Guselkumab in biologic-naïve patients with active psoriatic arthritis (DISCOVER-2) a double-blind, randomised, placebo-controlled phase 3 trial

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Summary

Background The interleukin-23 (IL-23)/T-helper 17 cell pathway is implicated in psoriatic arthritis pathogenesis. Guselkumab, an IL-23 inhibitor that specifically binds the IL-23 p19 subunit, significantly and safely improved psoriatic arthritis in a phase 2 study. DISCOVER-2 was a phase 3 trial to assess guselkumab in biologic-naive patients with psoriatic arthritis.

Methods This phase 3, double-blind, placebo-controlled study was done at 118 sites in 13 countries across Asia, Europe, and North America. We enrolled biologic-naive patients with active psoriatic arthritis (at least five swollen joints, at least five tender joints, and C-reactive protein ≥0·6 mg/dL) despite standard therapies. Patients were randomly assigned (1:1:1, computer-generated permuted blocks; stratified by baseline disease-modifying antirheumatic drug use and C-reactive protein concentration) to subcutaneous injections of guselkumab 100 mg every 4 weeks; guselkumab 100 mg at weeks 0, 4, then every 8 weeks; or placebo. The primary endpoint was American College of Rheumatology 20% improvement (ACR20) response at week 24 in all patients per assigned treatment group. Safety was assessed in all patients per treatment received. This trial is registered at ClinicalTrials.gov, NCT03158285 (active, not recruiting).

Findings From July 13, 2017, to Aug 3, 2018, 1153 patients were screened, of whom 741 were randomly assigned to receive guselkumab every 4 weeks (n=246), every 8 weeks (n=248), or placebo (n=247). One patient in the every 4 weeks group and one in the placebo group did not start treatment, and the remaining 739 patients started treatment; 716 patients continued treatment up to week 24. Significantly greater proportions of patients in the guselkumab every 4 weeks group (156 [64%] of 245 [95% CI 57–70]) and every 8 weeks group (159 [64%] of 248 [58–70]) than in the placebo group (81 [33%] of 246 [27–39]) achieved an ACR20 response at week 24 (percentage differences *vs* placebo 31% [95% CI 22–39] for the every 4 weeks group and 31% [23–40] for the every 8 weeks group; both p<0·0001). Up to week 24, serious adverse events occurred in eight (3%) of 245 patients receiving guselkumab every 4 weeks (three serious infections), three (1%) of 248 receiving guselkumab every 8 weeks (one serious infection), and seven (3%) of 246 receiving placebo (one serious infection). No deaths occurred.

Interpretation Guselkumab, a human monoclonal antibody that specifically inhibits IL-23 by binding the cytokine's p19 subunit, was efficacious and demonstrated an acceptable benefit–risk profile in patients with active psoriatic arthritis who were naive to treatment with biologics. These data support the use of selective inhibition of IL-23 to treat psoriatic arthritis.

Funding Janssen Research and Development.

Introduction

Psoriatic arthritis is a chronic inflammatory disease associated with peripheral joint inflammation, enthesitis, dactylitis, axial disease, and cutaneous and nail involvement, all of which can substantially limit physical function and impair quality of life. Although the introduction of biologics (eg, tumour necrosis factor-α [TNF] inhibitors, ustekinumab, interleukin-17A [IL-17A] inhibitors, and abatacept) and oral drugs (eg, apremilast and tofacitinib) has increased the extent and duration of achievable clinical responses, new therapies are needed to treat the diverse manifestations of psoriatic arthritis while maintaining a favourable benefit–risk profile.[1]

The origins of the varying clinical manifestations of psoriatic arthritis remain under study. The IL-23/T-helper cell 17 (Th17) pathway—via downstream IL-17 expression—appears crucial to skin manifestations. IL-23 can also induce IL-22, a cytokine implicated in enthesitis and bone formation,[2] and, in part via IL-17A and TNF induction, elicit the joint symptoms and damage that are hallmarks of psoriatic arthritis. IL-23 is a heterodimer formed by pairing p19 and p40 subunits, the latter of which is shared with IL-12. Although IL-12 and IL-23 share the p40 subunit, they also encompass unique subunits (p35 for IL-12 and p19 for IL-23).[3,4] IL-23 has been established to be a predominant driver of autoimmune-mediated articular inflammation,

Research in context

Evidence before this study

We searched PubMed on Oct 7–8, 2019, for original research and review articles published in English since Jan 1, 2000, with the following search terms: "biologic", "cytokine", "dactylitis", "enthesitis", "interleukin", "outcome", "psoriasis", "psoriatic arthritis", "radiograph", "structural damage", and "treatment". Current literature indicates that IL-23 is instrumental in driving the chronic inflammation associated with several immune-mediated diseases, including psoriasis and psoriatic arthritis. Guselkumab is a high-affinity, anti-IL-23 human monoclonal antibody that specifically binds the cytokine's p19 subunit and is approved to treat moderate-to-severe psoriasis. In a phase 2 study, selective blockade of IL-23 by guselkumab significantly improved signs and symptoms of active psoriatic arthritis and was well tolerated during 1 year of exposure.

Added value of this study

Results of DISCOVER-2, the larger of two trials comprising the first phase 3 programme investigating a novel mechanism of action to treat psoriatic arthritis, confirm that targeting the p19 subunit of IL-23 effectively treats the diverse manifestations across psoriatic arthritis domains. Specifically, in patients with active disease despite standard treatments, but no previous exposure to biologics, subcutaneous guselkumab 100 mg significantly improved joint symptoms, dactylitis, enthesitis, psoriasis, physical function, and health-related quality of life when administered every 4 or 8 weeks. Guselkumab given every 4 weeks afforded significantly less progression of structural damage up to week 24 than did placebo, providing evidence of inhibition of radiographic progression by an IL-23 inhibitor that targets the p19 subunit. The overall safety profile of guselkumab in psoriatic arthritis patients was similar to that observed in patients with psoriasis treated with guselkumab.

Implications of all the available evidence

Consistent with previous findings of a proof-of-concept study confirming that IL-23 plays a crucial role in the pathogenesis of psoriatic arthritis, data from this phase 3 trial provide pivotal evidence that guselkumab offers a novel mechanism of action to treat the diverse clinical manifestations and inhibit the structural damage progression of psoriatic arthritis.

whereas IL-12 is more likely to facilitate protection from autoimmune inflammation and T-cell exhaustion.[4–7] The divergent roles of these closely related cytokines are highlighted by differential skin effects, whereby abnormal differentiation of keratinocytes is triggered by IL-23 but not IL-12,[6] and differing roles in the body's response to bacterial and viral infections, as well as tumour control via their regulation of T-cell function.[5] Targeting the p19 subunit of IL-23, and thus sparing IL-12, has demonstrated robust efficacy in psoriasis,[7–10] suggesting a prominent upstream position of the cytokine in the inflammatory hierarchy across the psoriatic disease spectrum, and thereby meriting analysis of selective IL-23 inhibition via IL-23 p19 binding in psoriatic arthritis.

