Ann Rheum Dis 84 (2025) 979–991

Contents lists available at ScienceDirect

Annals of the Rheumatic Diseases

journal homepage: https://www.sciencedirect.com/journal/annals-of-the-rheumatic-diseases

Psoriatic arthritis

Efficacy and safety of izokibep in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study

Peter C. Taylor[1,*], Philip J. Mease[2], Kurt de Vlam[3,4], Shephard Mpofu[5], Dieter Wetzel[6], Anne M. Stevens[5,7], Brian Wiens[5], Lisa Osterling Koskinen[8], Sven Ohlman[8], Joachim Feldwisch[8], Fredrik Y. Frejd[8], Nikolai C. Brun[8], Jan Brandt-Juergens[9], Edit Drescher[10], Eva Dokoupilova[11,12], Anna Rowińska-Osuch[13], Nadia Abdel-Kader Martin[14], Frank Behrens[15,16]

[1] *Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom*
[2] *Providence Swedish Medical Center, Rheumatology Research, and University of Washington, Seattle, WA, USA*
[3] *Department of Rheumatology, University Hospitals Leuven, Leuven, Belgium*
[4] *Skeletal Biology and Engineering Research Center (SBE), Department of Development and Regeneration, Leuven, Belgium*
[5] *ACELYRIN, INC, Agoura Hills, CA, USA*
[6] *toclinco GmbH, Medical Sciences, Freiburg, Germany*
[7] *University of Washington, Seattle, WA, USA*
[8] *Affibody AB, Solna, Sweden*
[9] *Rheumatologische Schwerpunktpraxis, Berlin, Germany*
[10] *Vital Medical Center Rheumatology, Veszprém, Hungary*
[11] *Medical Plus, s.r.o., Uherske Hradiste, Czech Republic*
[12] *Department of Pharmaceutical Technology, Faculty of Pharmacy, Masaryk University, Brno, Czech Republic*
[13] *European Trial Group (ETG) Network, Rheumatology, Warsaw, Poland*
[14] *Hospital Infanta Luisa Quiron, Rheumatology, Sevilla, Spain*
[15] *Rheumatology, Immunology-Inflammation Medicine, Goethe University Frankfurt, University Hospital, Frankfurt, Germany*
[16] *Fraunhofer Institute for Translational Medicine and Pharmacology (ITMP) and Fraunhofer Cluster of Excellence Immune-Mediated Diseases, Frankfurt, Germany*

ARTICLE INFO

ABSTRACT

Objectives: To evaluate the efficacy and safety of izokibep, a small protein therapeutic designed to inhibit interleukin-17A, in patients with active psoriatic arthritis (PsA) over 46 weeks.
Methods: This phase 2, multicentre, placebo-controlled study randomised adult patients with active PsA 1:1:1 to izokibep 40 mg, izokibep 80 mg, or placebo every 2 weeks for 16 weeks; subsequently, placebo-treated patients switched to izokibep 80 mg. The primary end point was American College of Rheumatology criteria 50 (ACR50) at week 16 for izokibep 80 mg vs placebo. Additional efficacy end points and treatment-emergent adverse events were evaluated through week 16 (placebo-controlled) and week 46.

*Correspondence to Prof Peter C. Taylor, Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, Oxford, United Kingdom.
E-mail address: peter.taylor@kennedy.ox.ac.uk (P.C. Taylor).
Handling editor Josef S. Smolen.

https://doi.org/10.1016/j.ard.2025.02.019

Results: Of 172 patients screened, 135 were randomised to izokibep 40 mg (n = 44), izokibep 80 mg (n = 47), or placebo (n = 44). ACR50 response rates were significantly higher for izokibep 80 mg vs placebo at week 16 (52% vs 13%; 2-sided $P = .0006$) and week 12 (50% vs 6%; $P < .0001$); lower rates were observed for izokibep 40 mg (48% and 43% for weeks 16 and 12, respectively). Additional analyses of arthritis, psoriasis, enthesitis, dactylitis, and quality of life outcomes supported the efficacy of izokibep at both doses. Response rates generally continued to increase through week 46 with izokibep 80 mg. Treatment-emergent adverse event rates were generally similar across treatment groups except for injection site reactions.

Conclusions: Izokibep resulted in significant and clinically meaningful improvements over placebo across multiple disease domains, and the originally randomised 80-mg dose showed continued improvements to week 46. There were no unexpected safety risks identified. Izokibep's small size and high potency have the potential for further improved disease control, justifying additional investigation of higher doses.

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Inhibition of interleukin (IL)-17 reduces symptoms, preserves function and improves quality of life in many patients with psoriasis and psoriatic arthritis (PsA). IL-17 inhibitors in clinical use for PsA are monoclonal antibodies of approximately 150 kDa in size and demonstrate efficacy in responsive patients following a variable time of exposure (~6 months).

WHAT THIS STUDY ADDS

- This randomised, double-blind, phase 2 study is the first evaluation of izokibep, a small protein therapeutic designed to inhibit IL-17A, in patients with PsA. Izokibep's unique properties, including its small size (18.6 kDa), high affinity for IL-17A (equilibrium dissociation constant [K_D] 0.3 pM), and albumin-binding domain, may provide an advantage over antibodies in penetrating inflamed tissues to improve levels of efficacy.
- Subcutaneous izokibep every other week resulted in significant improvements in PsA disease activity in adults with active PsA compared with placebo over 16 weeks of treatment, with continued increase in the frequency of improvement to week 46, while being generally well tolerated.
- Rates of enthesitis resolution at 16 weeks were particularly high for a manifestation that is historically difficult to treat.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- The findings support the continued development of izokibep as a novel therapeutic agent for PsA. Higher doses are being explored in a clinical study to assess whether greater levels of disease control might be possible.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic, systemic, immune-mediated, inflammatory disease characterised by multidomain manifestations, including peripheral arthritis, psoriasis (PsO), enthesitis, spine involvement, dactylitis, and nail disease, with PsA increasing in prevalence with PsO duration [1,2]. PsA is associated with other comorbidities and an increased risk of mortality due to cardiovascular events [3,4]. PsA appears to be driven by T-cell activation associated with the secretion of proinflammatory cytokines such as interleukin (IL)-17, tumour necrosis factor (TNF) and IL-23 [5]. IL-17A is a critical effector cytokine in PsA that regulates multiple cellular targets within the skin and musculoskeletal tissue by promoting inflammation, coagulation, and structural damage to the osseous, cartilaginous, and entheseal elements of the joint, which can lead to pain and disability [6–8]. Agents that target proinflammatory cytokines have greatly improved the treatment landscape for PsA, but <50% of patients achieve a ≥50% improvement from baseline based on American College of Rheumatology (ACR) criteria (ACR50) response at 6 months [9–13]; additionally, remission rates are low and treatment discontinuations are common and typically result from inadequate response or intolerance [14–18]. Enthesitis, dactylitis, and nail disease resolution remain key areas of unmet need [15,19,20].

Izokibep is a small protein therapeutic designed to inhibit IL-17A with high affinity (equilibrium dissociation constant [K_D] 0.3 pM) [21]. Izokibep's small size (18.6 kDa) has the potential to enhance access to inflamed tissues and may overcome limitations associated with the larger monoclonal antibodies of approximately 150 kDa in size, including poor tissue distribution [21]. Further, izokibep possesses an albumin-binding domain, which increases its half-life [21]. The simultaneous binding of izokibep to both subunits of IL-17A enhances its inhibitory capacity when compared with the monomeric precursor or other IL-17A–directed therapies [21]. Previous studies in PsO, including a phase 2 dose-ranging study (NCT03591887) evaluating izokibep at doses up to 160 mg every 2 weeks (Q2W) for 24 weeks (followed by every 4 or 8 weeks), have established that izokibep was efficacious and well tolerated for up to 3 years [22]. The aim of this study was to evaluate the efficacy and safety of izokibep vs placebo in adults with active PsA.

METHODS

Study design

This phase 2, multicentre, randomised, double-blind, placebo-controlled, parallel-group study at 28 European clinical sites (Austria, Belgium, Czech Republic, Germany, Hungary, Poland, and Spain) (Supplementary Table S1) recruited adult patients with active PsA. The study was conducted in accordance with the tenets of the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. Ethics approval was obtained from national and site-specific independent ethics committees at participating sites, and all patients provided written consent. This study was registered with EudraCT (number 2019-003405-94) prior to enrolment of the first patient and subsequently registered with ClinicalTrials.gov (NCT04713072).

The study included a screening period of up to 4 weeks, a 16-week, placebo-controlled, double-blind treatment period, a subsequent 28-week treatment period in which patients in the placebo arm were switched to active treatment (izokibep 80 mg Q2W) and an end of treatment visit scheduled 2 weeks after the

last dosing (week 46) (Supplementary Fig S1); blinding with respect to doses was maintained during the entire 46-week study period. An interactive web response system, overseen by an unblinded team member, was used for randomisation of eligible patients to treatment at baseline, using 1:1:1 randomisation to 1 of the 3 parallel treatment groups: izokibep 40 mg, izokibep 80 mg, and placebo, stratified by concomitant conventional synthetic disease-modifying antirheumatic drug (csDMARD) use (yes/no), previous TNF inhibitor (TNFi) exposure (yes/no), and country. As the injectable volumes differed (izokibep 40 mg, 0.5 mL; izokibep 80 mg, 1.0 mL; placebo, 1.0 mL of 0.9% saline solution in a single-use vial), doses were prepared and injected by an independent, unblinded, authorised member of the site team to maintain the blinding of study patients, the site personnel caring for the patient and the sponsor. Unblinding was allowed only in case of a medical emergency to treat a patient's adverse event (AE) and done in consultation with the medical monitor.

