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Psoriatic arthritis

Highly selective tyrosine kinase 2 inhibition with zasocitinib (TAK-279) improves outcomes in patients with active psoriatic arthritis: a randomised phase 2b study

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ABSTRACT

Objectives: To assess the efficacy, safety, and tolerability of the investigational, oral, allosteric, highly selective, and potent tyrosine kinase 2 inhibitor zasocitinib (TAK-279) in patients with active psoriatic arthritis (PsA).

Methods: In this phase 2b, randomised, multicentre, double-blind, placebo-controlled, multiple-dose study, patients (≥18 years, with PsA symptoms for ≥6 months) received 30 mg, 15 mg, or 5 mg zasocitinib or placebo (1:1:1:1) once daily for 12 weeks, with a 4-week safety follow-up. The primary endpoint was American College of Rheumatology (ACR)20 response at week 12. Secondary efficacy endpoints included ACR50 response, ACR70 response, Psoriasis Area and Severity Index (PASI) 75 response among those with ≥3% body surface area at baseline and minimal disease activity (MDA) at week 12.

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Results: Overall, 290 patients (mean [SD] age, 49.9 [11.6] years; 57.2% female) received treatment. At week 12, 30 mg or 15 mg zasocitinib treatment resulted in significantly higher ACR20 responses (54.2%; $P = .002$ and 53.3%; $P = .002$, respectively) than placebo (29.2%). A numerically higher number of ACR50 responses were achieved at week 12 with 30 mg (26.4%; nominal $P = .009$) or 15 mg (26.7%; nominal $P = .005$) zasocitinib than placebo (9.7%). In addition, 30 mg zasocitinib demonstrated a numerically higher number of ACR70 responses (13.9% versus 5.6%, respectively; nominal $P = .158$), PASI 75 responses (45.7% versus 15.4%, respectively; nominal $P = .002$), and MDA (29.2% versus 12.5%, respectively; nominal $P = .014$) at week 12 versus placebo. In this small study of limited duration, most adverse events were mild/moderate and were more frequently observed in the higher dose group. In this small sample size, no new safety signals or clear dose-dependent laboratory parameter changes were identified.
Conclusions: Here, 30 mg and 15 mg zasocitinib demonstrated efficacy across core domains in patients with active PsA with no new safety signals. These findings will be confirmed in ongoing larger studies of longer duration.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Tyrosine kinase 2 (TYK2) is a critical mediator of the proinflammatory pathways fundamental to the pathophysiology of some immune-mediated inflammatory diseases (IMIDs) including psoriatic arthritis (PsA).
- Zasocitinib (TAK-279) is an investigational, oral, allosteric, highly selective, and potent TYK2 inhibitor being developed for the treatment of IMIDs, including PsA and plaque psoriasis.

WHAT THIS STUDY ADDS

- This phase 2b study reports a significantly higher proportion of patients achieved an American College of Rheumatology 20 response at week 12 with once daily 30 mg or 15 mg zasocitinib than with placebo.
- Treatment with 30 mg or 15 mg zasocitinib resulted in a numerically higher number of patients achieving low disease activity or remission across multiple composite measures of disease activity versus placebo, as early as week 12.
- Zasocitinib (30 mg) demonstrated numerically greater efficacy versus placebo across all skin efficacy endpoints assessed, with rapid onset evident as early as week 2.
- The safety and laboratory parameter profile of zasocitinib was consistent with previous studies in patients with plaque psoriasis, supporting the high selectivity of zasocitinib for TYK2.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE, OR POLICY

- The efficacy and tolerability of zasocitinib in patients with active PsA demonstrated in this phase 2b study could propel further long-term comparative clinical trials, potentially leading to new oral therapeutic options for PsA with an improved benefit-risk profile.
- The rapid and meaningful clinical responses observed with zasocitinib suggest that it could become a valuable oral treatment in clinical practice for patients with PsA, providing more options for individualised patient care.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic, immune-mediated inflammatory disease (IMID) with diverse manifestations [1–3]. Patients with PsA have a high overall burden of disease and are more likely to develop comorbidities, including obesity, cardiovascular disease, and hypertension, than matched controls, and also have a high prevalence of anxiety and depression [4,5]. The Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA), in conjunction with Outcome Measures in Rheumatology (OMERACT), has developed a core set of domains for PsA aiming to standardise outcome measurements in randomised clinical trials and longitudinal observational studies [6]. The goals of PsA treatment are to ameliorate signs and symptoms across multiple domains of the disease, improve physical function, prevent structural damage, and enhance health-related quality of life (HRQoL) [4,7].

Despite current treatment options, some patients with PsA continue to experience a high disease burden because available treatments may not adequately address all core PsA domains, while also not providing acceptable long-term safety [5,8]. This highlights the need for more comprehensive treatment strategies in patients without adequate disease control or with tolerability issues with current treatments and ultimately improvement in the long-term outcomes and quality of life of these patients with PsA. Tyrosine kinase 2 (TYK2) is a critical mediator of the activation of proinflammatory pathways fundamental to the pathophysiology of some IMIDs, including interleukin (IL)-12, IL-23, and type I interferon signalling [9,10]. Loss-of-function variants in the *TYK2* gene have protective effects against psoriasis and other IMIDs without detrimental effects [11]. Therefore, TYK2 inhibition is being investigated for the treatment of IMIDs including PsA and plaque psoriasis [9,10,12,13].

Zasocitinib (TAK-279) is an investigational, oral, allosteric, highly selective, and potent TYK2 inhibitor being developed for the treatment of IMIDs, including PsA and plaque psoriasis [14]. Zasocitinib was designed to maximise specific TYK2 inhibition and prevent inhibition of Janus kinase (JAK)1, JAK2, and JAK3 [14]. *In vitro* studies of zasocitinib have demonstrated selectivity for the TYK2 Janus homology (JH)2 domain over the JAK JH1 domain, without affecting JAK-mediated signalling [14,15].

The efficacy, safety, and tolerability of zasocitinib were assessed in patients with moderate-to-severe plaque psoriasis in a phase 2b study (ClinicalTrials.gov: NCT04999839) [16]. The study met its primary endpoint (Psoriasis Area and Severity Index [PASI] 75 at week 12) at doses ≥5 mg, with about one-third of patients in the highest dose group (30 mg) achieving PASI 100 (complete skin clearance) at week 12. Zasocitinib was generally well tolerated with no clear dose-related treatment-emergent adverse events (TEAEs) observed.

The aim of this phase 2b, randomised, clinical trial was to assess the efficacy, safety, and tolerability of zasocitinib in patients with active PsA.

METHODS

Study design

This was a phase 2b, randomised, multicentre, double-blind, placebo-controlled, multiple-dose study (NCT05153148) [17]. Patients with active PsA from 45 centres across the USA (n = 17),

Poland (n = 18), Germany (n = 4), and the Czech Republic (n = 6) were enrolled. Patients were randomised 1:1:1:1 to receive orally administered 5 mg, 15 mg, or 30 mg zasocitinib or an identical placebo once daily for 12 weeks, with an additional 4-week follow-up period for safety monitoring (Supplementary Fig S1). Randomisation occurred at the day −7 visit, and patients were stratified according to region (USA/Germany, Czech Republic/Poland) and whether they had received prior treatment with biologic disease-modifying antirheumatic drugs (bDMARDs) or any other disease-modifying antirheumatic drugs (DMARDs) except for azathioprine, chloroquine, ciclosporin, hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.

Patient involvement

Patients and/or the public were not involved in the design, conduction, reporting, or dissemination of this research.

Patient population

Eligible patients were aged ≥18 years with active PsA and a history of PsA symptoms for ≥6 months before screening (screening occurred ≤30 days before day 1 of the study), had ≥3 tender and ≥3 swollen joints, and met the Classification Criteria for Psoriatic Arthritis (CASPAR) [3]. Additionally, eligible patients had active PsA despite previous therapy with nonsteroidal anti-inflammatory drugs; DMARDs including azathioprine, chloroquine, ciclosporin, hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine, or tumour necrosis factor inhibitors (TNFis). Alternatively, eligible patients were intolerant to these treatments. There was no limit to number or class of prior bDMARD exposure (excluding those with lack of response after 12 weeks of treatment or adverse events [AEs]) or minimum high-sensitivity C-reactive protein (hsCRP) requirement at baseline.

Patients were excluded if they previously had a lack of response to any therapeutic agent targeting IL-12, IL-17, and/or IL-23 (and/or received 1 of these therapies ≤6 months before baseline [day 1]) or to more than 1 TNFi or had any other disease that might confound evaluation of the benefit of zasocitinib.

Full inclusion and exclusion criteria are reported in the Supplementary Material.

The intent-to-treat analysis set included all patients who were randomised. The full analysis set comprised all patients who were randomised and received at least 1 dose of the study drug. The safety analysis set included all patients who were randomised and received at least one dose of the study drug, with patients analysed based on the actual treatment they received.

