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HAL Authorization

Bimekizumab in patients with psoriatic arthritis, naive to biologic treatment: a randomised, double-blind, placebo-controlled, phase 3 trial (BE OPTIMAL)

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Summary

Background Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17A and IL-17F. We assessed the efficacy and safety of bimekizumab in patients with active psoriatic arthritis who were naive to biologic disease-modifying antirheumatic drugs (DMARDs).

Methods BE OPTIMAL was a 52-week, phase 3, multicentre, randomised, double-blind, placebo-controlled, active reference (adalimumab) trial done at 135 sites (hospitals, clinics, doctors' offices, and research centres) in 14 countries. Eligible patients were 18 years or older with a documented diagnosis of adult-onset psoriatic arthritis that met the Classification Criteria for Psoriatic Arthritis for at least 6 months before screening. Participants were randomly assigned with an interactive-voice and web-response system on the basis of a predetermined randomisation schedule (3:2:1, stratified by region and bone erosion number at baseline) to bimekizumab 160 mg every 4 weeks, placebo every 2 weeks, or the reference group (adalimumab 40 mg every 2 weeks), all administered subcutaneously. At week 16, patients randomly assigned to placebo switched to bimekizumab 160 mg every 4 weeks. The primary endpoint was the proportion of patients reaching 50% or greater improvement in American College of Rheumatology criteria (ACR50) at week 16 (non-responder imputation). Efficacy analyses included all patients who were randomly assigned (intention-to-treat population); the safety analysis set comprised patients who received one or more doses of treatment. Data are presented to week 24 (preplanned analysis). This trial is registered at ClinicalTrials.gov, NCT03895203.

Findings Between April 3, 2019, and Oct 25, 2021, 1163 patients were screened and 852 were randomly assigned to bimekizumab (n=431), placebo (n=281), and reference (adalimumab; n=140) groups. At week 16, significantly more patients receiving bimekizumab (189 [44%] of 431) reached ACR50 response versus placebo (28 [10%] of 281; odds ratio 7·1 [95% CI 4·6–10·9], p<0·0001; adalimumab 64 [46%] of 140). All secondary hierarchical endpoints were met. Treatment-emergent adverse events up to week 16 were reported in 258 [60%] of 431 patients receiving bimekizumab, 139 [49%] of 281 patients receiving placebo, and 83 [59%] of 140 patients receiving adalimumab. No deaths occurred.

Interpretation Bimekizumab treatment had superior improvements in joint, skin, and radiographic efficacy outcomes at week 16 compared with placebo in patients with psoriatic arthritis who were naive to biologic DMARDs. The safety profile of bimekizumab, including the occurrence of fungal infections, was consistent with previous phase 3 studies in patients with plaque psoriasis, and with IL-17A inhibitors.

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Introduction

Psoriatic arthritis is a complex, immune-mediated inflammatory disease that manifests across peripheral and axial joints, entheses, skin, and nails.^{1,2} Most patients with psoriatic arthritis initiate conventional synthetic disease-modifying antirheumatic drugs (DMARDs) for musculoskeletal symptoms. International guidelines propose that patients with an inadequate response to conventional synthetic DMARDs can switch to, or add, biologic DMARDs with the overall aim of reducing disease activity as much as possible, across all disease domains.^{3,4}

The interleukin (IL)-17 family of cytokines has been implicated in the pathogenesis of psoriatic arthritis and

consists of several dimeric isoforms with overlapping and distinct functions.^{1,2} In particular, IL-17A and IL-17F, which share 50% homology and have overlapping proinflammatory activity,⁵ can form homodimers and heterodimers.⁶ Increased expression of IL-17A and IL-17F has been identified in synovial tissue, entheses, and skin of patients with psoriatic arthritis.²

IL-17A inhibition with secukinumab and ixekizumab is effective and well tolerated in patients with psoriatic arthritis.^{7,8} Bimekizumab is a humanised monoclonal IgG1 antibody that selectively inhibits IL-17A and IL-17F by binding to similar sites on the IL-17A and IL-17F molecules, inhibiting both homodimers and