Izokibep and placebo were administered as subcutaneous injections at clinical study sites at baseline and subsequently Q2W. Safety was assessed at every study visit. Efficacy outcomes were assessed at baseline and every 4 weeks (Q4W), with additional assessments at weeks 2, 18, and 46 (end of treatment visit).

There were 2 major amendments to the initial protocol. Amendment 1 allowed patients to continue treatment Q2W after week 16 instead of switching to treatment Q4W as originally planned. Amendment 2 established premature termination of treatment following the completion of all patients through the 16-week placebo-controlled period and was undertaken to allow acceleration of further dose-ranging studies with izokibep in PsA.

Patients

Patients aged 18 to 75 years with inflammatory musculoskeletal disease (joint, spine, or entheseal) who met the Classification Criteria for Psoriatic Arthritis (presence of ≥3 points from the 5 categories [23] at any time point in medical history), had active PsA (≥3 tender joints [of 68; TJC68] and ≥3 swollen joints [of 66; SJC66]), and had an insufficient response to nonsteroidal anti-inflammatory drugs (NSAIDs), csDMARDs, or TNFis were enrolled. Patients were required to have a history of, or current, plaque PsO. Patients with a history of, or current, relevant immune-mediated diseases other than PsO or PsA (including uncontrolled inflammatory bowel disease [IBD]) and those having previous exposure to any IL-17/IL-17 receptor inhibitors were excluded. Full inclusion and exclusion criteria are provided in the Supplementary Methods. During the study, patients were allowed to continue stable use of 1 csDMARD and oral glucocorticoid (up to 7.5 mg of prednisolone equivalent) and use of NSAIDs as needed. Other systemic PsA or any PsO therapies, except for topical mild glucocorticoids in selected areas, were not allowed.

Outcomes

The primary end point was the percentage of patients achieving an ACR50 response at week 16 vs placebo. Other ranked end points in hierarchical order were ACR50 response at week 12, followed by a ≥20% improvement (ACR20) and a ≥70% improvement (ACR70) in ACR criteria at week 16, ACR20 and ACR70 at week 12, and minimal disease activity (MDA) responses at weeks 16 and 12. The izokibep 80-mg dose vs placebo was evaluated for the above-mentioned end points before the izokibep 40-mg dose vs placebo, and then the izokibep 80- and 40-mg doses vs placebo were evaluated at week 8.

Additional efficacy end points measured included tender and swollen joint counts based on 68 and 66 joints, respectively, Psoriasis Area and Severity Index (PASI) score and ≥75%/≥90%/100% reduction from baseline in PASI (PASI75/90/100) response rates in patients with >3% body surface area (BSA) involvement at baseline, Nail Psoriasis Severity Index for a target nail (specified at baseline), patient's pain assessment (100-mm visual analogue score [VAS]), patient's global assessment (VAS), physician's global assessment (VAS), Disease Activity Score in 28 joints (DAS28) using C-reactive protein (CRP), Disease Activity in Psoriatic Arthritis (DAPSA), Health Assessment Questionnaire Disability Index (HAQ-DI) score and percentage of patients with a ≥0.35-unit improvement from baseline, Psoriatic Arthritis Impact of Disease based on 9 numerical rating scales (PsAID-9) score and percentage of patients with a ≥3-unit improvement from baseline, enthesitis indices including the Leeds Enthesitis Index (LEI) and the Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index, and Leed's Dactylitis Index-Basic (LDI-B) [24,25]. Safety outcomes included treatment-emergent AE (TEAEs), treatment-emergent serious AE (SAEs), TEAEs leading to withdrawals, AEs of special interest (*Candida* sp. infection, IBD, staphylococcal skin infection, and moderate or severe injection site reactions) and TEAEs based on clinically relevant abnormal laboratory results. TEAEs were coded by the Medical Dictionary of Regulatory Activities (version 22.1) and defined as any AE occurring or worsening on or after the first dose of the study drug up to week 46 or patient discontinuation.

Statistical analyses

A sample size of 129 patients was calculated to provide 80% power of the primary end point assuming an estimated 35% ACR50 response rate at week 16 in the izokibep 80-mg group and a 10% placebo response rate, as informed by previous ixekizumab PsA studies [26,27] and estimating a dropout rate of 5% before 16 weeks. Efficacy analyses were conducted on the full-analysis set (FAS), which included all randomised patients with at least 1 documented dose of study drug and at least 1 postbaseline ACR efficacy assessment and used a 1-sided *Z*-test with pooled variance at a significance level of 2.5%. Corresponding 2-sided *P* values are reported for ease of interpretability. Summaries of demographics, baseline disease characteristics, and efficacy analyses are presented for the FAS. The safety-evaluable population included all randomised patients with at least 1 documented dose of study drug.

Primary and secondary end points were tested hierarchically. If an end point did not meet statistical significance, subsequent tests of ranked end points were nonconfirmatory with nominal *P* values. The analysis for the 16-week primary end point was comparison of ACR50 response rates between the 80-mg group and placebo, followed by a comparison between these groups at week 12, tested sequentially in a logistic generalised estimating equation regression model with previous TNFi exposure, concomitant csDMARD use, country, treatment, visit (weeks 8, 12, and 16; week 4 was omitted due to convergence issues with the model) and treatment by visit interaction as fixed adjustment factors. Patients were considered nonresponders for binary end points if they did not meet clinical response criteria or had missing clinical response data at the respective time point. For primary and secondary end points during the 16-week placebo-controlled period, missing data were imputed using

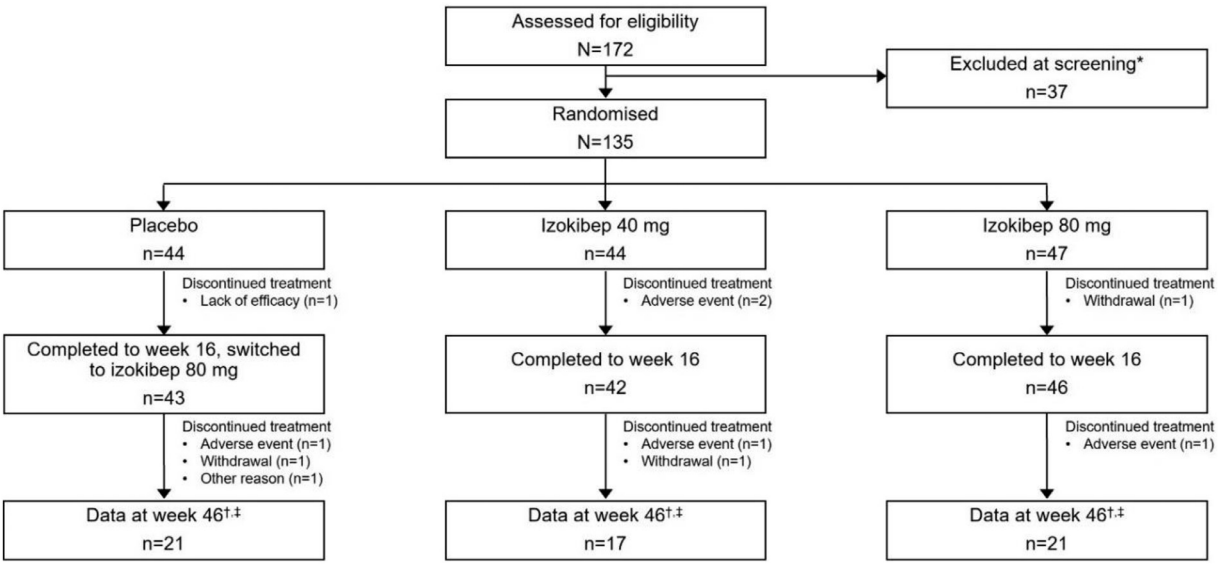

Figure 1. Study profile. *Includes n = 11 (30%) due to positive rheumatoid factor or positive anti-CCP antibody and n = 6 (16%) due to positive tuberculosis test. †The study was amended and terminated due to the sponsor's decision to continue exploring the effective dose range in the next phase 2b/3 study; as a result, 17 patients in the placebo/izokibep 80-mg group, 21 patients in the izokibep 40-mg group and 20 patients in the izokibep 80-mg group did not reach the week 46 visit. ‡Two patients in the placebo/izokibep 80-mg group, 2 patients in the izokibep 40-mg group, and 4 patients in the izokibep 80-mg group had visits outside of the predefined week 46 window (day 322 ± 6) and were not included in the week 46 analysis. CCP, cyclic citrullinated peptide.

nonresponder imputation (NRI). Other end points that were not part of the primary and secondary analyses set are presented as observed data. Due to the change in the design subsequent to all patients completing the 16-week placebo-controlled period, all analyses beyond week 16 are presented as observed data, as NRI was no longer an appropriate form of analysis given that the majority of discontinuations were due to the sponsor's decision to terminate the study and not related to patients' choice to discontinue (Fig 1).

RESULTS

Patient characteristics

From August 4, 2020, to June 9, 2021, 172 patients were screened for the study and 135 patients (62 [46%] male; 73 [54%] female) were randomised to izokibep 40 mg Q2W (n = 44), izokibep 80 mg Q2W (n = 47) or placebo (n = 44) (Fig 1). All randomised patients received at least 1 dose of study drug and had at least 1 ACR data point and safety information; thus, the FAS and safety set were identical.

Baseline characteristics were comparable between treatment groups with a mean (SD) age of 48.5 (12.0) years and a mean (SD) PsA duration of 7.1 (7.8) years (Table 1). In the overall patient population, evaluation of baseline disease activity showed a mean (SD) of 9.9 (6.6) swollen and 16.7 (10.4) tender joints, 98% of patients had plaque PsO, 77% had enthesitis per SPARCC Enthesitis Index (>0, 18 evaluated sites [0–16 scale]), 32% had enthesitis per LEI (>0, 6 evaluated sites [0–6 scale]), and 19% had dactylitis. Discontinuation rates were low (4 patients during the first 16 weeks) (Fig 1) and similar between treatment groups. The overall mean compliance as judged by the clinician based on visit attendance was 98% during the first 16 weeks and similar across the treatment groups.