Endpoints

Efficacy

The primary efficacy endpoint was the proportion of patients achieving an American College of Rheumatology (ACR)20 response at week 12. Secondary efficacy endpoints at week 12 were the proportion of patients achieving ACR50 response; proportion of patients achieving ACR70 response; proportion of patients achieving PASI 75 response among those with ≥3% body surface area (BSA) psoriatic involvement at baseline; proportion of patients achieving a Physician Global Assessment of Psoriasis (PGA-PsO) score of 0 (clear) or 1 (almost clear) and a ≥2-point improvement from baseline; change from baseline in Physician Global Assessment (PGA) score (investigator-assessed change from baseline in the patients' overall disease status using a visual analogue scale [VAS]: 0 indicated 'asymptomatic' and 100 indicated 'very severe symptoms'); proportion of patients achieving minimal disease activity (MDA) (the patient met at least 5 of the following criteria: (1) tender joint count [TJC] ≤1; (2) swollen joint count [SJC] ≤1; (3) PASI score ≤1 or ≤3% BSA; (4) pain VAS ≤15; (5) Patient Global Assessment [PtGA], using VAS score ≤20; (6) Health Assessment Questionnaire Disability Index [HAQ-DI] score ≤0.5; and (7) tender entheseal points, using the Leeds Enthesitis Index ≤1); change from baseline in Disease Activity Index for Psoriatic Arthritis (DAPSA) score; change from baseline in pain VAS; change from baseline in TJC (TJC68); change from baseline in SJC (SJC66); change from baseline in dactylitis count among patients who had dactylitis at baseline; and change from baseline in Leeds Enthesitis Index among patients who had enthesitis at baseline. The proportion of patients achieving low disease activity (LDA; DAPSA >4 and ≤14) and remission (REM; DAPSA ≤4) was assessed *post hoc*.

Patient-reported secondary efficacy endpoints assessed at week 12 were change from baseline in PtGA (patients rated their PsA using a VAS score in which 0 indicated 'very good, no symptoms' and 100 indicated 'very poor, severe symptoms') and HAQ-DI. Change from baseline to week 12 in Psoriatic Arthritis Disease Activity Score (PASDAS) was assessed as an exploratory endpoint. Further exploratory endpoints are reported in the Supplementary Material.

Additional skin endpoints analyses included least-squares mean (LSM) change from baseline in PASI response and the proportion of patients achieving PASI 90 or PASI 100 responses (among those with baseline BSA ≥3%).

Safety and tolerability

The severity of AEs was classified using Common Terminology Criteria for Adverse Events (CTCAE v5.0) and AEs were coded using Medical Dictionary for Regulatory Activities Version 26.0 or higher. Safety and tolerability endpoints comprised the incidence of TEAEs, treatment-emergent serious AEs, TEAEs of special interest (TEAESIs), and changes in vital signs, clinical laboratory parameters, and proportion of patients with clinically relevant electrocardiogram findings and physical examinations. TEAESIs included cytopenia (Grade ≥2), elevation of creatine kinase (Grade ≥3), major adverse cardiovascular events (MACEs), thromboembolic events, gastrointestinal perforation, malignancies, infections, AEs of abnormal liver function tests, and renal dysfunction. Liver function tests included Hy's Law, hepatobiliary investigations, liver-related investigations, signs and symptoms (including increase in liver enzymes), and drug-related hepatic disorders (CTCAE grades considered).

Statistical analysis

A sample size of 260 patients (65 patients per group) was determined to provide 83% power to detect an ACR20 response rate of 55% in each zasocitinib treatment group at a significance level of $\alpha = 0.05$ using a 2-sided chi-square test, assuming a placebo response rate of 30%. The sample size was calculated in nQuery 8.7 (Dotmatics) using a pooled variance estimate for difference of proportions.

Patient demographics and baseline clinical characteristics were summarised using descriptive statistics. Comparisons of the primary and binary secondary endpoints between each treatment group and placebo were made using a 2-sided Mantel–Haenszel test stratified by the randomisation stratification factors.

A fixed-sequence hierarchical testing approach was applied to the primary endpoint at a 2-sided significance level of 0.05 in the following prespecified order: 30 mg, 15 mg, and 5 mg zasocitinib versus placebo. If one comparison was found not to be significant,

all subsequent comparisons of lower doses could not be claimed and *P* values were considered nominal. No multiplicity adjustment was planned for other efficacy endpoints in this study, and nominal *P* values are presented where appropriate.

Patients who discontinued the study drug, used a prohibited medication expected to influence PsA clinical outcomes or with missing data for binary endpoints at week 12 were imputed as nonresponders.

Subgroup analysis for the primary efficacy endpoint was conducted using the same framework as the primary efficacy analysis. Longitudinal continuous secondary efficacy endpoints were analysed using a mixed model for repeated measures, in which the change from baseline was the dependent variable. The following were the fixed effects: treatment group, visit, treatment-by-visit interaction, and randomisation stratification factors. Baseline score was included as a covariate.

An analysis of the safety endpoints in the safety analysis set was conducted using descriptive statistics.

Ethics

This study was performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with Good Clinical Practice and applicable regulatory requirements. Patients provided written, informed consent before starting the study. The clinical study protocol (and amendments), investigator brochure, samples of informed consent forms, and other study-related documents were reviewed and approved by institutional review boards or independent ethics committees of all study sites.

RESULTS

Patients

The study was conducted from January 6, 2022 to June 2, 2023. In total, 387 patients were screened for eligibility, of

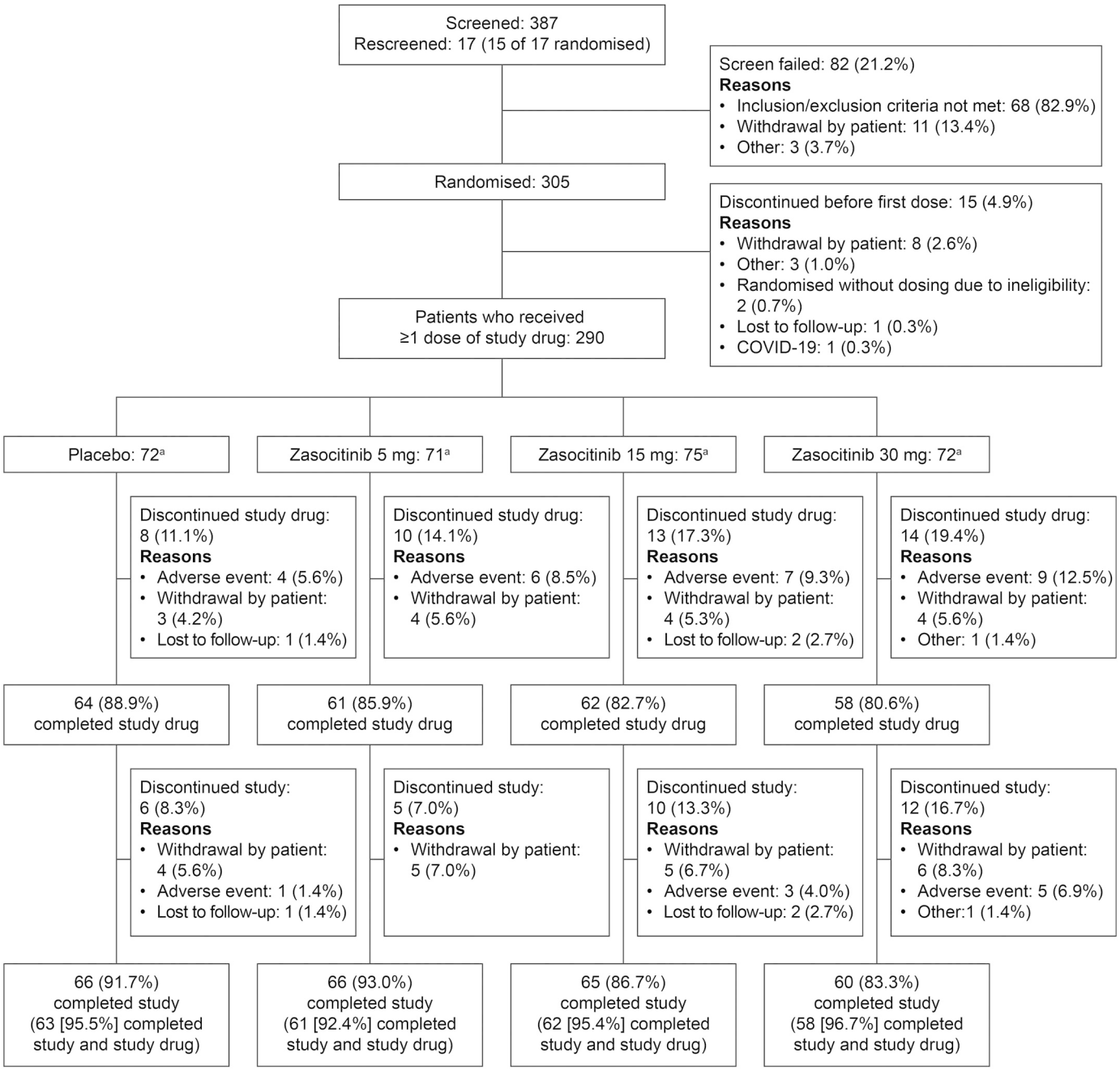

Figure 1. Patient disposition. [a]Patients who received ≥1 dose of study drug (randomised patients).

whom 305 were randomised to 1 of the 3 active treatment groups or placebo (intention-to-treat population), 290 received at least one dose of study treatment (full analysis set and safety analysis set populations), and 245 (84.5%) completed 12 weeks of treatment. Reasons for study discontinuation before receiving the first study drug dose are summarised in Figure 1.