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College of Medical Veterinary and Life Sciences, University of Glasgow, Glasgow, UK (Prof I B McInnes MD); Department of Dermatology, Jikei University School of Medicine, Tokyo, Japan (Prof A Asahina MD); Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Diseases, University of Oxford, Oxford, UK (L C Coates PhD); Oxford Biomedical Research Centre, Oxford University Hospitals NHS Trust, Oxford, UK (L C Coates); Amsterdam Rheumatology and Clinical Immunology Center, Amsterdam, Netherlands (Prof R Landewé MD); Zuyderland MC, Heerlen, Netherlands (Prof R Landewé); Harvard Medical School, Brigham and Women's Hospital, Boston, MA, USA (J F Merola MD); Department of Medicine, University of Rochester, Rochester, NY, USA (CT Ritchlin MD); The First Department of Internal Medicine, University of Occupational and Environmental Health, Japan, Kitakyushu, Japan (Prof Y Tanaka MD); Sorbonne Université, INSERM, Institut Pierre Louis d'Epidémiologie et de Santé Publique, Paris, France (Prof L Gossec MD); Rheumatology Department, AP-HP, Pitié-Salpêtrière Hospital, Paris, France (Prof L Gossec); Department of Dermatology, The Icahn School of Medicine at Mt Sinai, New York, NY, USA (Prof A B Gottlieb MD); Dermatology Centre, Salford Royal NHS Foundation Trust, Manchester NIHR Biomedical Research Centre, University of

Manchester, Manchester, UK
(Prof R B Warren MD); UCB
Pharma, Slough, UK (B Ink PhD,
D Assudani PhD,
R Bajracharya FPPM,
V Shende PhD); UCB Pharma,
Morrisville, NC, USA
(J Coarse MS); Swedish Medical
Center and Providence St
Joseph Health and University of
Washington, Seattle, WA, USA
(Prof P J Mease MD)
Correspondence to:
Prof Iain B McInnes, College of
Medical Veterinary and Life
Sciences, University of Glasgow,
Glasgow G12 8QQ, UK
iain.mcinnnes@glasgow.ac.uk

Research in context

Evidence before this study

We searched PubMed with the terms “arthritis, psoriatic” or “psoriatic arthritis” and screened titles to identify industry-sponsored clinical trials and systematic literature reviews of biologic agents in patients with psoriatic arthritis. Manuscripts published between June 28, 2015, and Dec 30, 2021, were extracted. Several therapeutic options have been approved for use in patients with psoriatic arthritis and demonstrate improved clinical responses compared with placebo. Nevertheless, some patients with psoriatic arthritis might not respond to treatment or might have persistent symptoms, such as joint pain, skin disease, fatigue, and suboptimal quality of life. Additional treatment options with long-term, sustained efficacy and a tolerable safety profile are required. The phase 2b BE ACTIVE study of bimekizumab showed the therapeutic benefit of inhibition of interleukin (IL)-17F in addition to IL-17A when administered to patients with psoriatic arthritis. Clinical efficacy was sustained for up to 3 years during the open-label extension study and bimekizumab was well tolerated.

Added value of this study

BE OPTIMAL is the first placebo-controlled phase 3 study to assess the efficacy and safety of subcutaneous bimekizumab (160 mg every 4 weeks) in patients with active psoriatic arthritis who are naive to biologic disease-modifying antirheumatic drugs. The study included an active reference (adalimumab 40 mg every 2 weeks); the study was not powered for statistical comparisons between adalimumab and bimekizumab.

heterodimers.^{5,9} In patients with moderate-to-severe plaque psoriasis, bimekizumab showed statistically significant superior skin response (as assessed by complete skin clearance) versus secukinumab in the phase 3b BE RADIANT study, with its clinical efficacy and tolerability in patients with psoriasis also shown in the phase 3 BE SURE and BE VIVID studies.^{10–12} The phase 2b BE ACTIVE study in patients with moderate-to-severe psoriatic arthritis also showed the clinical efficacy and tolerability of bimekizumab, with the open-label extension showing that improvements were sustained up to 3 years.^{13,14}

The efficacy and safety of bimekizumab were assessed in two phase 3 clinical trials run in parallel in overlapping countries and sites. These trials included patients with active psoriatic arthritis who were either naive to biologic DMARDs (BE OPTIMAL) or who had a previous inadequate response or intolerance to tumour necrosis factor- α (TNF α) inhibitors (BE COMPLETE).¹⁵ In this Article, we report the 24-week, preplanned primary analysis results from BE OPTIMAL. The study comprised a 16-week double-blind, placebo-controlled period, and a 36-week treatment-blind period. We included an active reference (adalimumab) group to provide a reference for the benefit–risk profile of

At week 16, patients receiving bimekizumab were significantly more likely to meet the primary endpoint of 50% improvement in the American College of Rheumatology response criteria (ACR50) than those receiving placebo. In addition, patients receiving bimekizumab showed significantly higher response rates than did patients who received placebo for all ranked secondary endpoints across joint, skin, and radiographic outcomes at week 16. Patients who switched from placebo to bimekizumab at week 16 showed improved outcomes at week 24, and responses of those remaining on bimekizumab were improved or sustained from week 16. The safety profile of bimekizumab in patients with psoriatic arthritis in BE OPTIMAL was consistent with that observed in the phase 2b BE ACTIVE study and studies of bimekizumab for other indications; no new safety signals were observed.

