of rosacea severity

Study or Subgroup	Topical metronidazole Events	Total	Oral (oxy) tetracycline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Monk 1991	8	16	12	17	23.0%	0.71 [0.40, 1.26]
Nielsen 1983b	22	25	21	23	77.0%	0.96 [0.80, 1.17]
Total (95% CI)		**41**		**40**	**100.0%**	**0.90 [0.66, 1.23]**
Total events	30		33			

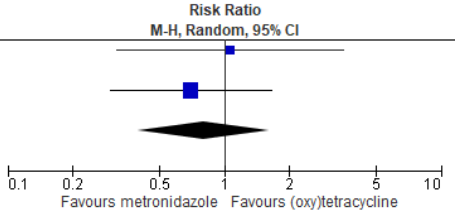
Heterogeneity: Tau² = 0.02; Chi² = 1.49, df = 1 (P = 0.22); I² = 33%
Test for overall effect: Z = 0.68 (P = 0.50)



10.2 Number of participants experiencing an adverse event

Study or Subgroup	Topical metronidazole Events	Total	Oral (oxy) tetracycline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Monk 1991	4	16	4	17	33.4%	1.06 [0.32, 3.55]
Nielsen 1983b	0	23	0	25		Not estimable
Veien 1986	7	38	10	38	66.6%	0.70 [0.30, 1.65]
Total (95% CI)		**77**		**80**	**100.0%**	**0.80 [0.40, 1.62]**
Total events	11		14			

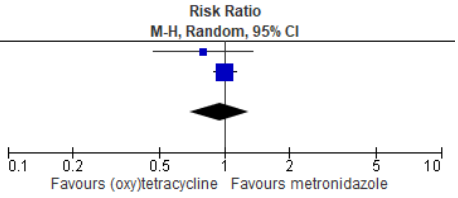
Heterogeneity: Tau² = 0.00; Chi² = 0.31, df = 1 (P = 0.58); I² = 0%
Test for overall effect: Z = 0.61 (P = 0.54)



10.3 Physician-assessed improvement

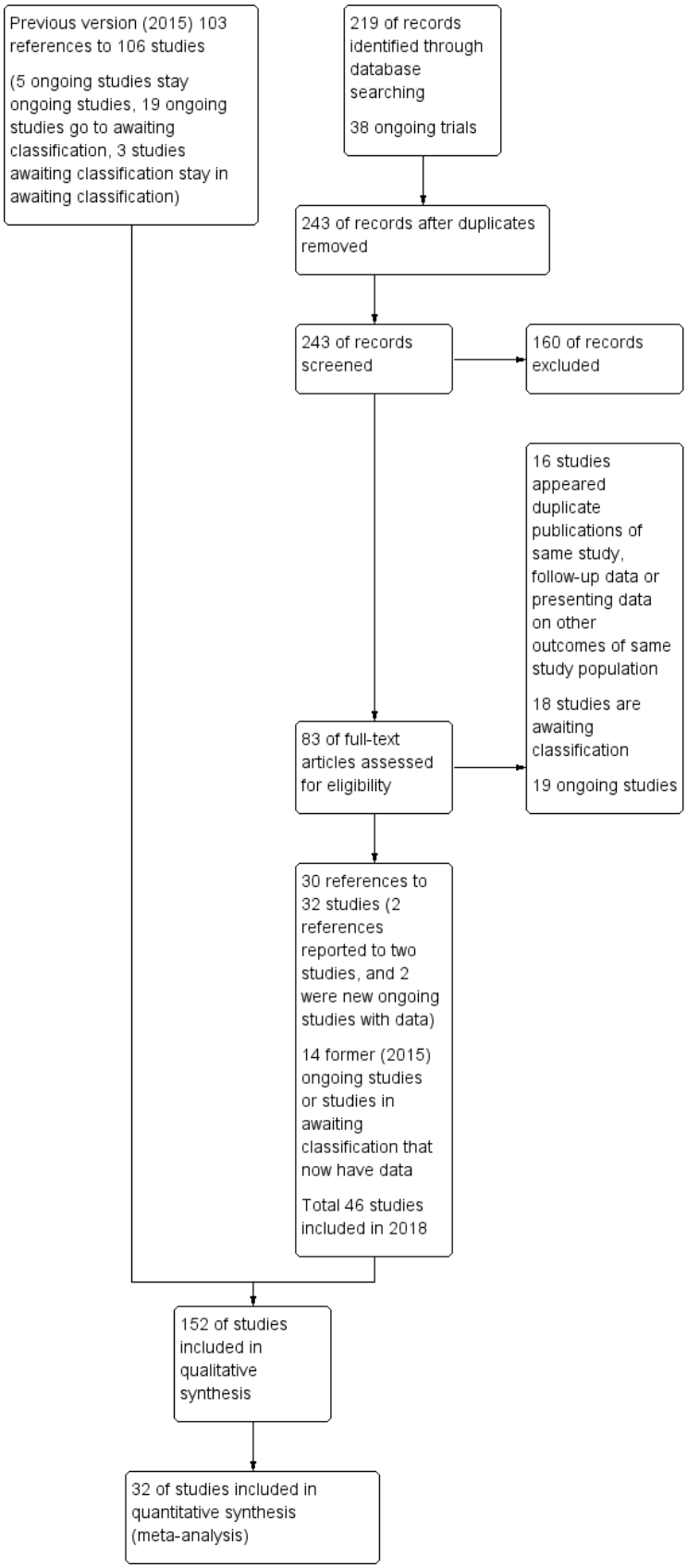
Study or Subgroup	Topical metronidazole Events	Total	Oral (oxy) tetracycline Events	Total	Weight	Risk Ratio M-H, Random, 95% CI
Monk 1991	9	16	12	17	24.3%	0.80 [0.47, 1.35]
Nielsen 1983b	24	25	22	23	75.7%	1.00 [0.89, 1.13]
Total (95% CI)		**41**		**40**	**100.0%**	**0.95 [0.70, 1.29]**
Total events	33		34			