Patient demographics and disease characteristics at baseline were generally similar across groups, except for a higher proportion of females in the 30 mg (59.7%) and 15 mg (61.3%) groups than in the 5 mg (56.3%) and placebo groups (51.4%) (Table 1, Supplementary Table S1). Lower mean TJC (14.0 vs 18.0-18.5) and SJC (8.5 vs 9.0-9.7) were observed in the zasocitinib 30 mg group compared with the other groups (Table 1). The mean (SD) age of patients was 49.9 (11.6) years, and the patient population was predominantly White (95.2%), female (57.2%), and from Eastern Europe (76.9%). At baseline, 62.4% of patients were receiving azathioprine, chloroquine, ciclosporin, hydroxychloroquine, leflunomide, methotrexate, and/or sulfasalazine; 57.6% of patients were receiving methotrexate. Approximately one-third of patients had received previous treatment with bDMARDs at baseline (31.0-33.3%), and the patient population contained both bDMARD-inadequate responders (reasons for discontinuing bDMARDs before the study included lack of efficacy, safety, and other; 7.2% of patients

Table 1
Baseline demographics and disease characteristics (FAS)

	Placebo (N = 72)	Zasocitinib 5 mg once daily (N = 71)	Zasocitinib 15 mg once daily (N = 75)	Zasocitinib 30 mg once daily (N = 72)	Total (N = 290)
Demographics					
Age, y, mean (SD)	49.7 (11.8)	48.3 (10.4)	52.5 (12.2)	49.0 (11.5)	49.9 (11.6)
Female, n (%)	37 (51.4)	40 (56.3)	46 (61.3)	43 (59.7)	166 (57.2)
Race, n (%)					
American Indian/Alaskan Native	0	1 (1.4)	0	0	1 (0.3)
Asian	0	0	2 (2.7)	0	2 (0.7)
Black/African American	1 (1.4)	1 (1.4)	2 (2.7)	3 (4.2)	7 (2.4)
Native Hawaiian/Other Pacific Islander	0	1 (1.4)	0	0	1 (0.3)
White	69 (95.8)	67 (94.4)	71 (94.7)	69 (95.8)	276 (95.2)
Unknown	2 (2.8)	0	0	0	2 (0.7)
Not available	0	2 (2.8)	0	0	2 (0.7)
BMI, kg/m^2, mean (SD)	29.5 (6.9)	29.8 (8.2)	30.0 (7.9)	30.2 (6.6)	29.9 (7.4)
Baseline DMARD treatment,[a] n (%)	43 (59.7)	45 (63.4)	46 (61.3)	47 (65.3)	181 (62.4)
Baseline methotrexate treatment,[b] n (%)	38 (52.8)	44 (62.0)	43 (57.3)	42 (58.3)	167 (57.6)
Baseline sulfasalazine treatment, n (%)	5 (6.9)	2 (2.8)	3 (4.0)	6 (8.3)	16 (5.5)
Baseline hydroxychloroquine,[c] treatment, n (%)	0	0	1 (1.3)	0	1 (0.3)
Baseline leflunomide treatment, n (%)	1 (1.4)	0	0	0	1 (0.3)
Previous DMARD treatment,[a] n (%)	33 (45.8)	35 (49.3)	32 (42.7)	31 (43.1)	131 (45.2)
Previous bDMARD treatment, n (%)	24 (33.3)	22 (31.0)	24 (32.0)	23 (31.9)	93 (32.1)
Previous TNF inhibitor use, n (%)	16 (22.2)	17 (23.9)	16 (21.3)	11 (15.3)	60 (20.7)
Disease characteristics					
Disease duration, y, median (range)	4.0 (0.2-30.9)	4.0 (0.5-37.7)	5.1 (0.1-24.3)	4.3 (0.1-30.7)	4.2 (0.1-37.7)
TJC, mean (SD)	18.5 (14.7)	18.4 (15.2)	18.0 (12.8)	14.0 (9.4)	17.2 (13.3)
SJC, mean (SD)	9.0 (6.1)	9.7 (6.6)	9.7 (6.1)	8.5 (5.7)	9.2 (6.1)
PGA,[d] mean (SD)	59.9 (16.0)	59.6 (17.4)	62.0 (15.1)	57.6 (19.8)	59.8 (17.1)
PtGA,[e] mean (SD)	55.3 (22.7)	52.2 (19.8)	59.6 (19.4)	53.2 (20.6)	55.1 (20.7)
Pain VAS,[f] mean (SD)	53.6 (24.1)	48.2 (21.0)	58.3 (20.9)	49.8 (22.4)	52.5 (22.4)
HAQ-DI, mean (SD)	1.1 (0.6)	1.1 (0.6)	1.2 (0.6)	1.1 (0.6)	1.1 (0.6)
hsCRP, mg/L, mean (SD)	5.8 (9.1)	8.1 (15.2)	6.4 (11.5)	7.6 (12.3)	7.0 (12.2)
Psoriasis BSA ≥3%, n (%)	39 (54.2)	39 (54.9)	46 (61.3)	46 (63.9)	170 (58.6)
PASI in patients with ≥3% BSA,[g] mean (SD)	7.1 (7.0)	5.9 (4.6)	5.4 (3.9)	6.5 (6.2)	6.2 (5.5)
Dactylitis count ≥1, n (%)	17 (23.6)	16 (22.5)	14 (18.7)	17 (23.6)	64 (22.1)
Dactylitis count,[h] mean (SD)	1.8 (1.2)	4.1 (4.3)	2.1 (1.8)	2.8 (3.7)	2.7 (3.1)
Enthesitis (LEI ≥1), n (%)	36 (50.0)	36 (50.7)	40 (53.3)	35 (48.6)	147 (50.7)
LEI absolute values,[i] mean (SD)	2.5 (1.5)	2.5 (1.7)	2.5 (1.5)	2.3 (1.4)	2.5 (1.5)

bDMARD, biologic disease-modifying antirheumatic drug; BMI, body mass index; BSA, body surface area; DMARD, disease-modifying antirheumatic drug; FAS, full analysis set; HAQ-DI, Health Assessment Questionnaire Disability Index; hsCRP, high-sensitivity C-reactive protein; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PtGA, Patient Global Assessment; SJC, swollen joint count; TJC, tender joint count; TNF, tumour necrosis factor; VAS, visual analogue scale.
BMI was calculated based on the collected weight and height values. Disease duration (years) was calculated as (date of day 1 visit - date of initial disease diagnosis + 1)/365.25. Mean (SD) values were based on nonmissing observations at baseline for continuous endpoints.
[a] DMARDs included azathioprine, chloroquine, ciclosporin, hydroxychloroquine, leflunomide, methotrexate, and sulfasalazine.
[b] Includes medications coded to methotrexate or methotrexate sodium.
[c] Includes medications coded to hydroxychloroquine or hydroxychloroquine phosphate.
[d] The investigator or qualified subinvestigator assessed the patients' overall disease status by considering the signs, symptoms, and function of all components of joint and skin affected at the time of the visit. This overall status was then rated using a VAS: 0 indicated 'very good, asymptomatic and no limitation of normal activities' and 100 indicated 'very poor, very severe symptoms that were intolerable and inability to carry out all normal activities'.
[e] Patients rated their assessment of their PsA using a VAS: 0 indicated 'very good, no symptoms' and 100 indicated 'very poor, severe symptoms'.
[f] Patients rated their assessment of their PsA pain using a VAS: 0 indicated 'no pain' and 100 indicated 'most severe pain'.
[g] Placebo: n = 38; zasocitinib 5 mg: n = 39; zasocitinib 15 mg: n = 46: zasocitinib 30 mg: n = 46; total: n = 169. One patient in the placebo group had a missing PASI score at baseline.
[h] In patients with dactylitis count ≥1.
[i] In patients with LEI score ≥1.

reported lack of efficacy as the reason for discontinuing TNFis) and bDMARD-exposed patients in each treatment group. Among enrolled patients with coexistent psoriasis, the mean (SD) PASI score in those with ≥3% BSA (n = 169 [58.3%]) was 6.2 (5.5). At baseline, 45.9% of patients had elevated hsCRP (≥3.0 mg/L).

Efficacy outcomes

The primary endpoint of this study was met, with a significantly higher proportion of patients (95% CI) receiving 30 mg or 15 mg zasocitinib achieving ACR20 response at week 12 (54.2% [42.7, 65.7] and 53.3% [42.0, 64.6], respectively; both P = .002) than those receiving placebo (29.2% [18.7, 39.7]) (Fig 2). The ACR20 response rate for the 5 mg zasocitinib group was 35.2% (24.1, 46.3; P = .446) at week 12. The proportions of patients achieving an ACR20 response in the 30 mg and 15 mg zasocitinib groups increased from baseline to week 12 (Supplementary Fig S2). Generally, numerically higher LSM improvements were observed at week 12 for the 30 mg or 15 mg zasocitinib groups across most of the ACR subcomponents versus placebo (nominal P = .003-.675) (Supplementary Table S2).