Efficacy outcomes for the 16-week placebo-controlled period

ACR50 response rates as determined by the logistic regression model at week 16 were 52% (95% CI: 32%, 71%) for izokibep 80 mg vs 13% for placebo (95% CI: 6%, 28%; 2-sided $P = .0006$) and 50% (95% CI: 30%, 69%) vs 6% (95% CI: 2%, 17%; $P < .0001$) at week 12, respectively (Table 2; Fig 2). The end point of ACR20 response rates for izokibep 80 mg vs placebo at week 16 was also achieved (75% vs 26%; $P < .0001$), but the subsequent hierarchical end point, ACR70 response rates for izokibep 80 mg vs placebo at week 16 (20% vs 5%; $P = .0678$), was not met (Table 2, Fig 2).

In subsequent analyses, izokibep 40 mg resulted in higher ACR20/50/70 response rates than placebo at weeks 8, 12, and 16 (Table 2, Fig 2). Higher rates of MDA were achieved with izokibep 80 mg (39%) or 40 mg (42%) at week 16 vs placebo (5%) (Table 2, Fig 2). For both doses, increases in ACR20 responses were evident at the earliest clinical visit (2 weeks) (Fig 2).

In analyses of additional key efficacy outcomes, the 80-mg dose led to lower disease activity scores vs the 40-mg dose as measured by TJC68, SJC66, DAPSA, DAS28-CRP, and physician's global assessment (Table 3). For DAPSA, low disease activity (≤14) was reached in 21% and 23% of patients treated with izokibep 80 and 40 mg, respectively, at week 4 and improved to 45% and 43% at week 16 (Supplementary Fig S2).

In analyses assessing additional PsA domains, izokibep was associated with higher rates of PASI75/90/100 response in patients with BSA >3% at baseline vs placebo at week 16 (Table 3, Fig 3, Supplementary Fig S3). Of patients treated with izokibep 80 and 40 mg, 37% and 39%, respectively, achieved PASI100 at week 16 vs 5% for placebo. Domains assessing izokibep 80 and 40 mg on nails, dactylitis, and enthesitis showed large improvements for patients treated with izokibep relative to placebo during the 16-week study period (Table 3, Supplementary Table S2). Higher rates of LEI resolution at 16 weeks were observed for the izokibep 80-mg group (15/17 [88%])

Table 1
Baseline characteristics of randomised patients

Characteristic	Placebo (n = 44)	Izokibep 40 mg Q2W (n = 44)	Izokibep 80 mg Q2W (n = 47)	All patients (N = 135)
Age (y)	47.6 (12.6)	47.6 (12.5)	50.1 (10.9)	48.5 (12.0)
Sex, n (%)				
Male	22 (50)	21 (48)	19 (40)	62 (46)
Female	22 (50)	23 (52)	28 (60)	73 (54)
Race: White[a]	44 (100)	44 (100)	47 (100)	135 (100)
Ethnicity,[a] n (%)				
Hispanic or Latino	0	1 (2)	1 (2)	2 (1)
Not Hispanic or Latino	44 (100)	43 (98)	46 (98)	133 (99)
BMI (kg/m^2)	28.2 (4.7)	30.2 (5.2)	28.5 (4.5)	29.0 (4.8)
PsA duration (y)	7.8 (9.2)	7.3 (7.9)	6.4 (6.2)	7.1 (7.8)
Previous anti-TNF exposure, n (%)	4 (9)	5 (11)	8 (17)	17 (13)
Concomitant csDMARD use, n (%)	35 (80)	35 (80)	38 (81)	108 (80)
Concomitant methotrexate use, n (%)	25 (57)	31 (70)	32 (68)	88 (65)
Plaque PsO duration (y)	18.5 (14.6)	16.7 (12.0)	18.8 (14.5)	18.0 (13.7)
Plaque PsO, n (%)	44 (100)	42 (95)	46 (98)	132 (98)
Nail PsO, n (%)	34 (77)	34 (77)	36 (77)	104 (77)
TJC68	16.4 (11.3)	16.7 (10.3)	17.0 (9.7)	16.7 (10.4)
SJC66	9.2 (6.4)	10.1 (7.0)	10.4 (6.4)	9.9 (6.6)
DAPSA score	47.1 (25.1)	47.1 (20.6)	46.3 (21.1)	46.8 (22.2)
DAS28-CRP	4.5 (0.9)	4.5 (1.0)	4.5 (1.1)[b]	4.5 (1.0)
Physician's global assessment VAS (mm)	64.1 (15.6)	61.4 (14.8)	64.0 (18.0)	63.2 (16.2)
CRP (mg/L)	9.3 (12.1)	8.3 (8.0)	6.0 (7.7)	7.8 (9.5)
SPARCC Enthesitis Index score				
SPARCC >0, n (%)	33 (75)	34 (77)	37 (79)	104 (77)
Mean value in patients with SPARCC >0	3.6 (3.3)	3.4 (2.6)	3.2 (2.5)	3.4 (2.8)
LEI				
LEI >0, n (%)	10 (23)	16 (36)	17 (36)	43 (32)
Mean value in patients with LEI >0	1.5 (0.5)	1.7 (0.5)	1.4 (0.5)	1.5 (0.5)
LDI-B				
LDI-B >0, n (%)	11 (25)	9 (20)	6 (13)	26 (19)
Mean value of LDI-B in patients with baseline dactylitis	22.1 (16.3)	18.6 (12.7)	29.5 (13.1)	22.6 (14.5)
PASI				
Patients with >3% of BSA-PsO, n (%)	23 (52)	23 (52)	28 (60)	74 (55)
PASI (in patients with >3% of BSA-PsO)	11.1 (7.0)	10.2 (6.8)	8.1 (4.9)	9.7 (6.3)
BSA affected by PsO (%)	8.7 (11.0)	8.0 (11.7)	8.5 (10.1)	8.4 (10.9)
NAPSI score (target nail)[c]	3.7 (2.1)	3.5 (2.4)	3.7 (2.5)	3.7 (2.3)
DLQI total sum score	8.4 (7.5)	7.9 (7.0)	9.3 (6.7)	8.5 (7.1)
PsAID-9	5.7 (1.7)	5.8 (2.1)	6.0 (1.6)	5.9 (1.8)
HAQ-DI score	1.2 (0.6)	1.2 (0.6)	1.3 (0.5)	1.3 (0.6)
Pain VAS (mm)	62.3 (18.9)	61.5 (20.4)	64.4 (20.3)	62.8 (19.8)
Patient's global assessment VAS (mm)	59.9 (19.7)	58.5 (21.4)	62.2 (20.1)	60.2 (20.3)
Itch NRS (average)	4.4 (2.4)	4.2 (2.9)	4.8 (2.4)	4.5 (2.6)

BMI, body mass index; BSA, body surface area; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28-CRP, Disease Activity Score in 28 joints using C-reactive protein; DLQI, Dermatology Life Quality Index (from 0 = no impact to 30 = extreme impact on quality of life); HAQ-DI, Health Assessment Questionnaire Disability Index (from 0 = without any difficulty to 3 = unable to do); LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; NAPSI, Nail Psoriasis Severity Index; NRS, numerical rating scale (from 0 = none to 10 = worst imaginable); PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsAID-9, Psoriatic Arthritis Impact of Disease based on 9 numerical rating scales; PsO, psoriasis; Q2W, once every 2 weeks; SJC66, swollen joint count based on 66 joints; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC68, tender joint count based on 68 joints; TNF, tumour necrosis factor; VAS, visual analogue scale (from 0 = none/very well to 100 = worst imaginable/very poor).
Data are mean (SD) unless otherwise specified.
[a] As reported by the patient.
[b] Evaluable n = 46.
[c] Evaluable n = 35 in each treatment group (total N = 105).

compared with the izokibep 40-mg group (10/15 [67%]) and placebo (1/9 [11%]) in patients with LEI >0 at baseline, and these findings were consistent with improvements in the SPARCC Enthesitis Index (Table 3, Fig 3). Marked mean reductions were observed in LDI-B scores at week 16 in patients with baseline dactylitis (Table 3).

Across patient-reported outcomes, patient-reported pain, patient-reported itch, HAQ-DI and the PsAID-9 questionnaire showed clinically important dose-dependent improvements at week 16 vs placebo (Table 3). Izokibep 80 mg achieved statistically significant improvements over placebo for all 9 PsAID-9 domains at week 16 (Fig 4); for all domains, greater improvements were observed for izokibep 80 vs 40 mg except for 'skin problems,' which showed similar levels of change.