Guselkumab (Janssen Biotech, Horsham, PA, USA), a high-affinity, human monoclonal antibody that binds specifically to the p19 subunit of IL-23, is approved to treat patients with moderate-to-severe psoriasis who are candidates for systemic or phototherapy. In a randomised, placebo-controlled, phase 2 trial in patients with psoriatic arthritis, guselkumab demonstrated efficacy across all endpoints related to joint signs and symptoms, physical function, skin disease, enthesitis, dactylitis, and health-related quality of life.[11]

Here, we report 24-week results from one of two phase 3 trials (DISCOVER-2), conducted to assess guselkumab in biologic-naive patients with active psoriatic arthritis. DISCOVER-2 assessed patient outcomes related to joint and skin manifestations as well as structural damage. Results from the other registrational trial of guselkumab in psoriatic arthritis (DISCOVER-1), which aimed to enrol patients with a broader range of baseline levels of disease activity, some of whom were previously treated with one or two TNF inhibitors, are reported separately.[12]

Methods

Study design

DISCOVER-2 is a randomised, double-blind, placebo-controlled, multicentre, three-arm phase 3 trial of guselkumab in patients with active psoriatic arthritis who were biologic naive and had inadequate response to standard therapies (non-biologic disease-modifying antirheumatic drugs [DMARDs], apremilast, or non-steroidal anti-inflammatory drugs [NSAIDs]). The trial was done at 118 sites in 13 countries (Bulgaria, Czech Republic, Estonia, Latvia, Lithuania, Malaysia, Poland, Russia, Spain, Taiwan, Turkey, Ukraine, and the USA). This clinical trial conforms with Declaration of Helsinki and Good Clinical Practice guidelines. The protocol was approved by each site's governing ethical body.

Participants

Adults with psoriatic arthritis for at least 6 months, fulfilling the classification criteria for psoriatic arthritis[13] and with at least five tender and five swollen joints; C-reactive protein (CRP) concentration of 0·6 mg/dL or more; current or documented history of psoriasis; and either inadequate response to, or intolerance of, standard non-biologic treatment were eligible. Standard treatment included at least 3 months of non-biologic DMARDs, at least 4 months of apremilast at the approved dose (if discontinued >4 weeks before receiving study treatment), or at least 4 weeks of NSAIDs for psoriatic arthritis. Previous exposure to biologics or Janus kinase inhibitors

precluded participation. Patients were permitted, but not required, to continue stable use of selected standard treatments, including NSAIDs or other analgesics up to the regional marketed dose approved; oral corticosteroids (≤10 mg/day of prednisone or equivalent dose); or non-biologic DMARDs (limited to methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day). Only one DMARD was permitted up to week 52. Patients also had to meet screening criteria for laboratory assessments and tuberculosis history, testing, and treatment (for latent tuberculosis). Full inclusion and exclusion criteria are in the appendix (pp 2–7). All patients provided written informed consent.

See Online for appendix

Randomisation and masking

At week 0, patients were centrally randomly assigned using an interactive web response system (with computer-generated permuted-block randomisation stratified by baseline non-biologic DMARD use [yes *vs* no] and most recent high-sensitivity serum CRP value before randomisation [<2·0 mg/dL *vs* ≥2·0 mg/dL]) in a 1:1:1 ratio to receive guselkumab every 4 weeks; guselkumab at week 0, week 4, and then every 8 weeks; or placebo. Placebo and guselkumab were provided in identical prefilled syringes with non-identifying labels, and patients in each treatment group received the same number of injections at the same timepoints (ie, guselkumab or matching placebo every 4 weeks) to ensure that patients and all study site personnel were masked to treatment assignment throughout the study.

Procedures

The trial design included a 6-week screening period; a 100-week treatment phase, with a placebo-controlled period from week 0 to week 24 and an active treatment period from week 24 to week 100; and 12-weeks of safety follow-up after the final administration of study treatment. At week 16, patients with less than 5% improvement in both swollen and tender joint counts were eligible for early escape, in which the investigator could initiate or increase the dose of NSAIDs or other analgesics (up to the regional marketed dose approved), oral corticosteroids (≤10 mg/day of prednisone or equivalent dose), or non-biologic DMARDs (limited to methotrexate ≤25 mg/week, sulfasalazine ≤3 g/day, hydroxychloroquine ≤400 mg/day, or leflunomide ≤20 mg/day). Study results up to week 24 are reported.

Guselkumab was administered as a 100-mg subcutaneous injection at week 0, week 4, and then every 4 weeks or every 8 weeks. Dose selection for DISCOVER-2 was as described for DISCOVER-1.[12] Clinical efficacy and safety assessments were done at screening, baseline, week 2, week 4, and every 4 weeks up to week 24. An independent joint assessor evaluated 66 joints for swelling and 68 joints for tenderness and established the presence and severity of enthesitis (using the Leeds enthesitis index) and dactylitis. Dactylitis severity for each digit was scored as 0 for none, 1 for mild, 2 for moderate, or 3 for severe dacytlitis (total score 0–60). Serum pharmacokinetic and immunogenicity assessments are as reported for DISCOVER-1.[12] Details of joint (American College of Rheumatology [ACR] response, 28-joint disease activity score incorporating CRP [DAS28-CRP]), skin (investigator's global assessment of psoriasis [IGA], psoriasis area and severity index [PASI]), physical function (health assessment questionnaire—disability index [HAQ-DI]), health-related quality of life (36-item short-form [SF-36] health survey), and safety (adverse events, routine haematology and chemistry assessments, and electronic Columbia suicide severity rating scale questionnaires) evaluations are as reported for DISCOVER-1.[12]

In DISCOVER-2, single radiographs of the hands (posteroanterior) and feet (anteroposterior) were obtained at screening and week 24. Radiographs were assessed independently by two central readers (masked to the order of radiographs and clinical data) using the van der Heijde-Sharp (vdHS) score modified for psoriatic arthritis (distal interphalangeal joints of hands added).[14] Adjudication was used as mandated by primary reader disagreement. The total psoriatic arthritis-modified vdHS score (range 0–528) sums the joint erosion score (range 0–320; 0 for no erosions to 5 for extensive loss of bone from >50% of the articulating bone) and the joint space narrowing score (range 0–208; 0 for no joint space narrowing to 4 for complete loss of joint space, bony ankylosis, or complete luxation). The average score of the two readers was used in analyses.

Outcomes

The primary endpoint was the ACR20 response rate at week 24. Major secondary endpoints at week 24 were ACR50 and ACR70 responses; changes from baseline in DAS28-CRP scores; IGA skin response (score 0 or 1 and ≥2-grade improvement from baseline) among patients with at least 3% body surface area of psoriasis and IGA score of at least 2 (mild-to-severe psoriasis) at baseline; changes from baseline in HAQ-DI and psoriatic arthritis-modified vdHS scores; changes from baseline in, and resolution of, enthesitis and dactylitis pooled across DISCOVER-1 and DISCOVER-2; changes in the SF-36 physical component summary (PCS) and mental component summary (MCS) scores; and at week 16, ACR20 and ACR50 response rates. Other selected key secondary outcomes were clinically meaningful improvement (≥0·35) in HAQ-DI scores in patients with baseline HAQ-DI scores of at least 0·35; improvement in PASI of at least 75% (PASI75), 90% (PASI90), and 100% (PASI100) in patients with mild-to-severe psoriasis at baseline; and minimal disease activity, all at week 24. Patients were considered to have achieved minimal disease activity if fulfilling at least five of the following seven criteria: tender joint count 1 or less, swollen joint count 1 or less, PASI score 1 or less, patient pain visual analogue scale (VAS)

score 15 or less, patient global disease activity VAS score 20 or less, HAQ-DI score 0·5 or less, and tender entheseal points 1 or less. Safety outcomes included adverse events, serious adverse events, adverse events resulting in discontinuation of study drug, infections, injection-site reactions, malignancies, major adverse cardiovascular events, suicidal ideation or behaviour (based on electronic Columbia Suicide Severity Rating Scale questionnaire or reported adverse events), and clinical laboratory abnormalities classified by National Cancer Institute common terminology criteria for adverse events (NCI-CTCAE) grades. A major adverse cardiovascular event was predefined as cardiovascular death, non-fatal myocardial infarction, or non-fatal stroke.