Data for all secondary endpoints are presented in Supplementary Table S2. ACR50 response rate (95% CI) at week 12 was numerically higher in the 30 mg (26.4% [16.2, 36.6], nominal P = .009) and 15 mg (26.7% [16.7, 36.7], nominal P = .005) zasocitinib groups versus the placebo (9.7% [2.9, 16.6]) group (Fig 2). A numerically higher proportion of patients achieved an ACR70 response (95% CI) in the zasocitinib 30 mg (13.9% [5.9, 21.9], nominal P = .158) and 15 mg (14.7% [6.7, 22.7], nominal P = .101) groups compared with placebo (5.6% [1.5, 13.6]). In addition, patients in the 30 mg and 15 mg zasocitinib groups reported numerically higher LSM (SE) reductions from baseline in PtGA scores of PsA at week 12 when compared with placebo (placebo: −11.1 [2.9]; 30 mg: −19.8 [2.9], nominal P = .030; 15 mg: −20.2 [2.9], nominal P = .021; Supplementary Table S2). Across all zasocitinib-treated groups, a numerical reduction from baseline in PGA was observed compared with placebo (nominal P = .003-.016) (Supplementary Table S2). Results for efficacy endpoint response rates stratified by geographic region are presented in Supplementary Table S3. Numerical differences between regions were observed in patients receiving zasocitinib 30 mg or placebo, with the Eastern Europe subgroup demonstrating generally higher response rates than those in the USA/Germany subgroup. The ACR20 treatment response differences versus placebo for the 30 mg, 15 mg, or 5 mg zasocitinib groups were 21.7%, 17.2%, and 2.6%, respectively, in the Eastern Europe subgroup and 29.7%, 39.1%, and 12.6%, respectively, in the USA/Germany subgroup, highlighting considerable variability in placebo response across regions.

Treatment with zasocitinib led to improvements in multiple skin disease activity endpoints, with the greatest improvements observed at the highest dose of zasocitinib. A numerically higher reduction in the LSM (SE) PASI score from baseline was observed in the 30 mg zasocitinib group compared with the placebo group as early as week 2 (−1.7 [0.4] vs −0.7 [0.4], nominal P = .023) and persisted through week 12 (Fig 3A). There were numerical improvements in PASI 75 response rate (95% CI) at week 12 for all zasocitinib groups compared with placebo (placebo: 15.4% [4.1, 26.7]; 30 mg: 45.7% [31.3, 60.0], nominal P = .002; 15 mg: 28.3% [15.2, 41.3], nominal P = .101; 5 mg: 25.6% [11.9, 39.3], nominal P = .186; Fig 3B). Consistent with PASI 75, similar trends were observed with higher threshold efficacy endpoints such as PASI 90 and PASI 100 (among patients with ≥3% BSA). Compared with placebo, a numerically higher proportion of patients achieved PASI 90 (37.0% versus

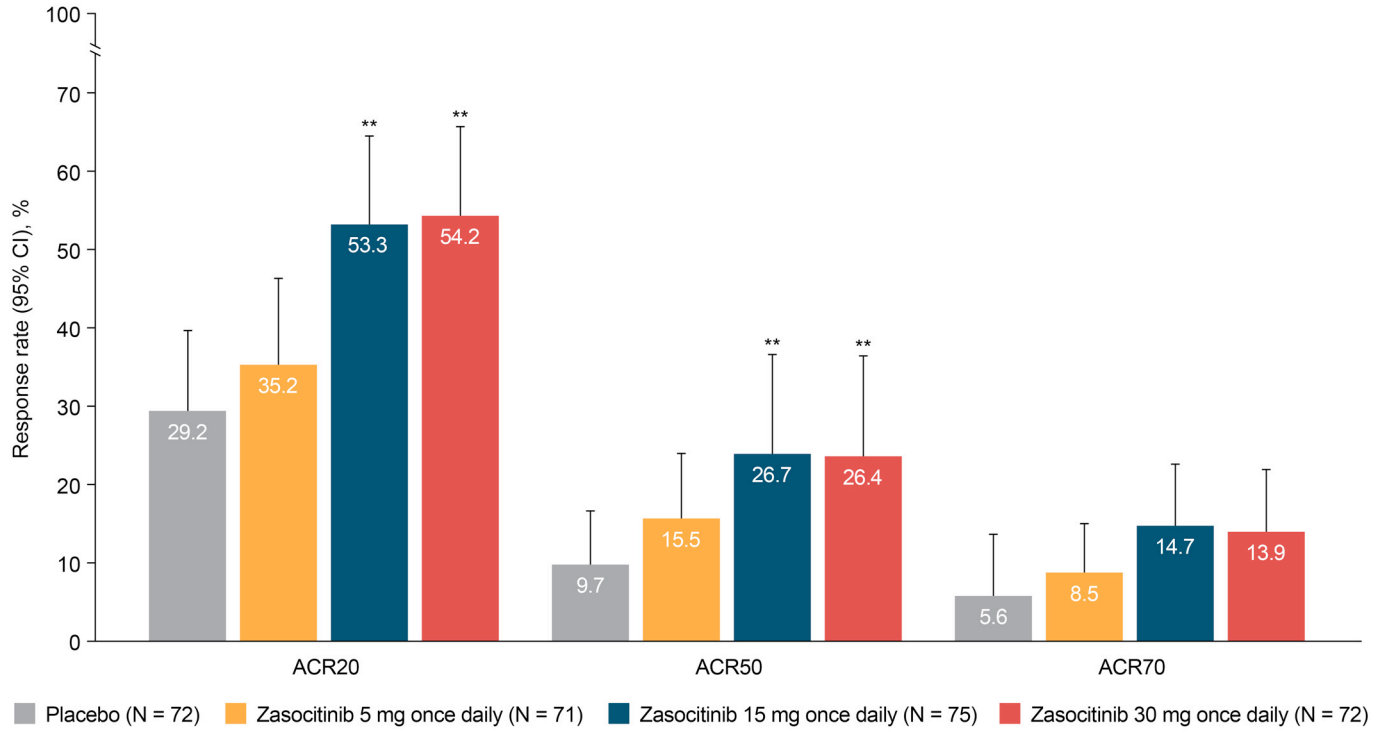

Figure 2. ACR20, ACR50, and ACR70 responses at week 12 (FAS). **$P \leq .01$. P values for secondary endpoints (ACR50/70) are nominal. ACR20/50/70 are composite measures defined as improvements from baseline of ≥20%/50%/70% in both the number of tender joints and swollen joints and ≥20%/50%/70% improvement from baseline in 3 of the following 5 criteria: Patient Global Assessment of psoriatic arthritis, Physician Global Assessment of psoriatic arthritis, Patient Global Assessment of psoriatic arthritis pain, Health Assessment Questionnaire Disability Index, and high-sensitivity C-reactive protein. ACR, American College of Rheumatology; FAS, full analysis set.