Heterogeneity: Tau² = 0.03; Chi² = 1.76, df = 1 (P = 0.18); I² = 43%
Test for overall effect: Z = 0.33 (P = 0.74)



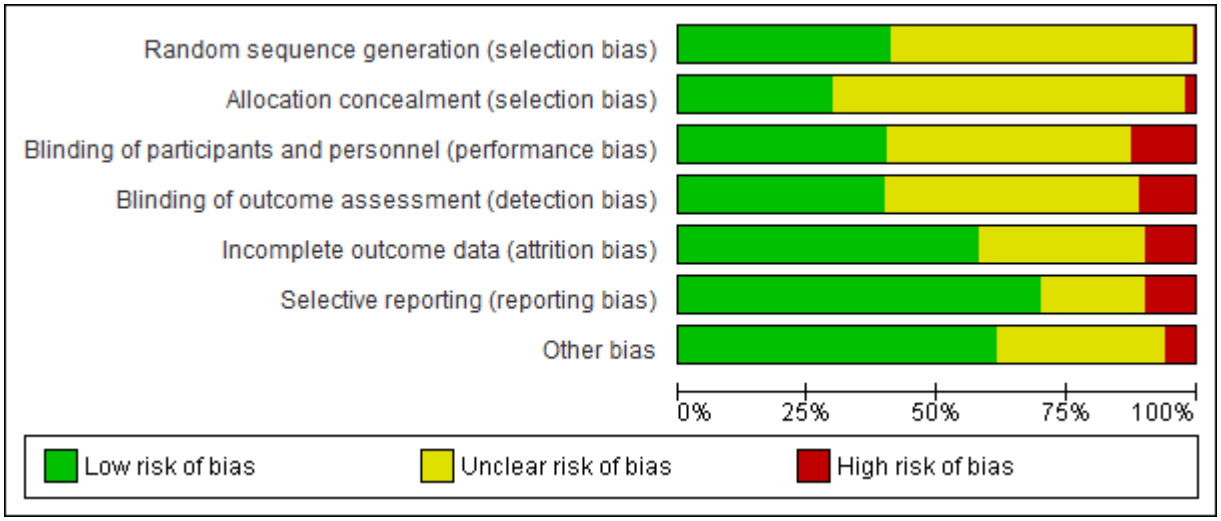
Figures

Figure 1



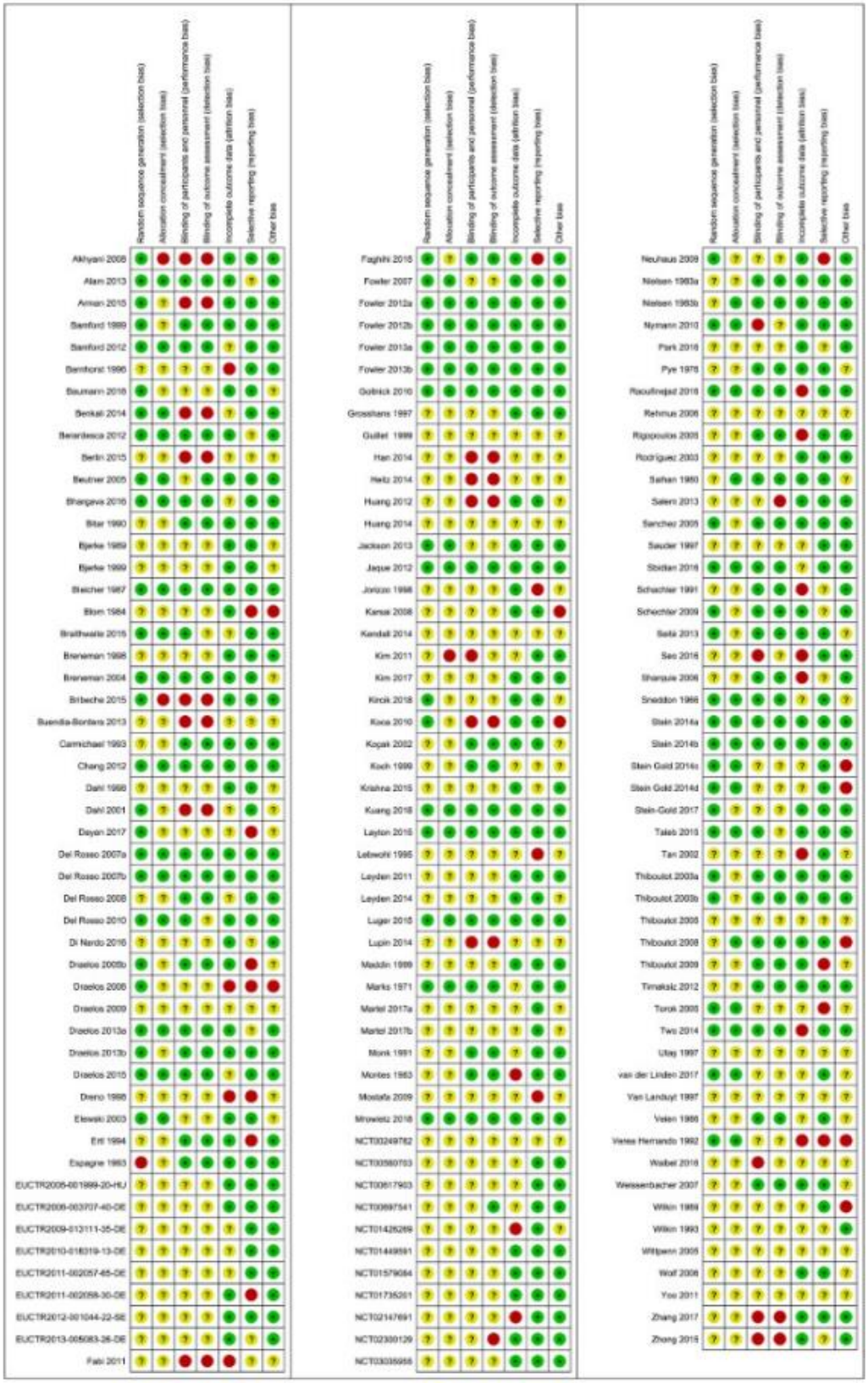
Study flow diagram.

Figure 2



Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3



Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Sources of support

Internal sources

- No sources of support found, Netherlands
- No sources of support found, UK
- No sources of support found, Canada

External sources

- Dutch Society of Dermatology and Venerology, Netherlands

Appendices

1 CENTRAL (the Cochrane Library) search strategy

#1 MeSH descriptor: [Rosacea] explode all trees
#2 rosacea:ti,ab
#3 rhinophyma:ti,ab
#4 "pyoderma faciale":ti,ab
#5 {or #1-#4}

2 MEDLINE (Ovid) search strategy

1. exp Rosacea/
2. rosacea.ti,ab.
3. Rhinophyma.ti,ab.
4. pyoderma faciale.ti,ab.
5. or/1-4
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. randomized.ab.
9. placebo.ab.
10. clinical trials as topic.sh.
11. randomly.ab.
12. trial.ti.
13. 6 or 7 or 8 or 9 or 10 or 11 or 12
14. exp animals/ not humans.sh.
15. 13 not 14
16. 5 and 15

3 EMBASE (Ovid) search strategy

1. rosacea/
2. rosacea.ti,ab.
3. rhinophyma.ti,ab.
4. pyoderma faciale.ti,ab.
5. or/1-4
6. crossover procedure.sh.
7. double-blind procedure.sh.
8. single-blind procedure.sh.
9. (crossover$ or cross over$).tw.
10. placebo$.tw.