Statistical analysis

Assuming week 24 ACR20 response rates of 45% with guselkumab versus 25% with placebo, 684 patients (228 per treatment group) were required to provide at least 99% statistical power (α=0·05; two-sided). With 684 patients, the study was estimated to have 90% power to detect a treatment difference in change from baseline in total psoriatic arthritis-modified vdHS scores, assuming mean changes from baseline at week 24 of 0·9 in the placebo group and 0·3 in the guselkumab groups and an SD of 2·5 for each treatment.

To increase sample size, endpoints related to enthesitis and dactylitis among the smaller number of patients with those conditions at baseline were prespecified to be tested by pooling data from this study with those from DISCOVER-1.[12] Results of these pooled analyses are presented here.

Because of differences in health authority requirements for multiplicity control between the USA and other countries, two graphical testing procedures were prespecified to control the overall type 1 error at α=0·05 (two-sided). For both approaches, the primary endpoint (ACR20 response at week 24) was first tested for the every 4 weeks group and then for the every 8 weeks group (each at 0·05 level). The first graphical procedure (appendix p 15) controlled the overall type 1 error rate across both dosing regimens at the 0·05 level for the primary endpoint and the following major secondary endpoints at week 24: IGA skin response among patients with mild-to-severe psoriasis at baseline; changes in HAQ-DI, psoriatic arthritis-modified vdHS, and SF-36 PCS scores; resolution of dactylitis and enthesitis among patients with the respective condition at baseline pooled across both DISCOVER trials; and changes in SF-36

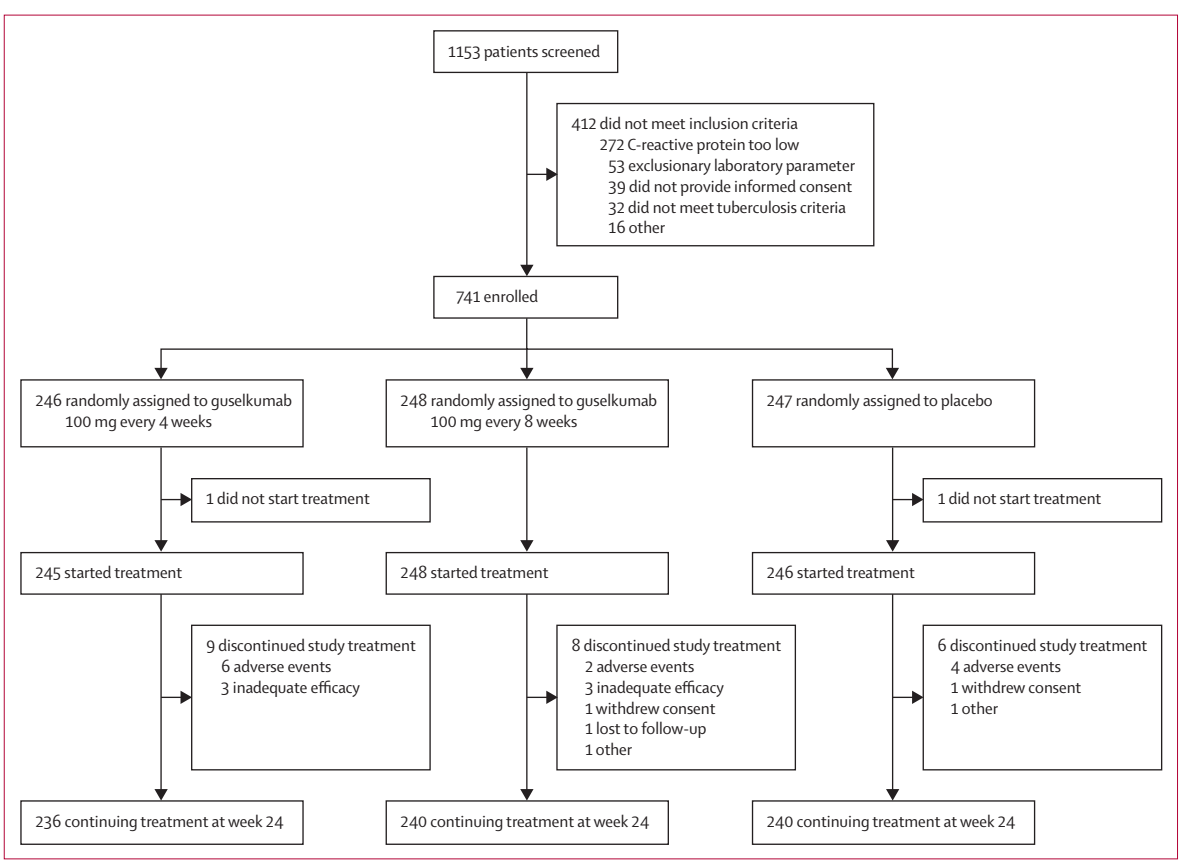

Figure 1: **Trial profile**
12 patients in the every 4 weeks group, 16 in the every 8 weeks group, and 38 in the placebo group were eligible for early escape at week 16.

MCS scores. Results of this testing procedure are presented in the main manuscript text and those from the second graphical procedure (appendix p 15), which controlled the overall type 1 error rate for each dosing regimen at the 0·05 level for all major secondary endpoints, except changes from baseline in enthesitis and dactylitis scores at week 24, with two parallel procedures, are in the appendix (pp 11–12). For endpoints not controlled for multiplicity, unadjusted (nominal) p values provided should be interpreted only as supportive.

Data handling rules were applied to all clinical efficacy analyses. Patients who met treatment-failure criteria (discontinued study treatment, terminated study participation, initiated or increased DMARD or oral corticosteroid doses, or initiated protocol-prohibited psoriatic arthritis treatment) were considered non-responders for binary endpoints and as having no improvement from baseline for continuous endpoints. Missing data, assumed to be missing at random, were imputed as non-responders for binary endpoints and using multiple imputation for continuous endpoints assuming they were missing at random and using the predicted value from the full conditional specification regression method (requiring 200 successful imputations) for any missing pattern. For radiographic endpoints, treatment failure rules were not applied, and missing data were assumed to be missing at random and were imputed using multiple imputation. Each variable eligible for imputation was to be restricted to only impute within its possible range of values.

Efficacy analyses up to week 24 included all randomly assigned patients who received at least one administration of study treatment, analysed according to assigned treatment groups. Treatment differences for binary endpoints were assessed via a Cochran-Mantel-Haenszel test; those for continuous endpoints used an analysis of covariance model. All models included treatment group, baseline non-biologic DMARD use (yes *vs* no), most current CRP value before group assignment (<2·0 mg/dL *vs* ≥2·0 mg/dL), and baseline value as explanatory factors. Including study and the randomisation factors as explanatory variables was intended to reduce variability arising from the study differences (eg, population and study regions). Continuous radiographic endpoints were compared using an analysis of covariance test. The 95% CIs surrounding the percentage differences versus placebo were established by the Wald statistic.