Implications of all the available evidence

The results presented here support previous findings showing the clinical effectiveness and tolerability of dual inhibition of IL-17A and IL-17F with bimekizumab in patients with active psoriatic arthritis. Bimekizumab showed greater improvements across multiple key domains of psoriatic arthritis, including joints and skin, to week 16 compared with placebo, and responses were improved or sustained to week 24. Bimekizumab also demonstrated tolerability and a safety profile consistent with previous reports. These results, alongside other published reports, provide evidence for the clinical efficacy of bimekizumab as a treatment for psoriatic arthritis.

bimekizumab alongside a commonly used standard-of-care treatment. The study was not powered for statistical comparisons between bimekizumab or placebo and the reference. Results from the BE COMPLETE study are reported separately.¹⁵

Methods

Study design

BE OPTIMAL was a 52-week, phase 3, multicentre, randomised, double-blind, placebo-controlled, active reference (adalimumab) study. The study was done at 135 sites, including hospitals, clinics, doctors' offices, and research centres, in 14 countries (Australia, Belgium, Canada, Czech Republic, France, Germany, Hungary, Italy, Japan, Poland, Russia, Spain, the UK, and the USA).

The study included a 2–5-week screening period, followed by a 16-week placebo-controlled, double-blind treatment period and a 36-week active treatment-blind period. Patients completing week 52 and meeting eligibility criteria could be enrolled in an open-label extension study, receiving subcutaneous bimekizumab 160 mg every 4 weeks regardless of previous treatment. We conducted a safety follow-up 20 weeks after the last dose of bimekizumab for patients who did not enter the open-label extension, or who discontinued early

(appendix p 10). Here, data are reported to week 24 since first dose (which includes 16-week placebo-controlled period plus 8 weeks of the active treatment-blind period and excludes screening period).

The study was done in accordance with the Declaration of Helsinki and the International Conference on Harmonisation Guidance for Good Clinical Practice. Ethics approval was obtained from the relevant institutional review boards at participating sites.

Patients

Eligible patients were 18 years or older and had a documented diagnosis of adult-onset psoriatic arthritis that met the Classification Criteria for Psoriatic Arthritis¹⁶ for at least 6 months before screening. Patients had active psoriatic arthritis with a tender joint count (TJC) of three or more (of 68), swollen joint count (SJC) of three or more (of 66), and one or more active psoriatic lesions or a documented history of psoriasis (or both).

Concomitant non-steroidal anti-inflammatory drugs, analgesics, oral corticosteroids, or conventional synthetic DMARDs at stable doses were allowed, subject to restrictions outlined in the inclusion and exclusion criteria (appendix pp 3–8). Patients with current or previous exposure to any biologics for the treatment of psoriatic arthritis or psoriasis were excluded. All patients provided written informed consent in accordance with local requirements.

Randomisation and masking

Patients were randomly assigned 3:2:1 (stratified by region [North America, western Europe, eastern Europe, or Asia; appendix p 245] and bone erosion number at baseline [0 or ≥ 1]) to receive subcutaneous bimekizumab 160 mg every 4 weeks, subcutaneous placebo every 2 weeks, or reference (subcutaneous adalimumab 40 mg) every 2 weeks. At week 16, patients initially assigned to receive placebo were reallocated to subcutaneous bimekizumab 160 mg every 4 weeks through to week 52; patients initially assigned to bimekizumab or adalimumab continued their dosing to week 52. Patients were enrolled by investigators or a designee.

An interactive-voice or web-response system assigned eligible patients to a treatment regimen on the basis of a predetermined randomisation schedule produced by an independent biostatistician. To maintain treatment blinding, patients receiving bimekizumab were administered placebo to match the adalimumab dosing schedule. Throughout the study, patients, investigators, and sponsors remained masked to treatment assignment, except for specially designated, unmasked site staff responsible for the preparation and administration of study treatments. For the preplanned week 24 analysis, a masking plan with separate masked and unmasked teams was implemented to maintain the integrity of the active treatment-blind period, which was ongoing at the time of this analysis.

Procedures

Study visits occurred every 2 weeks. Bimekizumab, placebo, and adalimumab injections were administered at baseline; to maintain masking, bimekizumab was then administered every 4 weeks with placebo administered at the intervening visits. Placebo and adalimumab were administered every 2 weeks.