Efficacy outcomes weeks 16 to 46

The study was terminated once the last enrolled patient passed the 16-week primary time point, although many patients already had visits beyond 16 weeks. Patient numbers were balanced across treatment groups and not related to dose assignment, as expected considering study closure was administrative

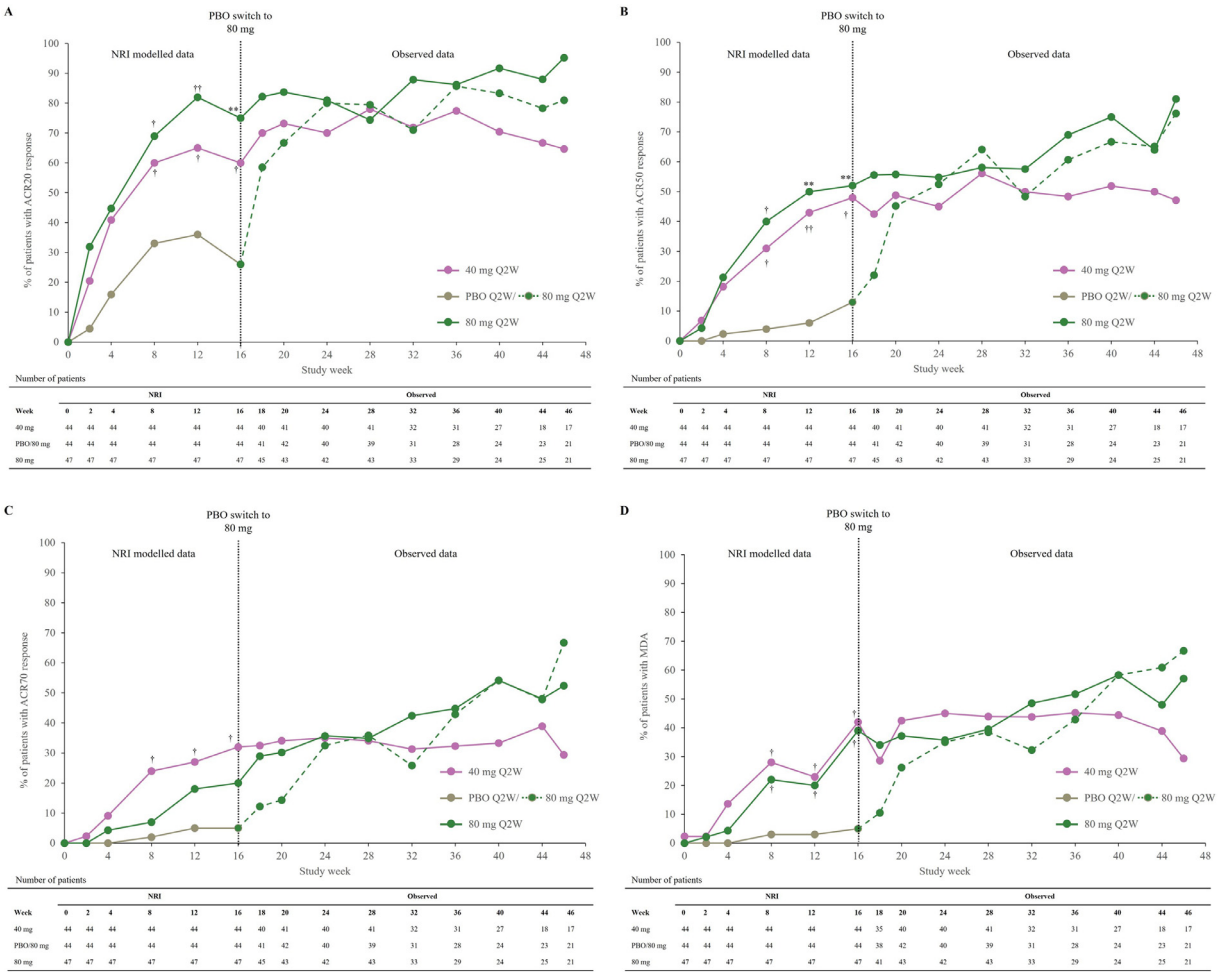

Figure 2. Percentages of patients achieving (A) ACR20, (B) ACR50, (C) ACR70, and (D) MDA from week 0 to week 46. NRI until week 16; logistic regression model with fixed factors (pooled) at weeks 8 to 16; observed data after week 16. *Significance within the hierarchical test chain. †Significance in descriptive test results in analyses of modelled NRI data for izokibep vs PBO during the PBO-controlled period. */†Two-sided P <.05. **/††Two-sided P < .001. ACR20/50/70, ≥20%/≥50%/≥70% improvement from baseline based on American College of Rheumatology criteria; MDA, minimal disease activity; NRI, nonresponder imputation; PBO, placebo; Q2W, every 2 weeks.

Table 2
Primary and secondary efficacy outcomes

Outcome	Hierarchical rank (placebo vs izokibep 80 mg)[a]	Placebo (N = 44)	Izokibep 40 mg (N = 44)		Izokibep 80 mg (N = 47)	
		Modelled NRI rate (95% CI) (%)	Modelled NRI rate (95% CI) (%)	Two-sided P vs placebo	Modelled NRI rate (95% CI) (%)	Two-sided P vs placebo
Primary outcomes						
ACR50, week 16	1	13 (6, 28)	48 (29, 68)	.0014	52 (32, 71)	**.0006**
ACR50, week 12	2	6 (2, 17)	43 (25, 62)	.0002	50 (30, 69)	**<.0001**
Secondary outcomes						
ACR20, week 16	3	26 (14, 44)	60 (40, 77)	.0028	75 (57, 88)	**<.0001**
ACR70, week 16	4	5 (1, 18)	32 (17, 53)	.0101	20 (8, 43)	.0678
Additional secondary outcomes						
ACR20, week 12	NA	36 (20, 55)	65 (46, 80)	.0086	82 (67, 91)	<.0001
ACR70, week 12	NA	5 (1, 18)	27 (13, 46)	.0176	18 (7, 36)	.0831
MDA, week 16	NA	5 (1, 20)	42 (24, 62)	.0020	39 (22, 59)	.0032
MDA, week 12	NA	3 (0, 17)	23 (11, 41)	.0285	20 (9, 38)	.0434
ACR50, week 8	NA	4 (1, 16)	31 (17, 50)	.0039	40 (21, 62)	.0012
ACR20, week 8	NA	33 (18, 52)	60 (40, 77)	.0179	69 (50, 83)	.0015
ACR70, week 8	NA	2 (0, 15)	24 (11, 43)	.0243	7 (2, 21)	.3186
MDA, week 8	NA	3 (0, 17)	28 (15, 47)	.0143	22 (11, 40)	.0316

ACR20/50/70, ≥20%/≥50%/≥70% improvement from baseline based on American College of Rheumatology criteria; MDA, minimal disease activity; NA, not applicable; NRI, nonresponder imputation.
Modelled response rates using NRI for primary and secondary outcomes are shown in hierarchical order. Two-sided P values <.05 were considered statistically significant and are shown in bold.
[a] The fourth-ranked outcome failed to be statistically significant (2-sided P value >.05), so a formal statistical analysis could not be performed on subsequent ranked outcomes and additional statistical analyses were descriptive only, including all comparisons of izokibep 40 mg and placebo.

Table 3
Key efficacy end points at week 16 (observed data)

Outcome	Placebo (N = 44)	Izokibep 40 mg (N = 44)		Izokibep 80 mg (N = 47)	
	Percent or mean (SD) [n/N or n]	Percent or mean (SD) [n/N or n]	Two-sided *P* vs placebo[a]	Percent or mean (SD) [n/N or n]	Two-sided *P* vs placebo[a]
TJC68	10.7 (9.1) [43]	7.1 (7.7) [42]	<.0001	5.6 (6.8) [46]	<.0001
SJC66	5.0 (5.7) [43]	2.4 (3.7) [42]	<.0001	1.7 (2.7) [46]	<.0001
SPARCC Enthesitis Index					
Mean value in patients with SPARCC >0 at baseline[b]	2.8 (2.6) [32]	1.2 (1.7) [33]	<.0001	1.2 (2.0) [36]	<.0001
SPARCC = 0 for patients with SPARCC >0 at baseline[b]	19 [6/32]	45 [15/33]	.0344	56 [20/36]	.0028
LEI					
Mean value in patients with LEI >0 at baseline[b]	1.3 (0.7) [9]	0.5 (0.7) [15]	.0191	0.2 (0.7) [17]	.0006
LEI = 0 for patients with LEI >0 at baseline[b]	11 [1/9]	67 [10/15]	.0143	88 [15/17]	.0001
LDI-B					
Mean score in patients with LDI-B >0 at baseline	17.6 (15.9) [10]	2.0 (4.0) [9]	<.0001	4.4 (8.1) [6]	<.0001
LDI-B = 0 in patients with LDI-B >0 at baseline[c]	30 [3/10]	78 [7/9]	Not calculated	67 [4/6]	Not calculated
PASI in patients with >3% BSA at baseline					
PASI75	14 [3/22]	83 [19/23]	<.0001	85 [23/27]	<.0001
PASI90	14 [3/22]	57 [13/23]	.0009	48 [13/27]	.0022
PASI100	5 [1/22]	39 [9/23]	.0029	37 [10/27]	.0013
NAPSI score (target nail)	2.7 (2.1) [36]	1.2 (1.4) [33]	<.0001	1.8 (2.2) [36]	.0028
Patient-reported outcomes[d]					
PsAID-9 (0–10)	4.79 (2.06) [43]	3.63 (2.50) [42]	.0022	3.42 (2.35) [46]	<.0001
PsAID-9 ≥3-unit improvement[e]	12 [5/43]	31 [13/42]	.0418	41 [19/46]	.0017
HAQ-DI (0–3)	1.08 (0.59) [43]	0.84 (0.70) [42]	.0166	0.86 (0.67) [46]	.0001
HAQ-DI ≥0.35-unit improvement[e]	26 [11/43]	43 [18/42]	Not calculated	54 [25/46]	Not calculated
Patient's global assessment (0–100)	49.6 (22.7) [43]	35.0 (27.8) [42]	.0030	34.3 (26.4) [46]	.0001
Patient's pain assessment (0–100)	51.3 (24.5) [43]	35.3 (27.6) [42]	.0007	33.4 (26.0) [46]	<.0001
Average itch NRS (0–10)	3.7 (2.9) [43]	2.3 (2.5) [42]	.0053	2.7 (2.1) [46]	.0008
Composite and global scores					
DAPSA composite score	34.1 (19.0) [43]	22.3 (16.3) [42]	<.0001	17.7 (12.0) [44]	<.0001
DAS28-CRP	3.87 (1.06) [43]	2.93 (1.15) [42]	<.0001	2.85 (0.90) [44]	<.0001
Physician's global assessment (0–100)	44.8 (23.4) [43]	20.3 (17.4) [42]	<.0001	16.5 (14.3) [46]	<.0001