An independent data monitoring committee examined data on a continuing basis up to the week 24 database lock to ensure the safety of the study participants. Statistical analyses were done using SAS, version 9.4, with SAS/STAT, version 14.2. This study is registered in ClinicalTrials.gov (NCT03158285) and recruitment is finished.

	Guselkumab 100 mg		Placebo (n=246)
	Every 4 weeks (n=245)	Every 8 weeks (n=248)	
Age, years	45·9 (11·5)	44·9 (11·9)	46·3 (11·7)
Sex			
Female	103 (42%)	119 (48%)	129 (52%)
Male	142 (58%)	129 (52%)	117 (48%)
Race			
White	242 (99%)	240 (97%)	242 (98%)
Asian	3 (1%)	8 (3%)	4 (2%)
Bodyweight, kg	85·8 (19·5)	83·0 (19·3)	84·0 (19·7)
Psoriatic arthritis duration, years	5·5 (5·9)	5·1 (5·5)	5·8 (5·6)
Number of swollen joints, 0–66	12·9 (7·8)	11·7 (6·8)	12·3 (6·9)
Number of tender joints, 0–68	22·4 (13·5)	19·8 (11·9)	21·6 (13·1)
Patient's assessment of pain, 0–10 cm VAS	6·2 (2·0)	6·3 (2·0)	6·3 (1·8)
Patient's global assessment—arthritis, 0–10 cm VAS	6·4 (1·9)	6·5 (1·9)	6·5 (1·8)
Physician's global assessment, 0–10 cm VAS	6·6 (1·5)	6·6 (1·6)	6·6 (1·5)
HAQ-DI score, 0–3	1·2 (0·6)	1·3 (0·6)	1·3 (0·6)
C-reactive protein, mg/dL	1·2 (0·6–2·3)	1·3 (0·7–2·5)	1·2 (0·5–2·6)
Psoriatic body surface area, 0–100%	18·2% (20·0)	17·0% (21·0)	17·1% (20·0)
Investigator's global assessment score of 3 or 4	117 (48%)	108 (44%)	115 (47%)
PASI score, 0–72	10·8 (11·7)	9·7 (11·7)	9·3 (9·8)
Psoriatic arthritis-modified vdHS score, 0–528	27·2 (42·2)	23·0 (37·8)	23·8 (37·8)
Patients with enthesitis	170 (69%)	158 (64%)	178 (72%)
Leeds enthesitis index score, 1–6*	3·0 (1·7)	2·6 (1·5)	2·8 (1·6)
Patients with dactylitis	121 (49%)	111 (45%)	99 (40%)
Dactylitis score, 1–60†	8·6 (9·6)	8·0 (9·6)	8·4 (9·3)
Short form-36			
Physical component summary score, 0–100	33·3 (7·1)	32·6 (7·9)	32·4 (7·0)
Mental component summary score, 0–100	48·4 (11·0)	47·4 (10·8)	47·2 (12·0)
Previous apremilast use	5 (2%)	4 (2%)	4 (2%)
Drug use at baseline			
DMARDs	170 (69%)	170 (69%)	172 (70%)
Methotrexate	146 (60%)	141 (57%)	156 (63%)
Methotrexate dose, mg/week	15·6 (5·0)	15·3 (5·2)	15·2 (4·6)
Oral corticosteroids for psoriatic arthritis	46 (19%)	50 (20%)	49 (20%)
Dose equivalent to prednisone, mg/day	7·0 (2·4)	6·8 (2·5)	7·8 (2·5)
NSAIDs for psoriatic arthritis	171 (70%)	165 (67%)	168 (68%)

Data are n (%), mean (SD), or median (IQR). DMARDs=disease-modifying antirheumatic drugs. HAQ-DI=health assessment questionnaire—disability index. NSAIDs=non-steroidal anti-inflammatory drugs. PASI=psoriasis area and severity index. VAS=visual analogue scale. vdHS=van der Heijde-Sharp. *Among patients with available Leeds enthesitis index score at baseline (every 4 weeks group n=166; every 8 weeks group n=157; and placebo group n=175). †Among patients with available dactylitis score at baseline (every 4 weeks group n=121; every 8 weeks group n=111; and placebo group n=99).

Table 1: **Summary of DISCOVER-2 baseline patient characteristics (all treated patients, per random group assignment)**

Role of the funding source

Employees of the funder had a role in study design, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all study data and had final responsibility to submit for publication.

Results

From July 13, 2017, to Aug 3, 2018, we screened 1153 patients, of whom 412 were not eligible, most often for having serum CRP levels lower than 0·6 mg/dL. 741 patients were enrolled and randomly assigned to receive either guselkumab every 4 weeks (n=246), guselkumab every 8 weeks (n=248), or placebo (n=247). All patients received treatment except one in the every 4 weeks group and one in the placebo group, who were therefore not included in analyses (figure 1). At week 16, 12 (5%) of 245 guselkumab every 4 weeks, 13 (5%) of 248 guselkumab every 8 weeks, and 38 (15%) of 246 placebo-treated patients had less than 5% improvement in both tender and swollen joint counts and qualified for early escape, of which seven patients in the guselkumab every 4 weeks group, six in the every 8 weeks group, and 14 in the placebo group initiated or increased the dose of NSAIDs, oral corticosteroids, or permitted non-biologic DMARDs. 23 (3%) of 739 treated patients discontinued study treatment before week 24, most commonly due to adverse events.

Baseline characteristics were generally well balanced across the groups. Modest numerical differences were observed between the guselkumab and placebo groups for the proportions of men, severity of psoriasis assessed by the PASI score, and presence of dactylitis and enthesitis at study outset. Background medication use was consistent across the treatment groups (table 1). When pooled across DISCOVER-1 and DISCOVER-2, enthesitis and dactylitis scores and the proportion of patients with dactylitis at baseline were similar across the treatment groups. The proportion of patients with enthesitis at baseline was slightly higher in the placebo group than in the guselkumab groups. The proportions of patients with a history of enthesitis or dactylitis, as well as the median duration of enthesitis or dactylitis at baseline, were similar across the treatment groups. Thus, no notable imbalance across treatment groups was observed with respect to enthesitis and dactylitis disease characteristics at baseline or psoriatic arthritis disease characteristics in patients with enthesitis or dactylitis at baseline. At baseline, most patients (713 [96%] of 739) had a psoriatic arthritis-modified vdHS score greater than 0, including 241 (98%) of 245 in the every 4 weeks group, 234 (94%) of 248 in the every 8 weeks group and 238 (97%) of 246 in the placebo group.

The final week 24 visit occurred on March 6, 2019. Major protocol deviations were evenly distributed between the combined guselkumab groups (35 [7%] of 493) and the placebo group (23 [9%] of 246). Overall, 11 patients (five guselkumab and six placebo) entered the study without satisfying all criteria, six (four guselkumab and two placebo) received the incorrect treatment or dose), six (three guselkumab and three placebo) received a prohibited medication, and one (guselkumab) met a withdrawal criterion but was not withdrawn. No deviation was considered to affect the overall results.