Bimekizumab was administered via a 1 mL prefilled syringe containing 160 mg/mL. Placebo was provided as 0.9% sodium chloride aqueous solution in a 1 mL prefilled syringe. Adalimumab was supplied as a prefilled syringe containing 40 mg per 0.8 mL or 40 mg per 0.4 mL, depending on regional availability. Study treatments were administered by subcutaneous injections on the lateral abdominal wall and upper outer thigh on a rotational basis.

Efficacy was assessed at baseline and weeks 2, 4, 8, 12, 16, 20, and 24 after baseline. Safety was assessed at baseline and each study visit. Structural damage progression in the hands, wrists, and feet was assessed on plain radiographs using the van der Heijde modified Total Sharp Score (vdHmTSS),¹⁷ quantifying the extent of bone erosions and joint space narrowing. Hand and feet radiographs were taken at baseline and week 16. These were read centrally and independently by two experienced readers, masked to treatment assignment and time course of the films; their scores were averaged, and, in the event of substantial disagreement, a third reviewer adjudicated.

From week 16 onwards, patients who did not respond to treatment as per investigator assessment were eligible for rescue therapy with prespecified background medications. Patients who required rescue therapy continued their assigned treatment.

Outcomes

The primary endpoint was the proportion of patients achieving 50% or greater response in the American College of Rheumatology criteria (ACR; ACR50) at week 16 (bimekizumab vs placebo).¹⁸ Ranked secondary endpoints at week 16, in hierarchical order (appendix p 11), were change from baseline in Health Assessment Questionnaire-Disability Index (HAQ-DI) total score, 90% or greater improvement in the Psoriasis Area and Severity Index (PASI90) in patients with baseline psoriasis affecting 3% or more body surface area (BSA), change from baseline in Short Form 36-item Health Survey Physical Component Summary (SF-36 PCS) norm-based score, proportion of patients achieving minimal disease activity (MDA) response (achievement of five or more of: TJC of one or less, SJC of one or less, PASI of ≤ 1 or BSA of $\leq 3\%$, patients' pain visual analogue scale [VAS; 0–100] of ≤ 15 , Patient Global Assessment [PGA] for psoriatic arthritis of ≤ 20 [0–100], HAQ-DI of ≤ 0.5 , and tender enthesal points ≤ 1 measured using the Leeds Enthesitis Index [LEI]), change from baseline in vdHmTSS in patients with one

See Online for appendix

or both of high-sensitivity C-reactive protein (CRP) concentration of 6 mg/L or more or at least one bone erosion, resolution of enthesitis assessed using the LEI, resolution of dactylitis assessed using the Leeds Dactylitis Index (LDI; LEI and LDI results from BE OPTIMAL and BE COMPLETE were pooled), and change from baseline in vdHmTSS in the overall radiographic set.

Additional, preplanned efficacy outcomes at week 16 included: a 20% or greater response in ACR criteria (ACR20), a 70% or greater response in ACR criteria (ACR70), a 75% or greater improvement in PASI for patients with psoriasis BSA of 3% or more (PASI75), a 100% improvement in PASI for patients with psoriasis BSA of 3% or more (PASI100), proportion of patients (with psoriasis BSA $\geq 3\%$) with both ACR50 and PASI100, proportion of patients with very low disease activity (VLDA; meeting all seven MDA criteria), proportion of patients with an Investigator Global Assessment (IGA) score of 0 or 1 and at least a two-grade reduction from baseline in patients with psoriatic skin lesions at baseline, proportion of patients with a minimal clinically important difference (MCID) in HAQ-DI (≥ 0.35) in patients with HAQ-DI of 0.35 or more at baseline, change from baseline in Psoriatic Arthritis Impact of Disease-12 (PsAID-12) total score, change from baseline in Patient's Assessment of Arthritis Pain (PtAAP) score, and change from baseline in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-Fatigue) score.

Safety outcomes included incidence of treatment-emergent adverse events (TEAEs), incidence of treatment-emergent serious adverse events (SAEs), and TEAEs leading to study withdrawal. TEAEs were reported for all study groups from weeks 0 to 16 and, for bimekizumab and adalimumab groups, from weeks 0 to 24. For patients initially assigned to placebo who switched to bimekizumab, events on bimekizumab from week 16 to week 24 are reported.