BSA, body surface area; DAPSA, Disease Activity in Psoriatic Arthritis; DAS28-CRP, Disease Activity Score in 28 joints using C-reactive protein; HAQ-DI, Health Assessment Questionnaire Disability Index; LDI-B, Leeds Dactylitis Index-Basic; LEI, Leeds Enthesitis Index; NAPSI, Nail Psoriasis Severity Index; NRS, numeric rating scale; PASI, Psoriasis Area and Severity Index; PASI75/90/100, ≥75%/≥90%/100% reduction from baseline in PASI; PsAID-9, Psoriatic Arthritis Impact of Disease based on 9 numerical rating scales; SJC66, swollen joint count based on 66 joints; SPARCC, Spondyloarthritis Research Consortium of Canada; TJC68, tender joint count based on 68 joints.
Results for additional efficacy end points during the placebo-controlled period are presented in Supplementary Table S2.
[a] Two-sided *P* values of <.05 were considered statistically significant.
[b] The subpopulation with enthesitis at baseline was not prespecified in the study protocol. Two-sided *P* values for enthesitis resolution analyses (LEI and SPARCC) were determined by Fisher exact test of observed data in post hoc analyses.
[c] Dactylitis resolution in the subpopulation with dactylitis at baseline was not prespecified in the study protocol.
[d] Lower scores are better for all patient-reported outcomes.
[e] The analysis was not prespecified in the study protocol.

and not related to patients' choice. Of the original 135 patients randomised, 59 (44%) had available week 46 data (Fig 1).

Among patients who started on izokibep 80 mg, rates of response generally increased to week 46, with 81% attaining an ACR50 response, 52% attaining ACR70, 71% attaining PASI100, and 89% attaining LEI complete resolution (Figs 2 and 3). In patients initially randomised to the 80-mg group, improvements over time were generally seen in all outcome measures, including ACR20/50/70 and MDA scores (Fig 2), PASI75/90/100 (Fig 3, Supplementary Fig S3), and composite disease activity scores (DAPSA, DAS28-CRP) (Supplementary Table S3). Responses were typically higher for izokibep 80 vs 40 mg for clinical and patient-reported outcomes (Figs 2–4, Supplementary Table S3). Patients who switched from placebo to izokibep 80-mg Q2W therapy showed responses mirroring the continuous 80-mg Q2W group by approximately week 24 (Figs 2 and 3) and

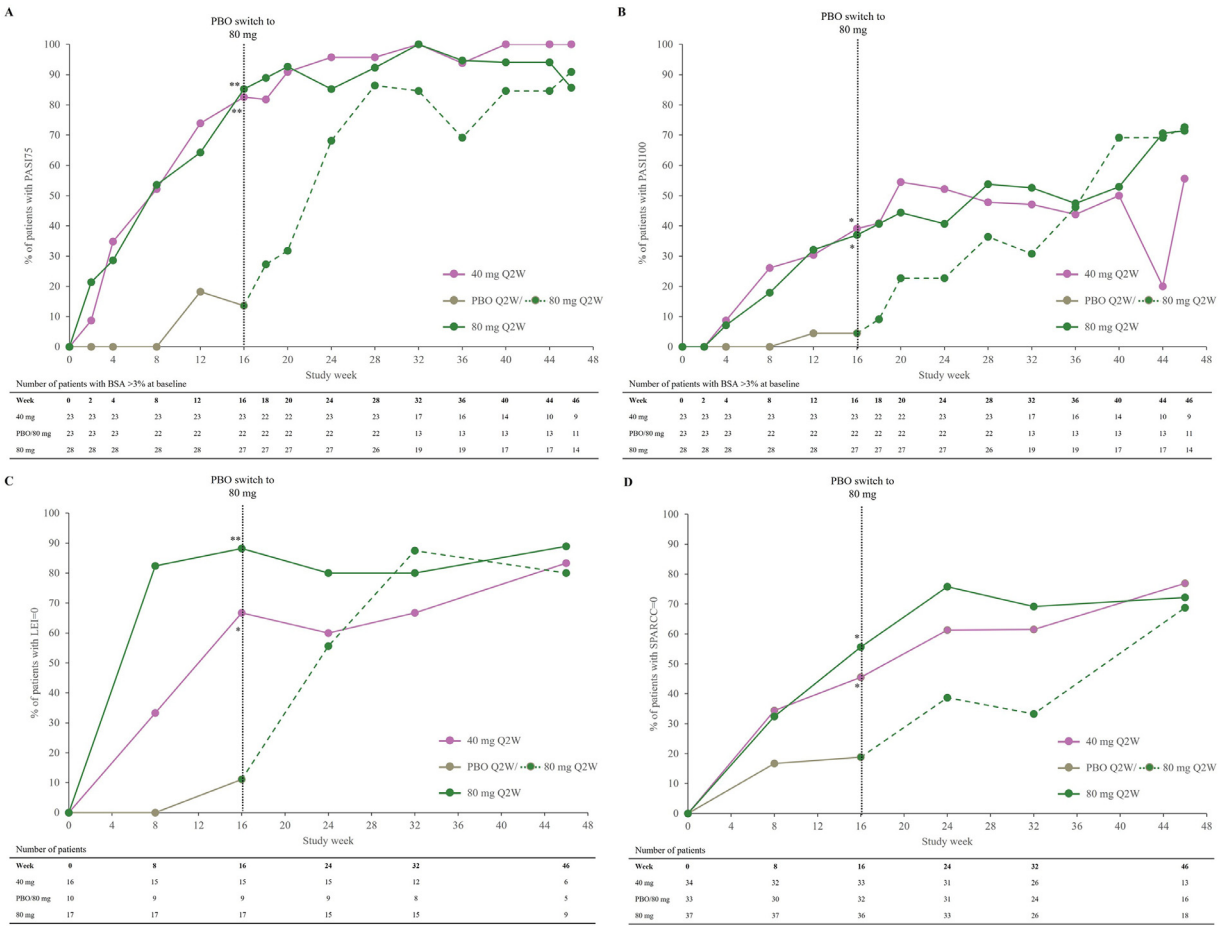

Figure 3. Percentages of patients achieving (A) PASI75, (B) PASI100, (C) LEI = 0 in patients with LEI >0 at baseline and (D) SPARCC = 0 in patients with SPARCC >0 at baseline from week 0 to 46. Data shown are observed data. PASI analyses were conducted in patients with >3% BSA at baseline. *Statistically significant differences for izokibep vs PBO during the PBO-controlled period. *P* values (2-sided) for PASI values were determined based on modelled observed data. *P* values (2-sided) for enthesitis resolution analyses (LEI and SPARCC) were determined by Fisher exact test of observed data in post hoc analyses. *Descriptive $P < .05$. **Descriptive $P < .001$. BSA, body surface area; LEI, Leeds Enthesitis Index; PASI, Psoriasis Area and Severity Index; PASI75/100, ≥75%/100% reduction from baseline in PASI; PBO, placebo; Q2W, every 2 weeks; SPARCC, Spondyloarthritis Research Consortium of Canada.

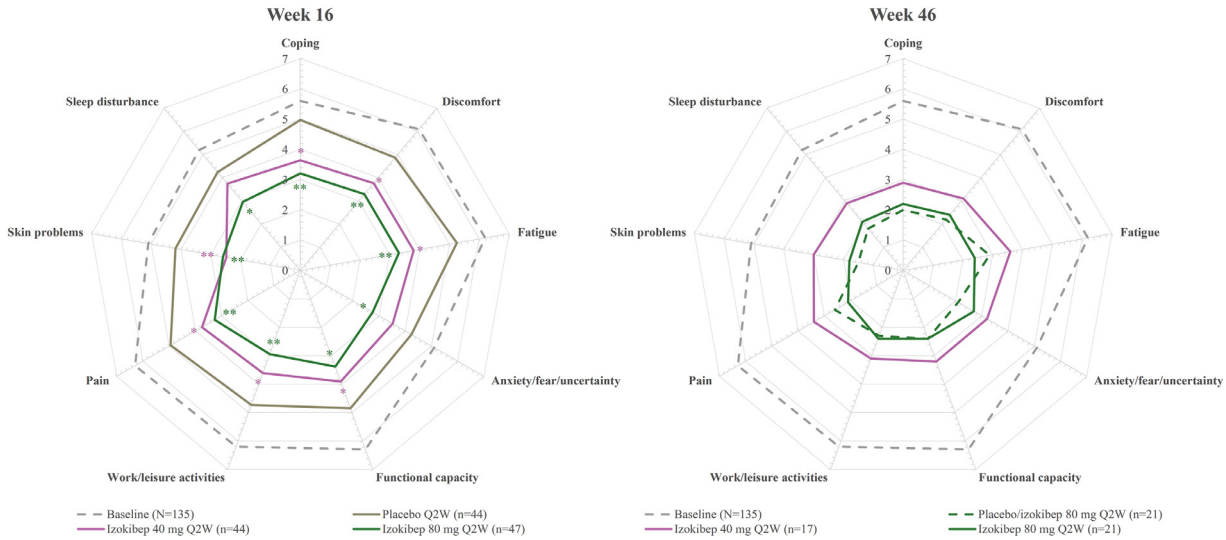

Figure 4. PsAID-9 subdomain mean values at week 16 (model adjusted) and week 46 (observed). *Statistically significant differences in analyses of modelled data for izokibep vs placebo during the placebo-controlled period. *Two-sided descriptive $P < .05$. **Two-sided descriptive $P < .001$. PsAID-9, Psoriatic Arthritis Impact of Disease based on 9 numerical rating scales; Q2W, every 2 weeks.

at all time points beyond (Supplementary Table S3). Those originally randomised to izokibep 40 mg typically maintained responses between weeks 16 and 46 (Figs 2 and 3).