For the study's primary endpoint, significantly greater proportions of patients in the guselkumab every 4 weeks (156 [64%] of 245 [95% CI 57–70]) and every 8 weeks

	Guselkumab 100 mg		Placebo (n=246)
	Every 4 weeks (n=245)	Every 8 weeks (n=248)	
Primary endpoint			
ACR20 response at week 24	156 (64%)	159 (64%)	81 (33%)
Percentage difference *vs* placebo	31% (22 to 39)	31% (23 to 40)	..
US procedure-adjusted p value	<0·0001	<0·0001	..
Major secondary endpoints controlled by US procedure			
Investigator's global assessment response at week 24*	126/184 (68%)	124/176 (70%)	35/183 (19%)
Percentage difference *vs* placebo	50% (41 to 58)	51% (42 to 60)	..
US procedure-adjusted p value	<0·0001	<0·0001	..
HAQ-DI, least squares mean change at week 24	−0·40 (−0·46 to −0·34)	−0·37 (−0·43 to −0·31)	−0·13 (−0·19 to −0·07)
Least squares mean difference *vs* placebo	−0·27 (−0·35 to −0·19)	−0·24 (−0·32 to −0·15)	..
US procedure-adjusted p value	<0·0001	<0·0001	..
Psoriatic arthritis-modified vdHS, median (IQR) change at week 24	0·00 (−0·50 to 0·50)	0·00 (−0·50 to 1·00)	0·00 (0·00 to 1·00)
Least squares mean change at week 24	0·29 (−0·05 to 0·63)	0·52 (0·18 to 0·86)	0·95 (0·61 to 1·29)
Least squares mean difference *vs* placebo	−0·66 (−1·13 to −0·19)	−0·43 (−0·90 to 0·03)	..
US procedure-adjusted p value	0·011	0·072	..
Short form-36 physical component summary, least squares mean change at week 24	7·04 (6·14 to 7·94)	7·39 (6·50 to 8·29)	3·42 (2·53 to 4·32)
Least squares mean difference *vs* placebo	3·62 (2·39 to 4·85)	3·97 (2·75 to 5·20)	..
US procedure-adjusted p value	0·011	0·011	..
Short form-36 mental component summary, least squares mean change at week 24	4·22 (3·14 to 5·29)	4·17 (3·10 to 5·23)	2·14 (1·07 to 3·22)
Least squares mean difference *vs* placebo	2·07 (0·60 to 3·54)	2·02 (0·56 to 3·49)	..
US procedure-adjusted p value	0·072	0·072	..
Major secondary endpoints not controlled by US procedure			
ACR20 response at week 16	137 (56%)	137 (55%)	83 (34%)
Percentage difference *vs* placebo	22% (14 to 31)	22% (13 to 30)	..
Unadjusted p value	<0·0001	<0·0001	..
ACR50 response at week 24	81 (33%)	78 (31%)	35 (14%)
Percentage difference *vs* placebo	19% (12 to 26)	17% (10 to 24)	..
Unadjusted p value	<0·0001	<0·0001	..
ACR70 response at week 24	32 (13%)	46 (19%)	10 (4%)
Percentage difference *vs* placebo	9% (4 to 14)	14% (9 to 20)	..
Unadjusted p value	0·0004	<0·0001	..
ACR50 response at week 16	51 (21%)	71 (29%)	23 (9%)
Percentage difference *vs* placebo	12% (5 to 18)	19% (13 to 26)	..
Unadjusted p value	0·0004	<0·0001	..
DAS28-CRP, least squares mean change at week 24	−1·62 (−1·76 to −1·49)	−1·59 (−1·72 to −1·45)	−0·97 (−1·11 to −0·84)
Least squares mean difference *vs* placebo	−0·65 (−0·83 to −0·47)	−0·61 (−0·80 to −0·43)	..
Unadjusted p value	<0·0001	<0·0001	..

(Table 2 continues on next page)

	Guselkumab 100 mg		Placebo (n=246)
	Every 4 weeks (n=245)	Every 8 weeks (n=248)	
(Continued from previous page)			
Additional secondary endpoints not controlled by US procedure			
HAQ-DI improvement ≥0·35† at week 24	128/228 (56%)	114/228 (50%)	74/236 (31%)
Percentage difference *vs* placebo	24% (16 to 33)	19% (10 to 27)	..
Unadjusted p value	<0·0001	<0·0001	..
PASI75 response at week 24*	144/184 (78%)	139/176 (79%)	42/183 (23%)
Percentage difference *vs* placebo	55% (47 to 64)	56% (47 to 64)	..
Unadjusted p value	<0·0001	<0·0001	..
PASI90 response at week 24*	112/184 (61%)	121/176 (69%)	18/183 (10%)
Percentage difference *vs* placebo	51% (43 to 59)	59% (51 to 67)	..
Unadjusted p value	<0·0001	<0·0001	..
PASI100 response at week 24*	82/184 (45%)	80/176 (45%)	5/183 (3%)
Percentage difference *vs* placebo	42% (35 to 50)	42% (35 to 50)	..
Unadjusted p value	<0·0001	<0·0001	..
Minimal disease activity response at week 24	46 (19%)	62 (25%)	15 (6%)
Percentage difference *vs* placebo	13% (7 to 18)	19% (13 to 25)	..
Unadjusted p value	<0·0001	<0·0001	..

Data are n (%) or n/N (%) unless otherwise specified. Ranges in parentheses are 95% CIs unless otherwise specified. 13 (5%) patients in the every 4 weeks group, 12 (5%) in the every 8 weeks group, and 17 (7%) in the placebo group met treatment failure criteria. After application of treatment failure rules ACR20 data were missing for two every 8 weeks and one placebo patients; DAS28-CRP for two every 8 weeks and three placebo patients; investigator's global assessment for one in each group; HAQ-DI for two every 8 weeks and two placebo patients; vdHS for five every 4 weeks, one every 8 weeks, and one placebo patients; short form-36 scores for two every 8 weeks and two placebo patients; PASI for one per group; and enthesitis or dactylitis resolution for one every 8 weeks and one placebo patients. Unadjusted (nominal) p values are not controlled for multiplicity and should be interpreted only as supportive. ACR20=American College of Rheumatology 20% improvement. ACR50=ACR 50% improvement. ACR70=ACR 70% improvement. DAS28-CRP=28-joint disease activity score based on C-reactive protein. HAQ-DI=health assessment questionnaire—disability index. PASI75=psoriasis area and severity index 75% improvement. PASI90=PASI 90% improvement. PASI100=PASI 100% improvement. vdHS=van der Heijde-Sharp. *Assessed in patients with at least 3% body surface area affected by psoriasis and investigator's global assessment of psoriasis score of at least 2 at week 0. †Assessed in patients with HAQ-DI of at least 0·35 at week 0.

Table 2: **Summary of DISCOVER-2 efficacy findings (all treated patients, per random group assignment)**

(159 [64%] of 248 [58–70]) groups than in the placebo group (81 [33%] of 246 [27–39]) achieved an ACR20 response at week 24 (percentage differences *vs* placebo 31% [95% CI 22–39] for the every 4 weeks group and 31% [23–40] for the every 8 weeks group; both p<0·0001; table 2). Results of all prespecified sensitivity analyses were consistent with the primary analysis (data not shown).