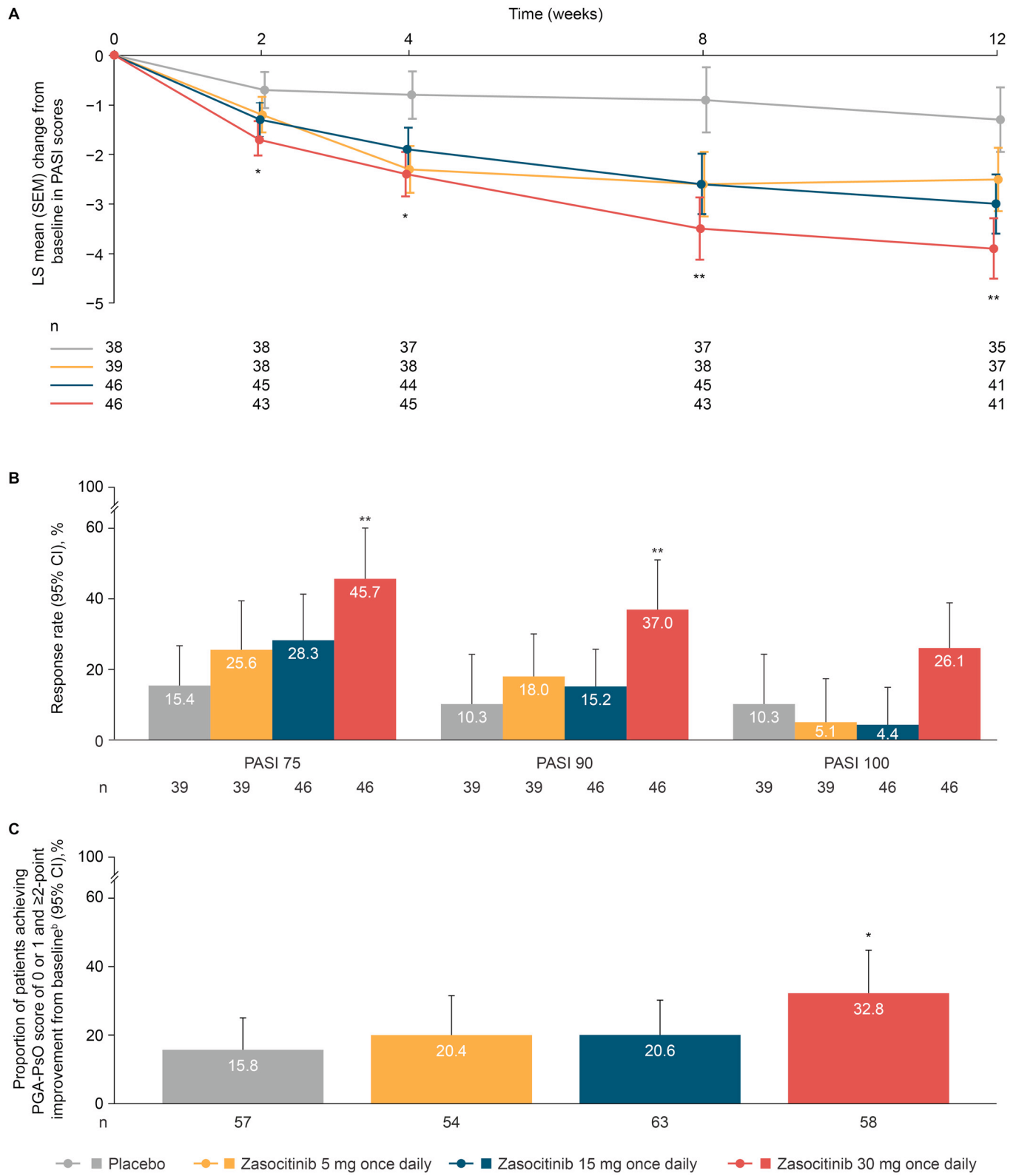

Figure 3. A, LS mean change from baseline to week 12 in PASI[a] scores. B, Week 12 PASI 75/90/100 response rates[a]. C, Patients achieving PGA-PsO score of 0 or 1 and ≥2-point improvement from baseline[b] (FAS). *$P \leq .05$; **$P \leq .01$. P values for secondary endpoints are nominal. FAS included all randomised patients who received ≥1 dose of the study drug. Patients were included in the analysis as randomised. [a]In patients with ≥3% BSA involvement at baseline. [b]Among those with a PGA-PsO score ≥2 at baseline. BSA, body surface area; FAS, full analysis set; LS, least-squares; PASI, Psoriasis Area and Severity Index; PGA, Physician Global Assessment; PsO, psoriasis.

10.3%, nominal $P = .0054$) and PASI 100 responses (26.1% versus 10.3%, nominal $P = .0941$) at week 12 in the 30 mg zasocitinib group (Fig 3B). Numerical improvements at week 12 were also observed in the proportions of patients (95% CI) achieving a PGA-PsO score of 0 or 1 and ≥2-point improvement from baseline in the 30 mg zasocitinib group compared with placebo (placebo: 15.8% [6.3, 25.3]; 30 mg: 32.8% [20.7, 44.8], nominal $P = .034$; 15 mg: 20.6% [10.6, 30.6], nominal $P = .466$; 5 mg: 20.4% [9.6, 31.1], nominal $P = .540$; Fig 3C).

Treatment with zasocitinib led to improvements in various composite outcomes and disease activity scores, such as MDA, DAPSA, and PASDAS. Numerically higher improvements in

MDA (95% CI) at week 12 were observed in patients treated with 30 mg or 15 mg zasocitinib than those treated with placebo (placebo: 12.5% [4.9, 20.1]; 30 mg: 29.2% [18.7, 39.7]; 15 mg: 28.0% [17.8, 38.2]; 5 mg: 18.3% [9.3, 27.3]; nominal $P = .014$, $P = .017$, and $P = .349$, respectively, Fig 4A). Relative to placebo, the LS mean change from baseline in DAPSA score (SE) at week 12 was numerically higher in all zasocitinib-treated groups (placebo: −11.6 [1.9]; 30 mg: −16.8 [2.0]; 15 mg: −18.0 [1.9]; 5 mg, −15.3 [1.9]; nominal $P = .056$, $P = .018$, and $P = .167$, respectively, Fig 4B). Numerically higher proportions of patients achieved LDA ($4 < \text{DAPSA} \leq 14$ or $1.9 < \text{PASDAS} < 3.2$) and REM (DAPSA ≤ 4 or PASDAS ≤ 1.9) at week 12 in the 30 mg and 15 mg zasocitinib groups than in the placebo group (Fig 4C,D).

Safety outcomes

TEAEs occurred in 77.8%, 60.0%, 59.2%, and 54.2% of patients receiving zasocitinib 30 mg, 15 mg, 5 mg, or placebo, respectively. TEAEs leading to study treatment discontinuation occurred in 8.5% to 12.5% of patients in the zasocitinib treatment groups and 5.6% in the placebo group. The majority of TEAEs leading to study discontinuation were not considered related to the study drug, as assessed by the investigator. The most common TEAEs were nasopharyngitis (occurring in 9.7%, 9.3%, 8.5%, and 4.2% of patients receiving zasocitinib 30 mg, 15 mg, 5 mg, or placebo, respectively) and upper respiratory tract infections (occurring in 9.7%, 4.0%, 11.3%, and 2.8% of patients receiving zasocitinib 30 mg, 15 mg, 5 mg, or placebo, respectively) (Table 2). One patient in each of the placebo and 15 mg zasocitinib groups experienced a nondisseminated case of herpes zoster infection (Supplementary Table S4). Most TEAEs were Grade 1 or 2 in severity. In total, 22 (7.6%) patients reported at least one Grade 3 TEAE (placebo: n = 7 [9.7%]; zasocitinib 30 mg: n = 3 [4.2%]; 15 mg: n = 7 [9.3%]; 5 mg: n = 5 [7.0%]), and 1 patient in the 5 mg group had a Grade 4 coronary artery disease event that was considered unrelated to study treatment, as assessed by the investigator. A higher rate of transient, Grade 1 or 2 dermatological events was observed in the 30 mg and 15 mg zasocitinib groups than in the other groups. All dermatological events resolved within a mean of 34 days mostly without pharmacologic intervention, except for 1 patient who experienced a Grade 2 maculopapular rash considered related to the study drug, which resolved with medication. Acneiform dermatitis (Grade 2), related to the study drug, led to study discontinuation in one patient. No deaths were reported in the study.

In this small study of limited duration, no systemic opportunistic infection, MACEs, thromboembolic event, gastrointestinal perforation, or malignancy TEAESIs were observed in patients treated with zasocitinib (Supplementary Table S4). Rates of discontinuation due to TEAESIs were numerically similar across study groups. One patient in each treatment group reported a treatment-related adverse event of special interest (AESI) that led to study drug discontinuation. Overall, serious infections were observed in 3 (1.0%) patients. These were observed in the 5 mg (n = 2; cellulitis and respiratory tract infection) and 30 mg (n = 1; pharyngitis) treatment groups, all of which resolved. According to the defined criteria in the study protocol, Grade ≥2 cytopenia and ≥3 elevations of creatine kinase were considered AESIs. Overall, 24 patients reported any cytopenia (n = 14) or creatine kinase (n = 10) related events. One patient in the placebo group reported both a leukopenia and lymphopenia event. Infrequent Grade ≥3 events of elevated creatine kinase (placebo: n = 1; 5 mg: n = 2; 15 mg: n = 3; 30 mg: n = 0) and Grade ≥2 cytopenia (placebo: n = 2; 5 mg: n = 5; 15 mg: n = 1; 30 mg: n = 5) were observed. Overall, 2 patients (one each in the 5 mg and 30 mg zasocitinib groups) with Grade ≥2 cytopenia reported clinical events with similar onset (lymphopenia and nasopharyngitis).

Laboratory parameters generally stayed within the normal range, with no clinically meaningful longitudinal changes observed across any groups and no clear dose-dependency in the zasocitinib groups. Shifts from baseline to postbaseline for haematology, lipid, and serum chemistry parameters were generally similar between all groups (Table 3). Over the study period, no notable differences in laboratory shifts and the frequency of Grade ≥2 changes between placebo and zasocitinib groups were observed (Supplementary Table S5). There were no clinically meaningful longitudinal changes throughout the 12-week study observed in haematology parameters (neutrophils, platelet counts, haemoglobin, lymphocytes), serum chemistry (creatine kinase, alanine aminotransferase, aspartate aminotransferase, bilirubin, creatinine), and no clinically meaningful elevations in cholesterol or triglyceride levels were observed at week 12 (Fig 5, Supplementary Fig S3).

Evaluated vital signs included diastolic and systolic blood pressure, heart rate, temperature and body weight. No TEAEs related to these were reported.

DISCUSSION

Zasocitinib is an investigational, oral, allosteric, highly selective, and potent TYK2 inhibitor in late-stage clinical development for the treatment of IMIDs. In this phase 2b trial of patients with active PsA, the primary endpoint (ACR20 response at week 12) was met in the 30 mg and 15 mg groups. Treatment with once daily 30 mg or 15 mg zasocitinib was associated with numerically greater improvements in musculoskeletal and skin signs and symptoms, as well as in patient-reported and physician-assessed outcomes, compared with placebo. Notably, the ACR20 response curve observed with 30 mg or 15 mg zasocitinib increased over 12 weeks; studies of a longer duration will help determine whether the ACR20 response will further increase with treatment with zasocitinib.

PsA prevalence is equal in male and female patients; however, female patients typically exhibit higher disease activity, greater disease burden, increased pain, and poorer physical function than male patients [18–21]. Additionally, female patients appear more likely than male patients to experience a poorer clinical response to bDMARDs (including IL-17 and IL-23 inhibitors) versus targeted synthetic DMARDs (tsDMARDs) [22]. This was an all-comers study design, and a greater proportion of patients in the 30 mg and 15 mg groups were female compared with the 5 mg and placebo groups. Treatment with 30 mg and 15 mg zasocitinib resulted in greater ACR20 responses than placebo, regardless of sex, supporting the hypothesis that female patients may exhibit improved outcomes versus bDMARD treatment with tsDMARD treatment like zasocitinib [23]; these findings would need to be validated in studies of a longer duration.