SPARCC enthesitis outcomes also showed continued improvements with week 46 resolution rates for the original 80-mg dose (72%) and 40-mg dose (77%), paralleling the LEI resolution rates (Fig 3). At week 46, all 7 patients with LDI-B of >0 at baseline achieved dactylitis resolution (Supplementary Table S3). The mean values of all PsAID-9 subdomains continued to improve further from week 16 to 46, with responses for the 80-mg dose groups exceeding those in the 40-mg group (Fig 4).

Safety

By week 16, 26 (55%) and 29 (66%) patients in the izokibep 80- and 40-mg groups, respectively, and 23 patients (52%) in the placebo group reported at least 1 TEAE (Table 4). Treatment-related TEAEs were reported in 17 patients (36%) in the izokibep 80-mg group and 24 patients (55%) in the izokibep 40-mg group vs 9 (21%) patients in the placebo group; the different rates were primarily due to injection site reactions/injection site erythema related to izokibep treatment. All TEAEs were of mild or moderate severity, and no relationship between izokibep's dose and the incidence or severity of TEAEs was observed. Treatment with izokibep 40 mg was discontinued in 2 of the 44 (5%) patients due to TEAEs (1 injection site reaction and 1 injection site erythema) (Table 4). There were no treatment discontinuations due to TEAEs in the izokibep 80-mg group or placebo group. Injection site reactions were the most frequently reported TEAEs with izokibep (80 mg, 26%; 40 mg, 27%; vs 0% for placebo), followed by injection site erythema, hyperkalaemia, and upper respiratory tract infections. Hyperkalaemia events in the absence of clinical correlates were reported at specific clinical sites and were hypothesised to be related to blood sample management. No deaths occurred during the study, and there were no SAEs during the placebo-controlled period. There was 1 case of mild vulvovaginal candidiasis in the izokibep 40-mg group that resolved within 2 weeks.

Between weeks 16 and 46, the rates of injection site reactions decreased in the izokibep groups (to 15% and 12% for the 80- and 40-mg groups, respectively) and were 16% in placebo-randomised patients switched to izokibep 80 mg. Izokibep continued to be well tolerated for up to 46 weeks, and no new safety signals were observed. There were 3 treatment discontinuations due to TEAEs overall (1 per treatment group) after week 16. One treatment discontinuation in the izokibep 40-mg group was due to hepatic enzyme increased (initially reported in the first 16 weeks, with a persistent increase leading to discontinuation between weeks 16 and 46). One treatment discontinuation in the 80-mg group was due to a human papillomavirus–associated vulvar neoplasia (diagnosed after laser excision) after approximately 4 months of treatment, a latency period

Table 4
Treatment-emergent adverse events

	Placebo-controlled period (weeks 0–16)			Long-term treatment (weeks 16–46)		
TEAEs	Placebo (N = 44)	Izokibep 40 mg (N = 44)	Izokibep 80 mg (N = 47)	Placebo to izokibep 80 mg (N = 43)	Izokibep 40 mg (N = 42)	Izokibep 80 mg (N = 46)
Any TEAE	23 (52)	29 (66)	26 (55)	22 (51)	24 (57)	27 (59)
Serious TEAEs	0	0	0	3 (7)	1 (2)	3 (7)
Severe TEAEs	0	0	0	3 (7)	0	2 (4)
Deaths	0	0	0	0	0	0
TEAEs assessed as possibly drug related	9 (20)	24 (55)	17 (36)	15 (35)	13 (31)	14 (30)
Discontinuations due to TEAEs	0	2 (5)	0	1 (2)	1 (2)	1 (2)
TEAE by preferred term (in ≥5% of patients in any group and any period)						
Injection site reaction	0	12 (27) (none severe)	12 (26) (none severe)	7 (16)	5 (12)	7 (15)
Injection site erythema	0	8 (18) (none severe)	5 (11) (none severe)	5 (12)	6 (14)	5 (11)
Nasopharyngitis	0	1 (2)	2 (4)	2 (5)	3 (7)	4 (9)
Headache	4 (9)	0	4 (9)	2 (5)	1 (2)	4 (9)
γ-glutamyltransferase increased	1 (2)	0	0	2 (5)	0	3 (7)
Back pain	0	0	0	2 (5)	3 (7)	2 (4)
Hypertension	4 (9)	2 (5)	0	1 (2)	0	2 (4)
Hyperkalaemia	2 (5)	3 (7)	2 (4)	0	4 (10)	1 (2)
Upper respiratory tract infection	1 (2)	2 (5)	3 (6)	0	3 (7)	1 (2)
Arthralgia	1 (2)	0	0	1 (2)	3 (7)	1 (2)
Diarrhoea	3 (7)	0	2 (4)	1 (2)	0	0
Corona virus infection	2 (5)	1 (2)	1 (2)	2 (5)	2 (5)	3 (7)

	Placebo-controlled period (weeks 0–16)			Long-term treatment (weeks 16–46)	
AEs of special interest	Placebo (N = 44)	Izokibep 40 mg (N = 44)	Izokibep 80 mg (N = 47)	Izokibep 40 mg (N = 42)	Izokibep 80 mg (N = 89)[a]
Injection site reaction	0	2 (5)	0	1 (2)	1 (1)
Injection site erythema	0	0	0	1 (2)	0
Candidiasis	0	1 (2)[b]	0	0	0
Groin abscess	0	0	0	0	1 (1)

AE, adverse event; TEAE, treatment-emergent adverse event.
Data are from the safety-evaluable set and presented as the number (%) of patients with the AE.
[a] Data were pooled from placebo to izokibep 80-mg and izokibep 80-mg treatment groups from weeks 16 to 46.
[b] Mild vulvovaginal candidiasis resolving within 2 weeks while the patient stayed on therapy.

considered too short to be related to the drug product. One treatment discontinuation in the placebo to 80-mg group resulted from an injection site reaction, which was moderate in intensity and considered related to treatment. Seven patients experienced 8 SAEs between weeks 16 and 46 (placebo to 80-mg group, n = 3; 80-mg group, n = 3; 40-mg group, n = 1) (Supplementary Table S4). There was no pattern to the SAEs observed, and 6 of the 7 patients were reported as recovered/resolved by end of study (the status of 1 was unknown).

DISCUSSION

IL-17A is a key driver of immune-mediated inflammatory disorders including PsO and PsA [6]. In this phase 2, randomised, double-blind, placebo-controlled study, izokibep, a novel, small protein therapeutic designed to inhibit IL-17A, significantly improved musculoskeletal and skin disease in adult patients with active PsA and varying exposures to previous therapies. An ACR50 response at week 16, the primary efficacy end point, was achieved by 52% and 48% of patients in the izokibep 80- and 40-mg groups, respectively, compared with 13% of placebo-treated patients. At week 16, approximately 40% of patients in the izokibep treatment groups achieved MDA, which is a widely used measure of multidimensional disease control [28,29]. More than 80% of izokibep-treated patients with a baseline BSA of >3% achieved a PASI75 response at week 16 (vs 14% of placebo-treated patients), and complete skin clearance (PASI100 response) was observed in almost 40% of izokibep-treated patients (vs 5% of placebo-treated patients). The PASI data for izokibep are in line with those reported for other anti–IL-17A agents in PsA [11,13,26,27,30–32].

Improvements in efficacy outcomes observed at week 16 generally increased further with the higher 80-mg dose and were maintained with the lower 40-mg dose to week 46. Patients treated with placebo during the initial 16-week period showed rapid improvements in symptoms when switched to izokibep 80 mg. Dose-dependent improvements were also seen in patient-reported outcomes including PsAID-9 and HAQ-DI through week 16, which were maintained or further improved through week 46.

Recent reports have highlighted a higher symptom burden in patients with PsA who have enthesitis [33]; the response of enthesitis to therapy is reduced compared with skin and joint outcomes [34], and enthesitis is associated with a lower probability of achieving remission or low disease activity [35]. In our study, patients with clinical enthesitis showed excellent responses to izokibep as evaluated by resolution of enthesitis by both SPARCC and LEI. The high rates of enthesitis resolution with izokibep 80 mg at week 16 are encouraging and perhaps indicative of the molecular properties of izokibep, warranting further study. We also observed marked and rapid reductions in dactylitis throughout this study. The magnitude of effects with izokibep in hard-to-treat tissues are hypothesised to be related to its unique potential to penetrate inflamed tissues (related to its small molecular size and albumin trafficking to sites of inflammation) and high binding affinity to IL-17A (0.3 pM) [21,36,37].

The clinical safety profile of izokibep in this study indicated good tolerability similar to other therapies targeting the IL-17A pathway, with lower rates of fungal infections than reported in previous studies with IL-17A and F inhibitors [11,13,30,31,38]. In this study, injection site reactions and injection site erythema were the predominant TEAEs reported with izokibep; these were typically mild in severity, resolved rapidly, and were more prevalent with earlier injections. Injection site reactions uncommonly led to discontinuation. There were otherwise no important differences in TEAEs vs placebo. Studies of IL-17 inhibitors in PsA have reported higher risks of *Candida* sp. infections, injection site reactions, and IBD associated with these agents [38–42]. In our study, 1 patient in the izokibep 40-mg group had mild vulvovaginal candidiasis (1% with izokibep). Infection rates were low and comparable with placebo over 16 weeks, and no cases of IBD were reported.