Similar response patterns were observed for both guselkumab dosing regimens across patient subgroups defined by demography, baseline disease characteristics, and previous and baseline medication use. ACR20 response at week 24 was similar to that of the overall study population in the subgroup of patients with methotrexate use at baseline (every 4 weeks 92 [63%] of 146 and every 8 weeks 85 [60%] of 141).

In both guselkumab groups, a greater proportion of patients achieved ACR20 responses than in the placebo group by week 4 (after one injection of guselkumab); response rates continued to increase up to week 24 (figure 2A). ACR50 and ACR70 response rates were also consistently higher with both guselkumab dosing regimens versus placebo from week 12 onwards (figure 2B, C). Further, greater improvements in DAS28-CRP scores at week 24 were observed with guselkumab every 4 weeks (least squares mean change –1·62 [95% CI –1·76 to –1·49]) and every 8 weeks (–1·59 [–1·72 to –1·45]) versus placebo (–0·97 [–1·11 to –0·84]; table 2).

Among DISCOVER-1[12] and DISCOVER-2 patients with the dactylitis at baseline, dactylitis resolved at week 24 in a significantly higher proportion of patients in the guselkumab every 4 weeks group (101 [64%] of 159; p=0·011 *vs* placebo) and every 8 weeks group (95 [59%] of 160; p=0·0301 *vs* placebo) than in the placebo group (65 [42%] of 154; table 3). In patients with enthesitis at baseline pooled across both trials, resolution of enthesitis was observed in significantly higher proportions of patients in the guselkumab every 4 weeks group (109 [45%] of 243; p=0·0301 *vs* placebo) and every 8 weeks group (114 [50%] of 230; p=0·0301 *vs* placebo) than in the placebo group (75 [29%] of 255). Improvements from baseline in the Leeds enthesitis index and dactylitis scores at week 24 were also numerically greater with both guselkumab dosing regimens than placebo when pooled across DISCOVER-1 and DISCOVER-2 (table 3), and consistent results were observed in the individual trials (appendix pp 13–14).

Patients treated with guselkumab every 4 weeks demonstrated significantly less progression of structural damage, as reflected by smaller changes from baseline in the psoriatic arthritis-modified vdHS score at week 24 than placebo-treated patients (least squares mean 0·29 [95% CI –0·05 to 0·63] in the every 4 weeks group *vs* 0·95 [0·61 to 1·29] in the placebo group; p=0·011). Guselkumab administered every 8 weeks resulted in a non-significant decrease in radiographic progression (least squares mean 0·52 [0·18 to 0·86]; p=0·072) compared with placebo (table 2). A cumulative probability plot of changes in modified vdHS scores from baseline at week 24 is in the appendix (p 16).

In patients with mild-to-severe psoriasis at baseline, guselkumab every 4 weeks and every 8 weeks significantly improved skin disease, as assessed by IGA response rates, at week 24 versus placebo (table 2, figure 2D). PASI75, PASI90, and PASI100 response rates at week 24 were also higher in the guselkumab groups than the placebo group (table 2).

Guselkumab significantly improved HAQ-DI scores from baseline at week 24 versus placebo. The proportions of patients with improvement in the HAQ-DI score of at least 0·35 at week 24, among those with baseline HAQ-DI of at least 0·35, also indicated that guselkumab improved physical function to a greater extent than placebo (table 2).

Patients started the study with impaired health-related quality of life as assessed by mean SF-36 PCS (range 32·4–33·3) and MCS (47·2–48·4) scores (USA general population norm is 50·0). Significant improvements in SF-36 PCS scores from baseline at week 24 were seen in

both guselkumab groups versus placebo. Non-significant improvements in SF-36 MCS scores were also observed for both guselkumab dosing regimens versus placebo; although the lower bounds of the 95% CIs of the differences from placebo exceeded 0, differences were not significant after multiplicity adjustment (table 2). At week 24, minimal disease activity was achieved by significantly greater proportions of patients in each of the guselkumab groups than in the placebo group (table 2).

An overview of guselkumab pharmacokinetic and immunogenicity findings is in the appendix (p 10).

Up to week 24, adverse events were reported by 113 (46%) of 245 patients in the every 4 weeks group, 114 (46%) of 248 in the every 8 weeks group, and 100 (41%) of 246 patients in the placebo group. Serious adverse events were reported by eight (3%) patients in the every 4 weeks group, three (1%) in the every 8 weeks group, and seven (3%) in the placebo group; and adverse events led to discontinuation of study treatment for six (2%) patients in the every 4 weeks groups, two (1%) in the every 8 weeks group, and four (2%) in the placebo group (table 4).

The adverse events reported by at least 3% of patients in any treatment group were infections (upper respiratory tract infection, nasopharyngitis, and bronchitis) and increased alanine aminotransferase and aspartate aminotransferase (table 4). Serious infections occurred in three (1%) patients receiving guselkumab every 4 weeks (acute hepatitis B [de novo], influenza pneumonia, and oophoritis), one (<1%) receiving guselkumab every 8 weeks (pyrexia, probably of urinary origin), and one (<1%) placebo-treated patient (post-procedural fistula). No *Candida* or opportunistic infections or cases of active tuberculosis occurred up to week 24. No adverse events of inflammatory bowel disease were reported in guselkumab-treated patients, whereas one was suspected in the placebo group.

No deaths were reported up to week 24. One patient in each of the guselkumab every 4 weeks (at week 2) and placebo (pre-existing and at week 12) groups had suicidal ideation (level 1—wish to be dead); no patient reported suicidal or self-injurious behaviour without suicidal intent. Two patients were diagnosed with a malignancy (melanoma in situ at week 4 in the every 8 weeks group and clear-cell renal cell carcinoma at week 12 in the placebo group). One patient had a major adverse cardiovascular event: a 58-year-old woman with a history of hypertension, hyperlipidaemia, and diabetes and who was receiving guselkumab 100 mg every 4 weeks had an ischaemic stroke at week 20. The patient recovered, and study treatment was discontinued.

Two patients had NCI-CTCAE grade 3 or 4 neutropenia, one in the placebo group (grade 3 [<1·0–0·5×10⁹/L] at week 8) and one in the guselkumab every 4 weeks group (did not recur upon retest the following week, not associated with infections or study drug interruptions). No other NCI-CTCAE grade 3 or higher haematology