The patient population in this study was not selectively enriched for elevated hsCRP levels. As such, baseline mean hsCRP concentrations across the study groups were comparatively low compared with some hsCRP levels reported in other PsA clinical trials [24–26]. However, as hsCRP levels are not consistently elevated in active PsA, the hsCRP levels in this

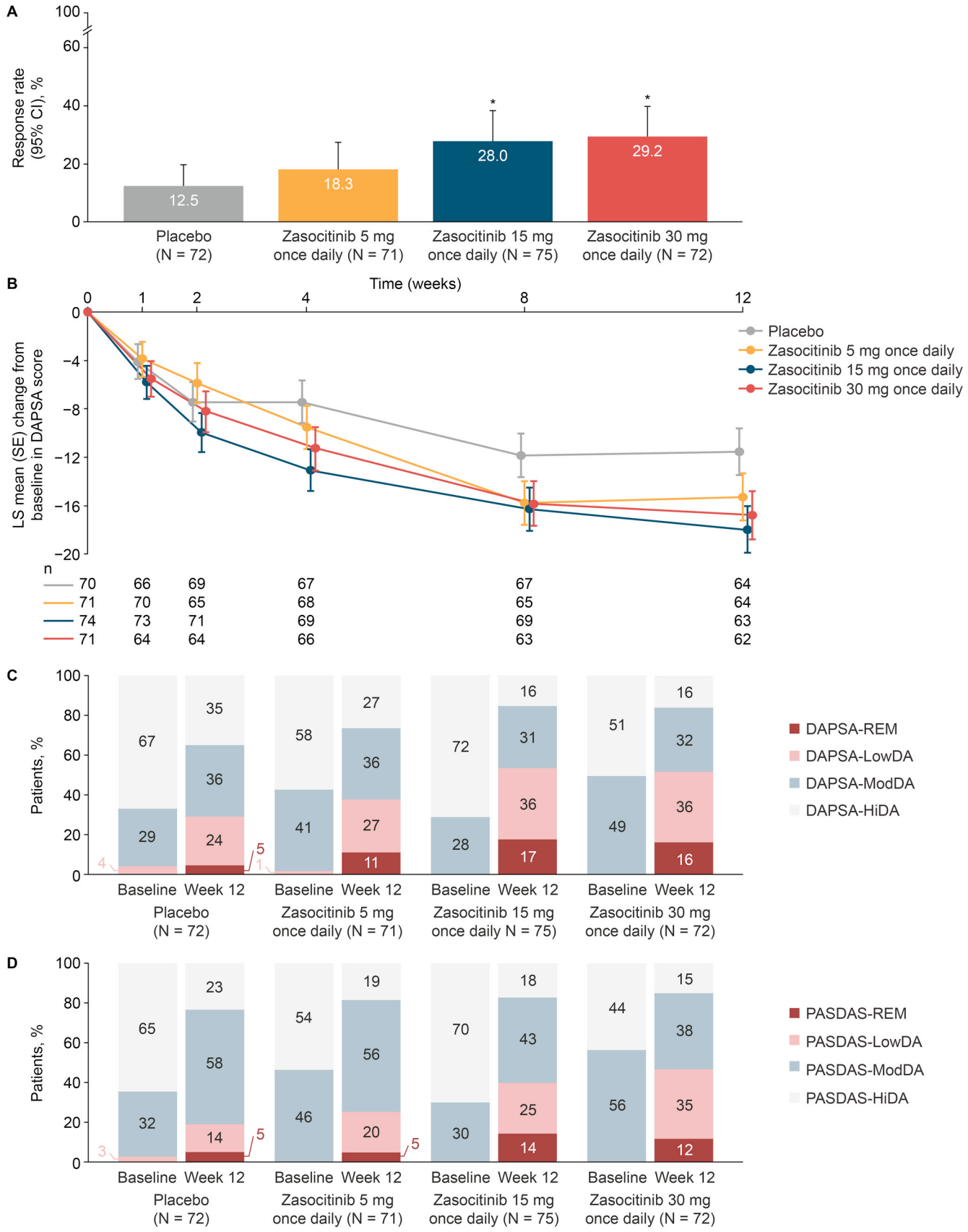

Figure 4. A, Proportion of patients achieving MDA. B, Change from baseline in DAPSA score. C, DAPSA state. D, PASDAS state at week 12 (FAS). *$P \leq .05$. *P* values in secondary endpoints are nominal. FAS included all randomised patients who received ≥1 dose of the study drug. Patients were included in the analysis as randomised. LDA = 4<DAPSA≤14 or 1.9<PASDAS<3.2; REM = DAPSA ≤4 or PASDAS ≤1.9. MDA is measured as the patient meeting ≥5 of the 7 criteria. The criteria are 1) tender joint count ≤1; 2) swollen joint count ≤1; 3) PASI score ≤1 or ≤3% BSA; 4) Patient Global Assessment of psoriatic arthritis pain, VAS ≤15; 5) Patient Global Assessment of psoriatic arthritis, VAS ≤20; 6) HAQ-DI score ≤0.5; 7) tender entheseal points, using the LEI score ≤1. DAPSA, Disease Activity in Psoriatic Arthritis; FAS, full analysis set; HiDA, high disease activity; LEI, Leeds Enthesitis Index; LowDA, low disease activity; LS, least squares; MDA, minimal disease activity; ModDA, moderate disease activity; PASDAS, Psoriatic Arthritis Disease Activity Score; PASI, Psoriasis Area and Severity Index; REM, remission; VAS, visual analogue scale.

Table 2
Number of patients with TEAEs, reported by treatment group (SAS)

n (%) [#]	Placebo (N = 72)	Zasocitinib 5 mg once daily (N = 71)	Zasocitinib 15 mg once daily (N = 75)	Zasocitinib 30 mg once daily (N = 72)
Any TEAE	39 (54.2) [87]	42 (59.2) [88]	45 (60.0) [106]	56 (77.8) [135]
Drug-related TEAEs	11 (15.3) [13]	15 (21.1) [23]	20 (26.7) [49]	29 (40.3) [61]
TEAEs leading to study drug discontinuation	4 (5.6) [4]	6 (8.5) [6]	7 (9.3) [9]	9 (12.5) [11]
TEAEs leading to study discontinuation	1 (1.4) [1]	0	3 (4.0) [5]	5 (6.9) [5]
Serious TEAEs	4 (5.6) [4]	4 (5.6) [4]	3 (4.0) [3]	2 (2.8) [2]
Grade 3 or higher TEAE	7 (9.7) [8]	6 (8.5) [6]	7 (9.3) [9]	3 (4.2) [3]
TEAEs leading to death	0	0	0	0
TEAESI[a]	19 (26.4) [27]	33 (46.5) [43]	22 (29.3) [25]	38 (52.8) [50]
Serious infections	0	2 (2.8) [2]	0	1 (1.4) [1]
Most frequent TEAEs, n (%)[b]				
Nasopharyngitis	3 (4.2) [4]	6 (8.5) [6]	7 (9.3) [7]	7 (9.7) [7]
URTIs	2 (2.8) [3]	8 (11.3) [8]	3 (4.0) [4]	7 (9.7) [7]
Headache	3 (4.2) [3]	2 (2.8) [3]	6 (8.0) [6]	4 (5.6) [6]
Rash	0	3 (4.2) [4]	6 (8.0) [6]	4 (5.6) [4]
Blood CK increased[c]	3 (4.2) [3]	2 (2.8) [2]	4 (5.3) [4]	1 (1.4) [1]
Dermatitis acneiform	0	0	2 (2.7) [4]	6 (8.3) [7]
Psoriatic arthropathy	5 (6.9) [6]	0	2 (2.7) [2]	1 (1.4) [1]
Rash papular	0	1 (1.4) [1]	3 (4.0) [3]	4 (5.6) [4]
Aphthous ulcer	0	0	1 (1.3) [1]	6 (8.3) [7]
Dermatitis allergic	0	1 (1.4) [1]	1 (1.3) [1]	4 (5.6) [5]
Rash maculopapular	0	0	2 (2.7) [4]	4 (5.6) [5]
Any TEAEs related to cytopenia[c]				
Anaemia	0	0	0	3 (4.2) [4]
Leukopenia[d]	1 (1.4) [1]	1 (1.4) [1]	0	0
Lymphopenia[d]	2 (2.8) [2]	4 (5.6) [5]	1 (1.3) [2]	3 (4.2) [3]
Any rash-related TEAEs[e]	0	6 (8.5) [7]	11 (14.7) [13]	13 (18.1) [15]
Rash erythematous	0	2 (2.8) [2]	0	2 (2.8) [2]

AE, adverse event; CK, creatine kinase; CTCAE, Common Terminology Criteria for Adverse Events; MedDRA, Medical Dictionary for Regulatory Activities; SAS, safety analysis set; TEAE, treatment-emergent adverse event; TEAESI, treatment-emergent adverse event of special interest; URTI, upper respiratory tract infection.
AEs were coded using MedDRA Version 26.0 or higher. The SAS included all randomised patients who received ≥1 dose of the study drug. Patients were included in the analysis based on actual treatment received, regardless of the treatment group to which they were randomised.
[#] is the number of individual occurrences of the TEAE in that category.
[a] Patients with at least one TEAESI including laboratory TEAESIs.
[b] TEAEs occurring at >5% in any treatment group, categorised by preferred term.
[c] According to the defined criteria in the study protocol, CTCAE Grade ≥2 cytopenia and ≥3 CK elevations are considered AESIs.
[d] One patient in the placebo group reported both a leukopenia and lymphopenia AE.
[e] Rash-related TEAEs included rash, rash popular, rash macropapular, and rash erythematous.