The approved IL-17A inhibitors do not have a clear dose-limiting AE profile, and empirical evidence has demonstrated their short-term and long-term safety in patients with PsA [38–40]. Based on indirect comparison with published data for other IL-17 inhibitors, the benefit–risk relationship in patients with PsA appears favourable for izokibep and highlights the potential opportunity for enhanced therapeutic effects on PsA symptoms, including difficult-to-treat domains such as enthesitis and dactylitis. The lack of dose-related AEs with izokibep, dose-related improvements in clinical signs and symptoms, and sustained efficacy support the potential for investigating higher doses in future studies, including those being conducted for other inflammatory conditions. Izokibep is being studied in patients with uveitis (NCT05384249 [phase 2b]), hidradenitis suppurativa (NCT05355805 [phase 2b]; NCT05905783 [phase 3]), and PsA (NCT05623345 [phase 2b/3]). Data from these studies will provide further information on the risks and benefits of izokibep in the management of chronic inflammatory diseases.

Limitations of this study include a modest sample size, consistent with the phase 2 stage of investigation. Patient numbers beyond 16 weeks declined related to the administrative decision to terminate the study following the last patient reaching the 16-week primary end point; this decision was made to accelerate further dose exploration to understand whether even greater responses might be achieved with higher doses without dose-related safety events. The study was not designed to directly compare izokibep doses.

CONCLUSION

In this phase 2 study in patients with active PsA, izokibep, a small protein therapeutic designed to inhibit IL-17A with high affinity, showed high levels of response differentiating from placebo across multiple measures of arthritis, enthesitis, PsO, and quality of life. Improvements began as early as 2 weeks and were continued or maintained through the end of the study; dose-related improvements were observed at later time points in patients exposed to izokibep 80 mg. Clinical responses in patients with enthesitis appeared to be promising in the study, and further exploration of izokibep's impact on enthesitis resolution is warranted. The safety profile of izokibep was generally consistent with other IL-17A inhibitors, and event rates were mostly similar to placebo with the exception of injection site reactions. Our study supports further investigation of the clinical potential of izokibep for achieving even greater disease control and quality of life goals in patients with active PsA.

Competing interests

PCT reports grants/research support from Galapagos and payments made to the University of Oxford; consulting fees from AbbVie, ACELYRIN, Biogen, Fresenius, Galapagos (Alfa-Sigma), Gilead Sciences, GSK, Janssen, Eli Lilly, Nordic Pharma, Pfizer, and UCB; support for attending meetings and/or travel from Eli Lilly; and safety monitoring board participation for

Immunovant, Moonlake, and Sanofi. PJM reports grants/research support from AbbVie, ACELYRIN, Inc, Amgen, Bristol Myers Squibb, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; consulting fees from AbbVie, ACELYRIN, Inc, Aclaris, Alumis, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Immagene, Janssen, Moonlake, Novartis, Pfizer, Takeda, UCB, and Ventyx; honoraria from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, and UCB; board participation for Genascence; and a leadership or fiduciary role in GRAPPA, OMERACT, and SPARTAN. SM is employed by ACELYRIN, Inc, and holds stock/stock options from ACELYRIN, Inc. DW reports consulting fees from ACELYRIN, Inc, and Affibody AB. AMS was employed by ACELYRIN, Inc, and held stock/stock options from ACELYRIN, Inc, at the time of the study. BW was employed by ACELYRIN, Inc, and held stock/stock options from ACELYRIN, Inc, and Horizon at the time of the study. LOK is employed by Affibody AB and holds stock/stock options from Affibody AB. SO is employed by Affibody AB and holds stock/stock options from Affibody AB. JF is employed by Affibody AB, is an inventor on patents protecting izokibep, and holds stock/stock options from Affibody AB and ACELYRIN, Inc. FYF is employed by Affibody AB, is an inventor on patents protecting izokibep, and holds stock/stock options from Affibody AB. NCB was employed by Affibody AB and held stock/stock options from Affibody AB at the time of the study. EDo reports grants/research support from AbbVie, Biopharma SPRL, Eli Lilly, Galapagos, Gilead Sciences, GSK, Hexal AG, Janssen, Novartis, Pfizer, and Sanofi. FB reports grants/research support from Bionorica, Bristol Myers Squibb, Chugai, Iron4u, Janssen-Cilag, LEO Pharma, Novartis, Pfizer, and Roche and meeting support, honoraria, or fees for serving as a speaker, consultant, and/or advisory board member from AbbVie, Affibody, Amgen, Bristol Myers Squibb, Boehringer Ingelheim, Eli Lilly, Galapagos, GSK, Janssen-Cilag, MoonLake, Merck Sharp & Dohme, Novartis, Pfizer, Sandoz, Sanofi, and UCB. KdV, JB-J, EDr, AR-O, and NA-KM report no conflicts of interest to disclose.

CRediT authorship contribution statement

Peter C. Taylor: Writing – review & editing, Investigation, Data curation, Conceptualization. **Philip J. Mease:** Writing – review & editing, Investigation, Data curation, Conceptualization. **Kurt de Vlam:** Writing – review & editing, Investigation, Data curation. **Shephard Mpofu:** Writing – review & editing, Supervision. **Dieter Wetzel:** Writing – review & editing, Writing – original draft, Visualization, Methodology, Investigation, Data curation, Conceptualization, Supervision. **Anne M. Stevens:** Writing – review & editing, Conceptualization. **Brian Wiens:** Writing – review & editing, Methodology, Formal analysis, Conceptualization. **Lisa Osterling Koskinen:** Writing – review & editing, Formal analysis, Visualization, Writing – original draft. **Sven Ohlman:** Writing – review & editing, Writing – original draft. **Joachim Feldwisch:** Writing – review & editing, Resources, Conceptualization. **Fredrik Y. Frejd:** Writing – review & editing, Resources, Conceptualization, Funding acquisition, Project administration, Supervision. **Nikolai C. Brun:** Writing – review & editing, Supervision, Writing – original draft. **Jan Brandt-Juergens:** Writing – review & editing, Investigation, Data curation. **Edit Drescher:** Writing – review & editing, Investigation, Data curation. **Eva Dokoupilova:** Writing – review & editing, Investigation, Data curation. **Anna Rowińska-Osuch:** Writing – review & editing, Investigation, Data curation. **Nadia Abdel-Kader Martin:** Writing – review & editing, Investigation, Data curation. **Frank Behrens:** Writing – review & editing, Methodology, Investigation, Data curation, Conceptualization.

Acknowledgements

We thank the patients, investigators, and health care teams who participated in this study. Medical writing and editorial assistance based on the authors' input and direction was provided by Sharon L. Cross, PhD (Mission Viejo, CA, USA), and by Sylvia Stankov, PhD, of Red Nucleus (funded by ACELYRIN, INC.). Third-party writing assistance was provided under the direction of authors in accordance with Good Publication Practice guidelines. Preliminary data from this study were previously presented at the 2022 EULAR conference (Behrens F, Taylor PC, Wetzel D, et al. Ann Rheum Dis. 2022;81:170-1 [abstract OP0258]); the 2022 ACR conference (Behrens F, Taylor PC, Mease PJ, et al. Arthritis Rheumatol. 2022;74:abstract 1597; de Vlam K, Taylor PC, Mease PJ, et al. Arthritis Rheumatol. 2022;74:abstract 2151; and Taylor PC, Behrens F, Mease PJ, et al. Arthritis Rheumatol. 2022;74:abstract 0199); and the 2023 ACR conference (Mease PJ, Taylor PC, de Vlam K, et al. Arthritis Rheumatol. 2023;75:abstract 1688 and Taylor PC, de Vlam K, Mease PJ, et al. Arthritis Rheumatol. 2023;75:abstract 1431).

Contributors

All authors met the International Committee of Medical Journal Editors criteria for authorship, critically reviewed manuscript drafts, and approved the final version of the article to be published. All authors had access to the data in the study and had final responsibility for the decision to submit for publication.

Funding

This study and medical writing assistance was supported by ACELYRIN, Inc, USA, and Affibody AB, Sweden.

Patient consent for publication

Not applicable.

Ethics approval

This study involved human participants and was approved by national ethics committees in each participating country and study site-specific independent ethics committees at participating sites, including the Principal Investigator's site (Ethik-Kommission des Fachbereichs Medizin, Universitätsklinikum der Goethe-Universität, approval number 19-479F). Upon study termination, the study investigators provided patients with access to several effective and safe marketed treatments for active PsA based on country of residence. Participants gave informed consent to participate in the study before taking part.

Provenance and peer review

Not commissioned; externally peer reviewed.

Data availability statement

Data from this manuscript can be requested from ACELYRIN, Inc, by qualified researchers 6 months after product approval in the United States or Europe, or global development is

discontinued, and 18 months after study completion. Investigators can request access to anonymised individual patient data and redacted study documents. Before use of the data, proposals need to be approved by an independent review panel, and a signed data sharing agreement will need to be executed.

Patient and public involvement

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

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ard.2025.02.019.