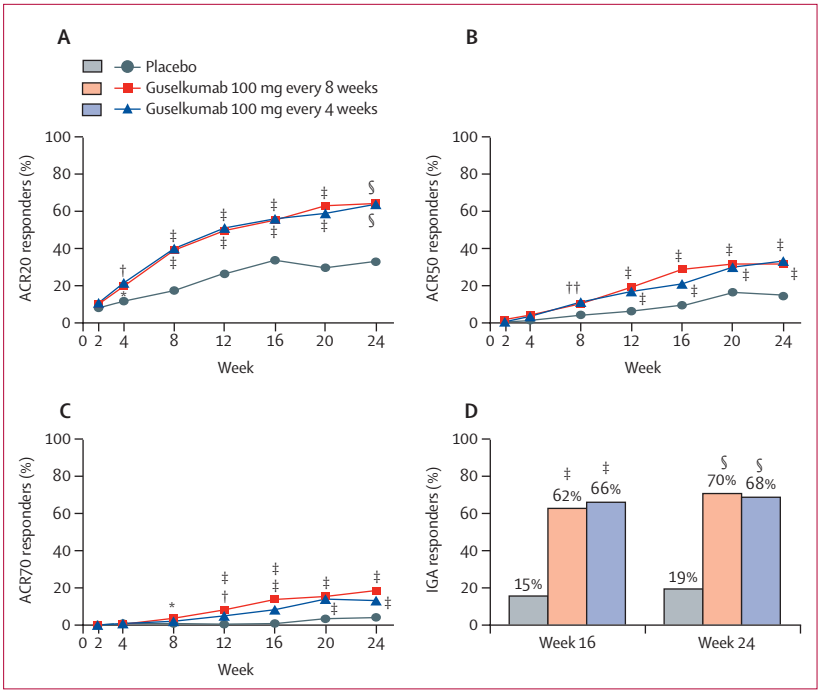

Figure 2: **DISCOVER-2 efficacy up to week 24 (all treated patients, per random group assignment)**
Proportions of patients with ACR20 response (A); ACR50 response (B); ACR70 response (C); and IGA response (D) over time. IGA response was assessed in patients with at least 3% body surface area of psoriasis and IGA score of at least 2 (mild-to-severe psoriasis) at baseline (n=184 for the every 4 weeks group; n=176 for the every 8 weeks group; and n=183 for the placebo group). ACR20=American College of Rheumatology 20% improvement. ACR50=ACR 50% improvement. ACR70=ACR 70% improvement. IGA=investigator's global assessment of psoriasis. *p<0·05. †p<0·01. ‡p<0·001. §Adjusted p<0·0001.

	Guselkumab 100 mg		Placebo
	Every 4 weeks	Every 8 weeks	
Major secondary endpoints controlled by US procedure*			
Resolution of dactylitis	101/159 (64%)	95/160 (59%)	65/154 (42%)
Percentage difference *vs* placebo	21% (10 to 32)	18% (7 to 29)	..
US procedure-adjusted p value	0·011	0·0301	..
Resolution of enthesitis	109/243 (45%)	114/230 (50%)	75/255 (29%)
Percentage difference *vs* placebo	15% (6 to 23)	20% (12 to 28)	..
US procedure-adjusted p value	0·0301	0·0301	..
Major secondary endpoints not controlled by US procedure			
Dactylitis score, least squares mean change	−5·97 (−6·84 to −5·11)	−6·10 (−6·92 to −5·27)	−4·21 (−5·05 to −3·36)
Least squares mean difference *vs* placebo	−1·77 (−2·87 to −0·66)	−1·89 (−2·99 to −0·79)	..
Unadjusted p value	0·0025	0·0020	..
Leeds enthesitis index score, least squares mean change	−1·59 (−1·79 to −1·38)	−1·52 (−1·73 to −1·31)	−1·02 (−1·22 to −0·82)
Least squares mean difference *vs* placebo	−0·57 (−0·83 to −0·31)	−0·50 (−0·77 to −0·23)	..
Unadjusted p value	0·0017	0·0003	..

Data are n/N unless otherwise specified. Ranges in parentheses are 95% CIs. Unadjusted (nominal) p values are not controlled for multiplicity and should be interpreted only as supportive. *Per the preplanned statistical analysis plan, resolution of dactylitis and enthesitis data were combined across DISCOVER-1 and DISCOVER-2 as major secondary endpoints in the US testing procedure.

Table 3: **Summary of pooled DISCOVER-1 and DISCOVER-2 dactylitis and enthesitis results at week 24 (all treated patients, per random group assignment)**

	Guselkumab 100 mg		Placebo (n=246)
	Every 4 weeks (n=245)	Every 8 weeks (n=248)	
Length of follow-up, weeks	23·8 (1·9)	23·9 (1·3)	24·0 (0·5)
Number of administrations	5·9 (0·7)	5·9 (0·5)	5·9 (0·3)
Patients with one or more adverse events	113 (46%)	114 (46%)	100 (41%)
Adverse events occurring in at least 3% of patients in any group (alphabetical order)			
Alanine aminotransferase increased	25 (10%)	15 (6%)	11 (4%)
Aspartate aminotransferase increased	11 (4%)	14 (6%)	6 (2%)
Bronchitis	10 (4%)	1 (<1%)	3 (1%)
Nasopharyngitis	12 (5%)	10 (4%)	9 (4%)
Upper respiratory tract infection	12 (5%)	6 (2%)	8 (3%)
Patients with one or more serious adverse events	8 (3%)*	3 (1%)†	7 (3%)‡
Patients with adverse event resulting in study drug discontinuation	6 (2%)§	2 (1%)¶	4 (2%)‖
Patients with major adverse cardiovascular event	1 (<1%)	0	0
Patients with malignancy	0	1 (<1%)	1 (<1%)
Patients with infection**	49 (20%)	40 (16%)	45 (18%)
Serious infection	3 (1%)	1 (<1%)	1 (<1%)
Patients with injection-site reaction	3 (1%)	3 (1%)	1 (<1%)
Patients with suicidal ideation	1 (<1%)	0	1 (<1%)

Data are mean (SD) or n (%). *One patient each with acute hepatitis B, blue toe syndrome, femur fracture, influenza pneumonia, ischaemic stroke, lower limb fracture and metal poisoning, oophoritis, and osteoarthritis. †One patient each with ankle fracture, coronary artery disease, and pyrexia. ‡One patient each with clear cell renal cell carcinoma, isoniazid-induced liver injury, inflammatory bowel disease (suspected), obesity, post-procedural fistula, tubulointerstitial nephritis, and unstable angina. §One patient each with acute hepatitis B (de novo); allergic dermatitis; isoniazid-induced liver injury; ischaemic stroke; rhinovirus infection; and injection-site erythema, swelling, and warmth. ¶One patient each with rash and malignant melanoma in situ. ‖One patient each with clear cell renal cell carcinoma, isoniazid-induced liver injury, inflammatory bowel disease (suspected), and tubulointerstitial nephritis. **Events identified by investigators as infections.

Table 4: **Summary of DISCOVER-2 safety results up to week 24 (all treated patients, per treatment received)**

abnormalities were observed in guselkumab-treated patients, except a case of anaemia in one guselkumab every 8 weeks patient (grade 3 haemoglobin [<80·0 g/L] of 69 g/L at week 16).

The proportions of patients with increased alanine aminotransferase or aspartate aminotransferase levels reported as adverse events appeared slightly higher in the guselkumab than placebo groups (table 4). Events of NCI-CTCAE grade 2–3 alanine aminotransferase and aspartate aminotransferase increases were low and slightly more common in the guselkumab groups than the placebo group (appendix p 14). None of these grade 2–3 increases were associated with clinically significant increases in bilirubin. These laboratory abnormalities resulted in study drug discontinuation in one placebo-treated patient (week 8 alanine aminotransferase of 1053 U/L and aspartate aminotransferase of 665 U/L related to serious isoniazid-induced hepatitis that resolved by week 12) and two patients receiving guselkumab every 4 weeks (one with week 4 alanine aminotransferase of 479 U/L and aspartate aminotransferase of 484 U/L related to a non-serious adverse event of isoniazid-induced hepatitis that resolved by week 16 and one with week 20 alanine aminotransferase of 373 U/L and aspartate aminotransferase of 238 U/L related to a serious adverse event of acute hepatitis B with no clinically significant increase in bilirubin; adverse events were resolving at last contact).