Table 3
Laboratory parameters: shift from baseline to postbaseline visits (SAS)

	Placebo (N = 72)	Zasocitinib 5 mg once daily (N = 71)	Zasocitinib 15 mg once daily (N = 75)	Zasocitinib 30 mg once daily (N = 72)
Haematology: shift from normal to low values, n (%)				
Haemoglobin	10 (13.9)	9 (12.7)	10 (13.3)	10 (13.9)
Lymphocytes	7 (9.7)	8 (11.3)	3 (4.0)	6 (8.3)
Neutrophils	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Platelets	1 (1.4)	3 (4.2)	0 (0.0)	1 (1.4)
Serum chemistry: shift from normal to high values, n (%)				
ALT	9 (12.5)	7 (9.9)	11 (14.7)	11 (15.3)
AST	6 (8.3)	3 (4.2)	10 (13.3)	9 (12.5)
CK	13 (18.1)	14 (19.7)	10 (13.3)	10 (13.9)
Creatinine	5 (6.9)	6 (8.5)	11 (14.7)	8 (11.1)
Lipids: shift from normal to high values, n (%)				
Cholesterol	8 (11.1)	7 (9.9)	11 (14.7)	8 (11.1)
LDL cholesterol	5 (6.9)	9 (12.7)	7 (9.3)	12 (16.7)
Triglycerides	5 (6.9)	3 (4.2)	6 (8.0)	5 (6.9)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; LDL, low-density lipoprotein; SAS, safety analysis set.
Laboratory parameter values were categorised as low, normal, or high based on the reference range for each laboratory variable. Data represent laboratory parameter shifts in patients who had normal values at baseline. The lowest/highest postbaseline value for each laboratory parameter was used to determine whether patients had shifted from a normal to a low/high value.

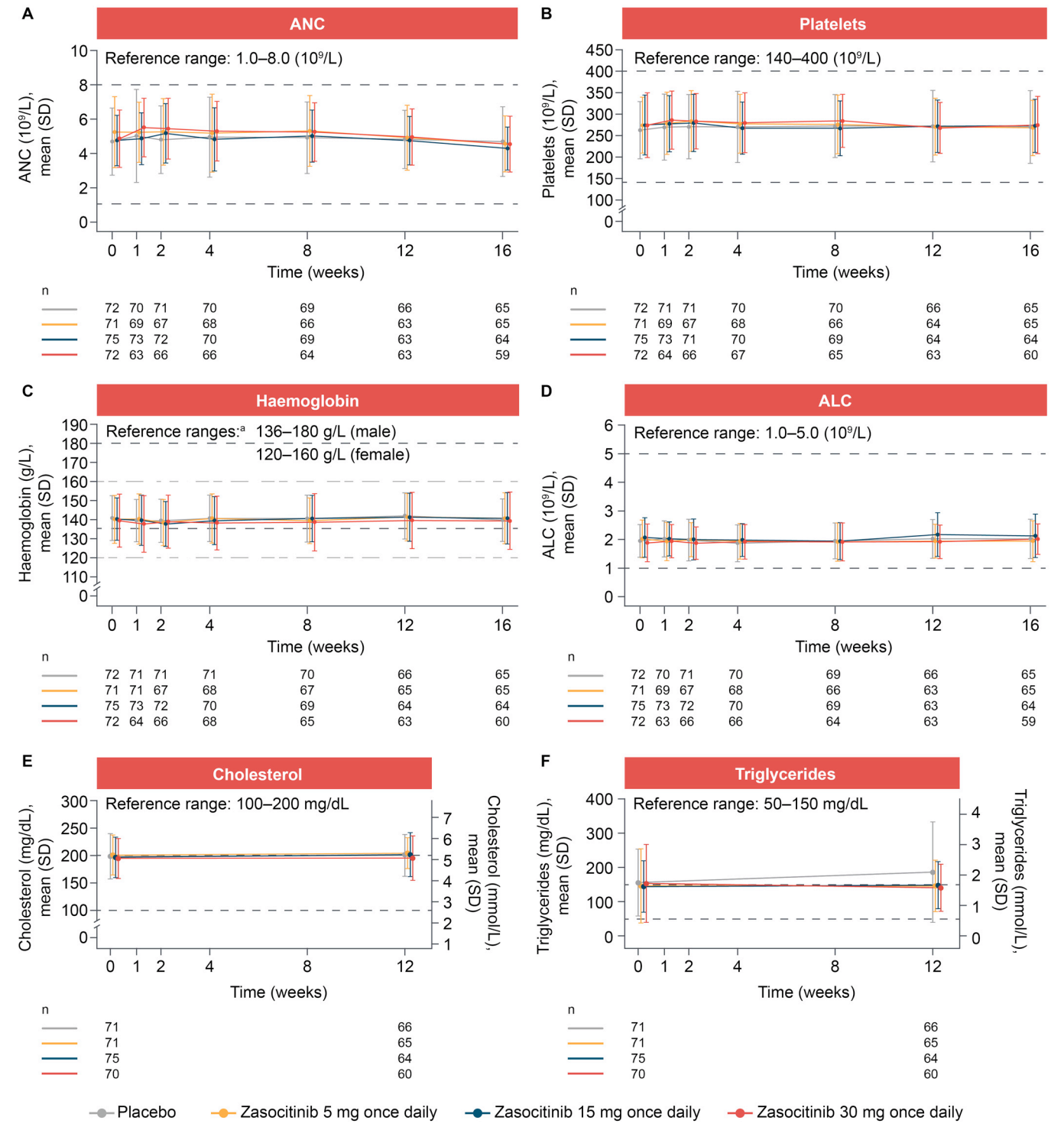

Figure 5. Key laboratory parameter changes over 16 weeks (SAS). A, Neutrophils. B, Platelets. C, Haemoglobin. D, Lymphocytes. E, Cholesterol. F, Triglycerides. Data are observed values from the safety analysis set and presented as mean ± SD. Dashed lines represent upper and lower limits of the normal range for each parameter. [a]For graphs with 4 dashed lines, the black lines represent the male limits, and the grey lines represent the female limits. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; SAS, safety analysis set.

study may be more reflective of a real-world PsA population [27].

Skin disease is one of the core domains of PsA [28,29], and it is estimated that as many as 82% of patients with PsA have coexisting psoriasis [30]. Patients with PsA and psoriasis exhibit worse physical function and higher disease activity scores, utilise more health care resources, and report greater impairment on HRQoL than those with PsA or psoriasis alone [31–35]. However, treatment with zasocitinib demonstrated early and greater improvements versus placebo across skin efficacy endpoints. Differences in PASI scores were observed between patients receiving zasocitinib 30 mg and placebo as early as week 2. At week 12, 26.1% of patients with skin involvement treated with 30 mg of zasocitinib experienced complete skin clearance (PASI 100), and 32.8% achieved clear or almost clear skin (PGA-PsO score of 0 or 1 with a ≥2-point improvement from baseline). The skin activity response data from this study are consistent with those observed in the phase 2b study of

zasocitinib in moderate-to-severe plaque psoriasis, in which one-third of patients receiving 30 mg zasocitinib achieved complete skin clearance after 12 weeks of treatment [16].

Several guidelines for PsA treatment support LDA and REM as treat-to-target goals [4,7,36,37]. MDA is a PsA specific composite measure, and achievement is shown to correspond with quality of life and a level of symptoms that are acceptable to patients [37]. Treatment with 30 mg and 15 mg zasocitinib consistently ameliorated disease activity, assessed by achievement of MDA and improvement in DAPSA and PASDAS. By week 12, 30 mg or 15 mg zasocitinib treatment resulted in higher rates of patients achieving LDA or REM versus placebo across multiple disease activity composite instruments.

Zasocitinib was generally well tolerated at all doses, with a low proportion of patients discontinuing the study owing to TEAEs across all groups. However, the number of discontinuations was numerically higher in the zasocitinib groups than the placebo group. These findings were consistent with those observed in healthy volunteers and patients with plaque psoriasis [16,38]. In the present study, an increase in dermatological TEAEs was observed with increasing doses of zasocitinib. However, these were generally mild to moderate in severity and resolved within a mean duration of 34 days mostly without pharmacological intervention; only 1 event led to study drug discontinuation. Few serious infections were observed. MACEs, systemic opportunistic infections, thromboembolic events, and malignancies were not observed in any zasocitinib group; larger studies will be needed to confirm the safety profile of zasocitinib. Over the study period, zasocitinib did not result in any dose-dependent clinically meaningful changes in the laboratory parameters, and there were no notable differences in laboratory shifts or frequency of Grade ≥2 changes between placebo and treatment groups. No correlations between laboratory changes associated with JAK1, JAK2, and JAK3 inhibitors (eg, cytopenia, renal and liver enzyme elevations, and lipid elevations) and zasocitinib were observed, consistent with the high selectivity of zasocitinib for TYK2.