11. (doubl$ adj blind$).tw.
12. allocat$.tw.
13. trial.ti.
14. randomized controlled trial.sh.
15. random$.tw.
16. or/6-15
17. exp animal/ or exp invertebrate/ or animal experiment/ or animal model/ or animal tissue/ or animal cell/ or nonhuman/
18. human/ or normal human/
19. 17 and 18
20. 17 not 19
21. 16 not 20
22. 5 and 21

4 LILACS search strategy

rosacea or rhinophyma

5 Science Citation Index search strategy

1. TS=("rosacea" OR "rhinophyma" OR "rozacea" OR "rosacea*" OR "rhinophyma*" OR "rozacea*" OR "flushing"
2. TS="facial" AND ("telangiectasis" OR "telangiectasia" OR "erythema" OR "edema" OR "oedema" OR "edema*" OR "oedema*")
3. 1 or 2
4. TS=("therap*" OR "therapy" OR "treat*" OR "treatment" OR "surgery" OR "surger*" OR "surgic*" OR "antibiotic" OR "anti-biotic*" OR "antibiotics" OR "antibiotic*" OR "tetracycline" OR "doxycycline" OR "minocycline" OR "permethrine" OR "benzoyl peroxide" OR "oral contraceptive" OR "oral contraceptives" OR "tetracyclin*" OR "doxycyclin*" OR "minocyclin*" OR "permethrin*" OR "benzoyl peroxid*" OR "oral contracept*" OR "diane 35" OR "diane35" OR "erythromycin" OR "sulphur" OR "sulfur" OR "erythromycin*" OR "sulphur*" OR "sulfur*" OR "azelaic acid" OR "tretinoin" OR "isotretinoin" OR "laser" OR "spironolactone" OR "tretinoin*" OR "isotretinoin*" OR "laser*" OR "spironolacton*" OR "adrenal cortex hormone" OR "adrenal cortex hormones" OR "adrenal cortex hormone*" OR "corticosteroid*" OR "corticosteroids" OR "corticosteroid" OR "metronidazole" OR "metronidazol*" OR "zinc" OR "massage*" OR "massage" OR "massages" OR "ivermectin" OR "brimonidine" OR "azithromycin" OR "doxycyclin" OR "intense pulsed light" OR "metronidazol" OR "ivermectin*" OR "brimonidin*" OR "azithromycin*" OR "doxycyclin*" OR "intense pulsed light*" OR "metronidazol*")
5. TS=(Randomized Controlled Trial OR Controlled Clinical Trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR randomized controlled trial OR controlled clinical trial OR randomized controlled trials OR random allocation OR double-blind method OR single-blind method OR clinical trial OR clinical trials OR "clinical trial" OR ((singl* OR doubl* OR trebl* OR tripl*) AND (mask* OR blind*)) OR "latin square" OR placebos OR placebo* OR random* OR research design [mh:noexp] OR comparative study OR evaluation studies OR follow-up studies OR prospective studies OR cross-over studies OR control* OR prospective* OR volunteer* OR randomised controlled trial OR randomised controlled trials OR randomized active control trials OR randomized active control trial OR RaCT OR RaCTs)
6. 3 and 4 and 5

6 BIOSIS search strategy

1(rosacea or rozacea).mp.[mp=title, keywords, heading words, registry words, abstracts, biosystematic codes/super taxa, title, book title, original language book title, title, original language book title, biosystematic codes/super taxa, subject headings, heading words]
2 clinical trial.mp. [mp=title, keywords, heading words, registry words, abstracts, biosystematic codes/super taxa, title, book title, original language book title, title, original language book title, biosystematic codes/super taxa, subject headings, heading words]
3 randomi$.mp.[mp=title, keywords, heading words, registry words, abstracts, biosystematic codes/super taxa, title, book title, original language book title, title, original language book title, biosystematic codes/super taxa, subject headings, heading words]
4 1 and 2 and 3
5 double blind.mp.[mp=title, keywords, heading words, registry words, abstracts, biosystematic codes/super taxa, title, book title, original language book title, title, original language book title, biosystematic codes/super taxa, subject headings, heading words]
6 1 and 5
7 6 not 4
8 from 7 keep 5,8,10-13, 15,17-19
9 from 8 keep 1