Discussion

Results of the DISCOVER-2 trial up to week 24 indicate that guselkumab, a selective IL-23 inhibitor that binds the cytokine's p19-subunit, effected robust improvements in signs and symptoms of joint disease in patients with psoriatic arthritis. The study met its primary endpoint for ACR20 response at week 24 in both the guselkumab 100 mg every 4 weeks and every 8 weeks groups compared with placebo-treated patients. Similarly, ACR50 and ACR70 response rates demonstrated that treatment with guselkumab results in clinically meaningful reductions in the joint signs and symptoms of psoriatic arthritis. Improvement occurred at early timepoints and increased over time up to week 24.

Guselkumab, whether administered every 4 weeks or every 8 weeks, elicited significant improvements in skin psoriasis, physical function, and health-related quality of life, all of which influence mental health, work productivity, and the economic burden of psoriatic arthritis.[15,16] Of particular note, more than 60% of guselkumab-treated patients achieved PASI90 and 45% achieved PASI100 responses at week 24. These findings are consistent with the established efficacy of guselkumab in treating moderate-to-severe plaque psoriasis.[7,9,10] Guselkumab every 4 weeks inhibited progression of structural damage versus placebo at week 24, based on changes in the psoriatic arthritis-modified vdHS score. Guselkumab every 8 weeks dosing also reduced structural damage progression, but the difference from placebo was not statistically significant. This observation could derive from differences in total guselkumab exposure between dosing every 4 weeks and every 8 weeks during weeks 0–24. Radiographic data being collected up to 1 year will provide additional data with which to assess the ability of the guselkumab dosing regimens to limit progression of structural damage.

Inflammation of periarticular tissues such as that leading to dactylitis and enthesitis is a hallmark of psoriatic arthritis that can present a treatment challenge.[17] IL-23 is essential for activating Th17 cells, which produce IL-17A.[2] IL-23 also regulates innate cells, which are predominantly located in non-lymphoid tissue and produce pro-inflammatory cytokines (IL-17, IL-22, and interferon-γ), thereby inducing local tissue inflammation.[18–21] Given that guselkumab 100 mg every 8 weeks has been shown to decrease serum IL-17A concentrations of patients with psoriatic arthritis to levels observed in healthy controls by week 16,[22] it is not unexpected that both guselkumab regimens afforded significantly higher proportions of patients with clinically resolved dactylitis and enthesitis at week 24 when data were pooled across DISCOVER-1 and DISCOVER-2.

As a downstream effector cytokine of IL-23, IL-17A has been implicated mechanistically in both inflammation and bone remodelling in a murine rheumatoid arthritis model by stimulating osteoclastogenesis; promoting bone resorption in fetal mouse long bones; and inducing expression of the receptor activator of nuclear factor κB ligand, an osteoclast differentiation factor, in osteoclast-supporting cells.[23] IL-23 can also induce IL-22, a cytokine implicated in bone formation.[2] Because IL-23 regulates several effector cytokines that are thought to contribute to psoriatic arthritis disease pathology, inhibition of multiple effector cytokines through IL-23 targeting might provide more effective modulation of these processes than single cytokine inhibition.

Guselkumab 100 mg was generally well tolerated in this psoriatic arthritis population, with no clinically meaningful differences between dosing every 4 or 8 weeks up to week 24. No *Candida* or opportunistic infections or cases of active tuberculosis were reported. One suspected case of inflammatory bowel disease was reported in a placebo-treated patient. There was no apparent association between the development of antibodies to guselkumab and the occurrence of injection-site reactions (appendix pp 10–11). The overall safety profile was generally consistent with that reported for patients with psoriasis.[7,9,24] In an analysis of data from more than 1800 patients enrolled in two phase 3 psoriasis studies,[24] guselkumab 100 mg every 8 weeks demonstrated a stable safety profile through 100 weeks of treatment with no safety signals related to serious infection, malignancy, major adverse cardiovascular events, or suicidality. Further, in more than 800 patients with psoriasis who participated in the VOYAGE-1 study,[25] no new safety signals were observed during up to 4 years of guselkumab 100 mg when given every 8 weeks.

The patients in DISCOVER-2 presented with an average of 12–13 swollen and 20–22 tender joints, along with substantial systemic inflammation (median serum CRP 1·2–1·3 mg/dL), possibly limiting the applicability of findings to patients with less active disease. The relatively high placebo response rates observed for joint (ACR20) and skin (IGA) outcomes might also affect data interpretation. However, these response rates are consistent with other recently reported findings in biologic-naive psoriatic arthritis populations,[26,27] and probably reflect higher expectations for efficacy as more potent therapies have become available for psoriatic arthritis. It will be important to assess whether the favourable responses and safety profile up to week 24 are maintained; such data are being collected throughout the 2-year DISCOVER-2 trial.

Thus, guselkumab was well tolerated and demonstrated robust efficacy in DISCOVER-2 across clinical domains crucial to achieving psoriatic arthritis remission, including reducing structural damage progression.[28] By binding to IL-23's p19 subunit, but not the p40 subunit it shares with IL-12, guselkumab targets the key upstream regulatory cytokine responsible for the Th17 pathway implicated in psoriatic arthritis, thereby providing a targeted but comprehensive approach to control the downstream inflammatory cascade and thus safely and effectively treat the diverse manifestations of psoriatic arthritis.

Contributors

All authors made substantial intellectual contribution to conception and design, or acquisition of data, or analysis and interpretation of data; drafted the article or revised it critically for important intellectual content; gave final approval of the version to be published; and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

PJM has received research grants, consultation fees, and speaker honoraria from AbbVie, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb (BMS), Celgene, Eli Lilly, Galapagos, Genentech, Gilead, GlaxoSmithKline, Janssen, Novartis, Pfizer, Sun Pharmaceuticals, and UCB. PR has received consulting fees from Abbott, AbbVie, Amgen, BMS, Celgene, Eli Lilly, Janssen, Novartis, and Pfizer, and has also received a research grant from Janssen. ABG has advisory board or consulting agreements with AbbVie, Allergan, Avotres Therapeutics, Beiersdorf, Boeringer Ingelheim, BMS, Celgene, Dermira, Eli Lilly, Incyte, Janssen, Leo Pharmaceuticals, Novartis, Reddy Labs, Sun Pharmaceutical Industries, UCB, Valeant, and Xbiotech; and research or educational grants from Boehringer Ingelheim, Incyte, Janssen, Novartis, Xbiotech, and UCB. APK, ECH, XLX, SS, PA, BZ, and YZ are employees of Janssen Research and Development (a subsidiary of Johnson & Johnson) and own Johnson & Johnson stock or stock options. DvdH has received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Cyxone, Daiichi, Eisai, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, and UCB; and serves as the director of Imaging and Rheumatology BV. IBM has received research grants or honoraria from AbbVie, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Janssen, Novartis, Pfizer, and UCB.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available online. Requests for access to the study data can be submitted through Yale Open Data Access Project.

For the **data sharing policy** see https://www.janssen.com/clinical-trials/transparency

For the **Yale Open Data Access Project site** see http://yoda.yale.edu

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