Orcid

Peter C. Taylor: http://orcid.org/0000-0001-7766-6167
Philip J. Mease: http://orcid.org/0000-0002-6620-0457
Kurt de Vlam: http://orcid.org/0000-0003-3848-5122
Anne M. Stevens: http://orcid.org/0009-0000-5742-6844
Sven Ohlman: http://orcid.org/0000-0001-8258-1643
Joachim Feldwisch: http://orcid.org/0009-0000-2043-2482
Fredrik Y. Frejd: http://orcid.org/0000-0002-6421-4142
Eva Dokoupilova: http://orcid.org/0009-0003-9363-145X
Frank Behrens: http://orcid.org/0000-0001-8750-7186

REFERENCES

[1] Hackett S, Coates LC. Outcome measures in psoriatic arthritis: where next? Musculoskeletal Care 2022;20(Suppl 1):S22–31.
[2] Christophers E, Barker JN, Griffiths CE, Daudén E, Milligan G, Molta C, et al. The risk of psoriatic arthritis remains constant following initial diagnosis of psoriasis among patients seen in European dermatology clinics. J Eur Acad Dermatol Venereol 2010;24:548–54.
[3] Chaudhary H, Bohra N, Syed K, Donato A, Murad MH, Karmacharya P. All-cause and cause-specific mortality in psoriatic arthritis and ankylosing spondylitis: a systematic review and meta-analysis. Arthritis Care Res (Hoboken) 2023;75:1052–65.
[4] Gupta S, Syrimi Z, Hughes DM, Zhao SS. Comorbidities in psoriatic arthritis: a systematic review and meta-analysis. Rheumatol Int 2021;41:275–84.
[5] Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet 2018;391:2273–84.
[6] Blauvelt A, Chiricozzi A. The immunologic role of IL-17 in psoriasis and psoriatic arthritis pathogenesis. Clin Rev Allergy Immunol 2018;55:379–90.
[7] Beringer A, Miossec P. Systemic effects of IL-17 in inflammatory arthritis. Nat Rev Rheumatol 2019;15:491–501.
[8] Lee S, Mendelsohn A, Sarnes E. The burden of psoriatic arthritis: a literature review from a global health systems perspective. P T 2010;35:680–9.
[9] Deodhar A, Helliwell PS, Boehncke WH, Kollmeier AP, Hsia EC, Subramanian RA, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet 2020;395:1115–25.
[10] McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet 2013;382:780–9.
[11] Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Ann Rheum Dis 2017;76:79–87.
[12] Mease P, van der Heijde D, Landewé R, Mpofu S, Rahman P, Tahir H, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Ann Rheum Dis 2018;77:890–7.
[13] McInnes IB, Asahina A, Coates LC, Landewé R, Merola JF, Ritchlin CT, et al. Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL). Lancet 2023;401:25–37.
[14] Zardin-Moraes M, da Silva A, Saldanha C, Kohem CL, Coates LC, Henrique LR, et al. Prevalence of psoriatic arthritis patients achieving minimal disease activity in real-world studies and randomized clinical trials: systematic review with metaanalysis. J Rheumatol 2020;47:839–46.
[15] Tahir H, Grewal S. Current unmet needs and emerging novel pharmacotherapies in psoriatic arthritis. Expert Opin Pharmacother 2022;23:417–20.
[16] Alten R, Conaghan PG, Strand V, Sullivan E, Blackburn S, Tian H, et al. Unmet needs in psoriatic arthritis patients receiving immunomodulatory therapy: results from a large multinational real-world study. Clin Rheumatol 2019;38:1615–26.
[17] Bhushan V, Lester S, Briggs L, Hijjawi R, Shanahan EM, Pontifex E, et al. Real-life retention rates and reasons for switching of biological DMARDs in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Front Med (Lausanne) 2021;8:708168.
[18] Spini A, Pellegrini G, Ingrasciotta Y, L'Abbate L, Bellitto C, Carollo M, et al. Switching patterns of biological drugs in patients with psoriasis and psoriatic arthritis: insight from the VALORE database network. Expert Opin Biol Ther 2024;24:399–409.
[19] Behrens F, Sewerin P, de Miguel E, Patel Y, Batalov A, Dokoupilova E, et al. Efficacy and safety of secukinumab in patients with spondyloarthritis and enthesitis at the Achilles tendon: results from a phase 3b trial. Rheumatology (Oxford) 2022;61:2856–66.
[20] Laheru D, Antony A, Carneiro S, Di Lernia V, Garg A, Love TJ, et al. Management of nail disease in patients with psoriatic arthritis: an updated literature review informing the 2021 GRAPPA treatment recommendations. J Rheumatol 2023;50:433–7.
[21] Klint S, Feldwisch J, Gudmundsdotter L, Dillner Bergstedt K, Gunneriusson E, Höidén Guthenberg I, et al. Izokibep: preclinical development and first-in-human study of a novel IL-17A neutralizing affibody molecule in patients with plaque psoriasis. MAbs 2023;15:2209920.
[22] Gerdes S, Staubach P, Dirschka T, Wetzel D, Weirich O, Niesmann J, et al. Izokibep for the treatment of moderate-to-severe plaque psoriasis: a phase II, randomized, placebo-controlled, double-blind, dose-finding multicentre study including long-term treatment. Br J Dermatol 2023;189:381–91.
[23] Taylor W, Gladman D, Helliwell P, Marchesoni A, Mease P, Mielants H, et al. Classification criteria for psoriatic arthritis: development of new criteria from a large international study. Arthritis Rheum 2006;54:2665–73.
[24] Mease PJ. Measures of psoriatic arthritis: Tender and Swollen Joint Assessment, Psoriasis Area and Severity Index (PASI), Nail Psoriasis Severity Index (NAPSI), Modified Nail Psoriasis Severity Index (mNAPSI), Mander/Newcastle Enthesitis Index (MEI), Leeds Enthesitis Index (LEI), Spondyloarthritis Research Consortium of Canada (SPARCC), Maastricht Ankylosing Spondylitis Enthesis Score (MASES), Leeds Dactylitis Index (LDI), Patient Global for Psoriatic Arthritis, Dermatology Life Quality Index (DLQI), Psoriatic Arthritis Quality of Life (PsAQOL), Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F), Psoriatic Arthritis Response Criteria (PsARC), Psoriatic Arthritis Joint Activity Index (PsAJAI), Disease Activity in Psoriatic Arthritis (DAPSA), and Composite Psoriatic Disease Activity Index (CPDAI). Arthritis Care Res (Hoboken). 2011;63(Suppl 11):S64–85.
[25] Orbai AM, Ogdie A. Patient-reported outcomes in psoriatic arthritis. Rheum Dis Clin North Am 2016;42:265–83.
[26] Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet 2017;389:2317–27.
[27] van der Heijde D, Gladman DD, Kishimoto M, Okada M, Rathmann SS, Moriarty SR, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: 52-week results from a phase III study (SPIRIT-P1). J Rheumatol 2018;45:367–77.
[28] Coates LC, Soriano ER, Corp N, Bertheussen H, Callis Duffin K, Campanholo CB, et al. Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA): updated treatment recommendations for psoriatic arthritis 2021. Nat Rev Rheumatol 2022;18:465–79.
[29] Gossec L, McGonagle D, Korotaeva T, Lubrano E, de Miguel E, Østergaard M, et al. Minimal disease activity as a treatment target in psoriatic arthritis: a review of the literature. J Rheumatol 2018;45:6–13.
[30] McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet 2015;386:1137–46.
[31] Merola JF, Landewé R, McInnes IB, Mease PJ, Ritchlin CT, Tanaka Y, et al. Bimekizumab in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor-alpha inhibitors: a randomised, double-blind, placebo-controlled, phase 3 trial (BE COMPLETE). Lancet 2023;401:38–48.

[32] Mease PJ, Helliwell PS, Hjuler KF, Raymond K, McInnes I. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis 2021;80:185–93.
[33] Orbai AM, Birt JA, Holdsworth EA, Booth N, Malatestinic WN, Sprabery AT, et al. Impact of enthesitis on psoriatic arthritis patient-reported outcomes and physician satisfaction with treatment: data from a multinational patient and physician survey. Rheumatol Ther 2020;7:937–48.
[34] McInnes IB, Sawyer LM, Markus K, LeReun C, Sabry-Grant C, Helliwell PS. Targeted systemic therapies for psoriatic arthritis: a systematic review and comparative synthesis of short-term articular, dermatological, enthesitis and dactylitis outcomes. RMD Open 2022;8:e002074.
[35] Helliwell PS, Mease PJ, Kavanaugh A, Coates LC, Ogdie A, Deodhar A, et al. Impact of clinical domains other than arthritis on composite outcomes in psoriatic arthritis: comparison of treatment effects in the SEAM-PsA trial. RMD Open 2022;8:e002366.
[36] Wunder A, Muller-Ladner U, Stelzer EH, Funk J, Neumann E, Stehle G, et al. Albumin-based drug delivery as novel therapeutic approach for rheumatoid arthritis. J Immunol 2003;170:4793–801.
[37] Rahimizadeh P, Yang S, Lim SI. Albumin: an emerging opportunity in drug delivery. Biotechnol Bioprocess Eng 2020;25:985–95.
[38] Deodhar AA, Combe B, Accioly AP, Bolce R, Zhu D, Gellett AM, et al. Safety of ixekizumab in patients with psoriatic arthritis: data from four clinical trials with over 2000 patient-years of exposure. Ann Rheum Dis 2022;81:944–50.
[39] Gao Q, Zhao YX, Wang XJ, Shi J, Wang HM. Efficacy and safety of IL-17 inhibitors for patients with psoriatic arthritis: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci 2021;25:2958–70.
[40] Gottlieb AB, Deodhar A, McInnes IB, Baraliakos X, Reich K, Schreiber S, et al. Long-term safety of secukinumab over five years in patients with moderate-to-severe plaque psoriasis, psoriatic arthritis and ankylosing spondylitis: update on integrated pooled clinical trial and post-marketing surveillance data. Acta Derm Venereol 2022;102:adv00698.
[41] Davidson L, van den Reek J, Bruno M, van Hunsel F, Herings RMC, Matzaraki V, et al. Risk of candidiasis associated with interleukin-17 inhibitors: a real-world observational study of multiple independent sources. Lancet Reg Health Eur 2022;13:100266.
[42] Penso L, Bergqvist C, Meyer A, Herlemont P, Weill A, Zureik M, et al. Risk of inflammatory bowel disease in patients with psoriasis and psoriatic arthritis/ankylosing spondylitis initiating interleukin-17 inhibitors: a nationwide population-based study using the French National Health Data System. Arthritis Rheumatol 2022;74:244–52.