This study had some limitations, including a potential lack of statistical power and a lack of hierarchical testing approach for secondary and exploratory endpoints, owing to the small sample size. This was particularly evident for endpoints with impacts on domains only present in subsets of patients, such as dactylitis and enthesitis. Larger studies are required to further assess the effect of zasocitinib on these disease domains. As shown by the lack of a plateau observed in ACR20 response at week 12, longer studies are also required to determine the timing of the maximal response associated with zasocitinib treatment across various endpoints representing the core domains of the disease. Finally, patient recruitment focused on 4 countries, with the majority of patients being recruited from Eastern Europe. The numerical differences in ACR20 responses for the placebo group between regions in this study are not uncommon and have also been observed between other randomised, placebo-controlled PsA trials; such variability in response may be due to several factors including differences in csDMARD treatment, publication year, and number of study sites [39].

In conclusion, 30 mg and 15 mg zasocitinib demonstrated efficacy versus placebo across key PsA domains (musculoskeletal and skin activity), with the highest dose consistently providing numerically superior responses on skin activity measures. Safety results were consistent with data previously reported in patients with plaque psoriasis and healthy volunteers [16,38]. The lack of safety events associated with JAK1, JAK2, or JAK3 inhibition is reflective of the highly selective TYK2 inhibition of zasocitinib. These results highlight the potential of zasocitinib as a new oral therapeutic option in patients with active PsA. Consequently, phase 3 studies are ongoing (NCT06671483 and NCT06671496) to explore its full potential and to confirm these preliminary results in larger, more diverse patient populations, aiming to improve management and outcomes for patients with PsA.

Competing interests

A Kivitz has received consulting fees from Fresenius Kabi, Genzyme, Gilead, Grunenthal, GSK, Horizon, Janssen, Pfizer, Selecta Biosciences, SynAct Pharma, and Takeda; has received payments or fees for lectures, presentations, speakers bureaus, manuscript writing or educational events from AbbVie, Amgen, Eli Lilly, GSK, Pfizer, and UCB; has been part of a board or advisory board for ChemoCentryx, Horizon Therapeutics, Janssen, Novartis, Princeton Biopartners, and UCB; and has stock or stock options in Amgen, Gilead, GSK, Novartis, and Pfizer. XB has received research grants and been a consultant and member of advisory boards for AbbVie, Alfasigma, Amgen, Bristol Myers Squibb, Celltrion, Cesas, Eli Lilly, Galapagos, Janssen, Moonlake Immunotherapies, Novartis, Pfizer, Roche, Sandoz, Springer, STADA, Takeda, UCB, and Zuellig Pharma. Non-commercial disclosures: ASAS President and EULAR President-Elect. ETM, TH, JC, and PP are employees and equity holders of Takeda Development Center Americas, Inc. A Kavanaugh has received consulting fees from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, Takeda, and UCB. DvdH has received consulting fees from AbbVie, Alfasigma, Argenx, Bristol Myers Squibb, Eli Lilly, GreyWolf Therapeutics, Janssen, Novartis, Pfizer, Takeda, and UCB Pharma and is an Associate Editor for *Annals of the Rheumatic Diseases*, an Editorial Board member for *The Journal of Rheumatology* and *RMD Open*, an advisor for the Assessment of Spondyloarthritis International Society, and Director of Imaging Rheumatology B.V. PAK has no potential conflicts of interest to disclose. GV has received grant/research support from Mallinckrodt Pharmaceuticals and has received consulting fees from, or been involved in, speakers bureaus for AbbVie, Alexion, Amgen, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Centocor, Eli Lilly, Esaote, Exagen, Genentech, Gilead, Global Health Living, Horizon Therapeutics, Image Analysis Group, Janssen, Mallinckrodt Pharmaceuticals, Merck, Novartis, Pfizer, Pharmacia, Radius, Regeneron, Sandoz, Sanofi, Takeda, and UCB. ED has received grant/research support from AbbVie, UCB Biopharma SPRL, Eli Lilly, Galapagos, Gilead, GSK, Hexal AG, Janssen, Nimbus Lakshmi, Inc, Novartis, Pfizer, Sanofi, and Samsung. GP is an employee and equity holder of Nimbus.* BS, SD, and XZ were employees and equity holders of Nimbus* at the time of the study. HHW is an employee of HW MedAdvice, LLC and received consultancy fees in relation to the conduct of this study. MT and AL were employees and equity holders of Takeda Development Center Americas, Inc, at the time of the study. *Nimbus refers to the group of entities including Nimbus Therapeutics, LLC; Nimbus Discovery, Inc; and Nimbus Lakshmi, Inc. (NB: Nimbus Lakshmi, Inc was acquired by Takeda Pharmaceuticals in February 2023). A video abstract of this article can be found in the Supplementary Materials.

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Patient consent for publication

Not applicable.

Ethics approval

This study was performed in accordance with ethical principles originating from the Declaration of Helsinki, which are consistent with Good Clinical Practice and applicable regulatory requirements. Patients provided written, informed consent before starting the study. The clinical study protocol (and amendments), investigator brochure, samples of informed consent forms and other study-related documents were reviewed and approved by institutional review boards or independent ethics committees of all study sites.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

The data sets, including the redacted study protocol, redacted statistical analysis plan, and individual participants' data supporting the results reported in this article, will be made available within 3 months from initial request to researchers who provide a methodologically sound proposal. The data will be provided after its deidentification, in compliance with applicable privacy laws, data protection, and requirements for consent and anonymisation.

Previous publications

1. ACR Convergence (2023) American College of Rheumatology 2023 Annual Scientific Meeting. Kivitz A, et al. Efficacy and safety outcomes of TAK-279, a selective oral tyrosine kinase 2 (TYK2) inhibitor, from a randomized, double-blind, placebo-controlled phase 2b trial in patients with active psoriatic arthritis. Poster presentation: 10–15 November, 2023.

2. IDEOM Annual Meeting (2024) International Dermatology Outcome Measures Annual Meeting. Winkelman W, et al. Efficacy and safety outcomes of TAK-279, a selective oral tyrosine kinase 2 (TYK2) inhibitor, from a randomized, double-blind, placebo-controlled phase 2b trial in patients with active psoriatic arthritis. Poster presentation: 4–6 April, 2024.

3. JCR Meeting (2024) Japan College of Rheumatology Meeting. Tanaka N, et al. Phase 2b study of tyrosine kinase 2 (TYK2) inhibitor TAK-279 in psoriatic arthritis (PsA) patients. Poster presentation: 18–20 April, 2024.

4. EULAR Congress (2024) European Alliance of Associations for Rheumatology Congress. Kivitz A, et al. Efficacy and safety outcomes of TAK-279, a selective oral tyrosine kinase 2 (TYK2) inhibitor, from a randomized, double-blind, placebo-controlled phase 2b trial in patients with active psoriatic arthritis. Oral presentation: 12–15 June, 2024.

5. IFPA Conference (2024) International Federation of Psoriasis Associations Conference. Kivitz A, et al. Efficacy and safety of zasocitinib (TAK-279), a selective oral TYK2 inhibitor, in a randomized, placebo-controlled phase 2b trial in psoriatic arthritis. Poster presentation: and oral presentation: 27–29 June, 2024.

6. APLAR Congress (2024) Asia-Pacific League of Associations for Rheumatology Congress. Kivitz A, et al. Efficacy and safety of zasocitinib (TAK-279), a selective, oral TYK2 inhibitor: a randomized, placebo-controlled phase 2b trial in psoriatic arthritis. Oral presentation: 21–25 August, 2024.

7. EADV Congress (2024) European Academy of Dermatology and Venereology Congress. Gottlieb A, et al. Zasocitinib (TAK-279), a highly selective oral tyrosine kinase 2 (TYK2) inhibitor, elicits early skin responses and minimal disease activity in patients with active psoriatic arthritis: results from a randomized phase 2b study. Oral presentation: 25–28 September, 2024.

8. ACR Convergence (2024) American College of Rheumatology 2024 Annual Scientific Meeting. Kavanaugh A, et al. Assessment of laboratory parameter changes in a phase 2b trial of zasocitinib (TAK-279), an oral, selective TYK2 inhibitor, in patients with active psoriatic arthritis. Poster presentation: 14–19 November, 2024.

9. ACR Convergence (2024) American College of Rheumatology 2024 Annual Scientific Meeting. Gottlieb A, et al. Zasocitinib

(TAK-279), a highly selective oral tyrosine kinase 2 (TYK2) inhibitor, elicits early skin responses and minimal disease activity in patients with active psoriatic arthritis: results from a randomized phase 2b study. Poster presentation: 14–19 November, 2024.

10. ACR Convergence (2024) American College of Rheumatology 2024 Annual Scientific Meeting. Mease P, et al. Zasocitinib (TAK-279), an oral, selective tyrosine kinase 2 inhibitor: additional improvements in disease activity and achievement of remission in patients with psoriatic arthritis enrolled in a phase 2b Trial. Oral presentation: 14–19 November, 2024.

Supplementary materials

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