Prespecified safety topics were infections (serious, opportunistic [as defined in the appendix p 9], fungal, and tuberculosis), neutropenia, hypersensitivity, suicidal ideation and behaviour, major adverse cardiovascular events, liver function test changes or enzyme concentration elevations, malignancies, and inflammatory bowel diseases. Suicidal ideation and behaviour, major adverse cardiovascular events, and inflammatory bowel disease events were adjudicated by external adjudication committees. An independent data monitoring committee, consisting of clinicians and a statistician knowledgeable about the disease or treatment, were responsible for periodically evaluating safety data collected during the trial.

Statistical analysis

All sample size calculations were at a significance level of 0.05 in a two-sided test, using nQuery Advisor

(version 7.0). Statistical powering for the comparison of bimekizumab with placebo, the primary endpoint, was based on available data from the phase 2 BE ACTIVE study subgroup data and published data from other interventions.^{14,19–21} These data provided assumed responder rates for ACR50 at week 16 of 43.8% for bimekizumab and 16.0% for placebo. Using these assumptions, we determined that a sample size of 420 patients receiving bimekizumab and 280 patients receiving placebo would provide greater than 99% power to show statistical superiority of bimekizumab relative to placebo for the primary endpoint and ensure adequate powering for all ranked secondary endpoints, including the detection of radiographic changes.

The study was powered to show the statistical superiority of bimekizumab compared with placebo for the primary endpoint of ACR50 at week 16. An active reference (adalimumab) group was included to enable an assessment of the benefit–risk profile of bimekizumab alongside a commonly used standard-of-care treatment and to allow masking to the active treatment. The study was not powered for statistical comparisons of adalimumab to bimekizumab or placebo. Supportive analyses of the primary outcome (ACR50) were conducted, including analysis on the COVID-19-free set using identical methods as for the primary analysis but in patients deemed as not having an important protocol deviation related to COVID-19. Additional details can be found in the appendix (p 244 and pp 286–289).

The week 24 efficacy and safety analysis of this study was preplanned and was done after all patients completed week 24 or discontinued the study before week 24. Unless stated otherwise, demographics, baseline disease characteristics, and primary and ranked secondary efficacy endpoints were analysed for the randomised set (intention-to-treat population) consisting of all participants who were randomly assigned. We present safety analyses for exposure to bimekizumab, placebo, and adalimumab from weeks 0 to 24 for all patients who received one or more doses of study medication (safety set). The study was not powered for statistical comparisons of adalimumab to bimekizumab or placebo. No statistical comparisons were made between adalimumab and bimekizumab or placebo.

The number of patients with enthesitis or dactylitis (or both) at baseline was lower than expected. Therefore, to ensure adequate power, the endpoints relating to resolution of these domains were prespecified to be pooled with data from BE COMPLETE.¹⁵ The pooled resolution data are presented in this Article.

We controlled for multiplicity and type I error in the primary and ranked secondary efficacy endpoints by use of a sequential testing procedure: statistical significance for each endpoint was evaluated only if the previous comparison in the sequence reached statistical significance with a two-sided test using an α -level of 0.05. We imputed missing data for the primary and other binary endpoints using non-responder imputation. We generated odds ratios (ORs), CIs, and p values for these

endpoints using logistic regression adjusted for treatment, region, and bone erosion at baseline (0 or ≥ 1). Continuous outcomes are reported using multiple imputation for missing data. We did hierarchical testing of ranked secondary continuous outcomes using reference-based multiple imputation, in which the multiple imputation model was based on data from the placebo group. We generated least square means, SEs, difference in least square means, CIs, and p values for these endpoints using ANCOVA adjusted for treatment, region, bone erosion at baseline, and the baseline value as covariate.

Bone erosion stratification for statistical analyses was based on actual erosion at baseline (as assessed with centrally read radiographs) and not the randomisation stratum for bone erosion, for which readings were less precise. All analyses were done with SAS (version 9.3 or higher).

This trial is registered with ClinicalTrials.gov, NCT03895203.

Role of the funding source

UCB Pharma contributed to study design, participated in data collection, completed the data analysis, and participated in data interpretation. UCB Pharma also participated in writing, review, and approval of the manuscript. All authors had full access to the data, reviewed and approved the final version, and were responsible for the decision to submit for publication. A medical writing agency, employed by UCB Pharma, assisted with manuscript preparation under the authors' direction.

Results

Between Apr 3, 2019, and Oct 25, 2021, 1163 patients were screened and 852 patients were randomly assigned. 431 patients were randomly assigned to subcutaneous bimekizumab 160 mg every 4 weeks, 281 to placebo every 2 weeks, and 140 to the reference group (adalimumab 40 mg every 2 weeks; figure 1). Discontinuation rates were low and similar between the treatment groups; 821 (96%)

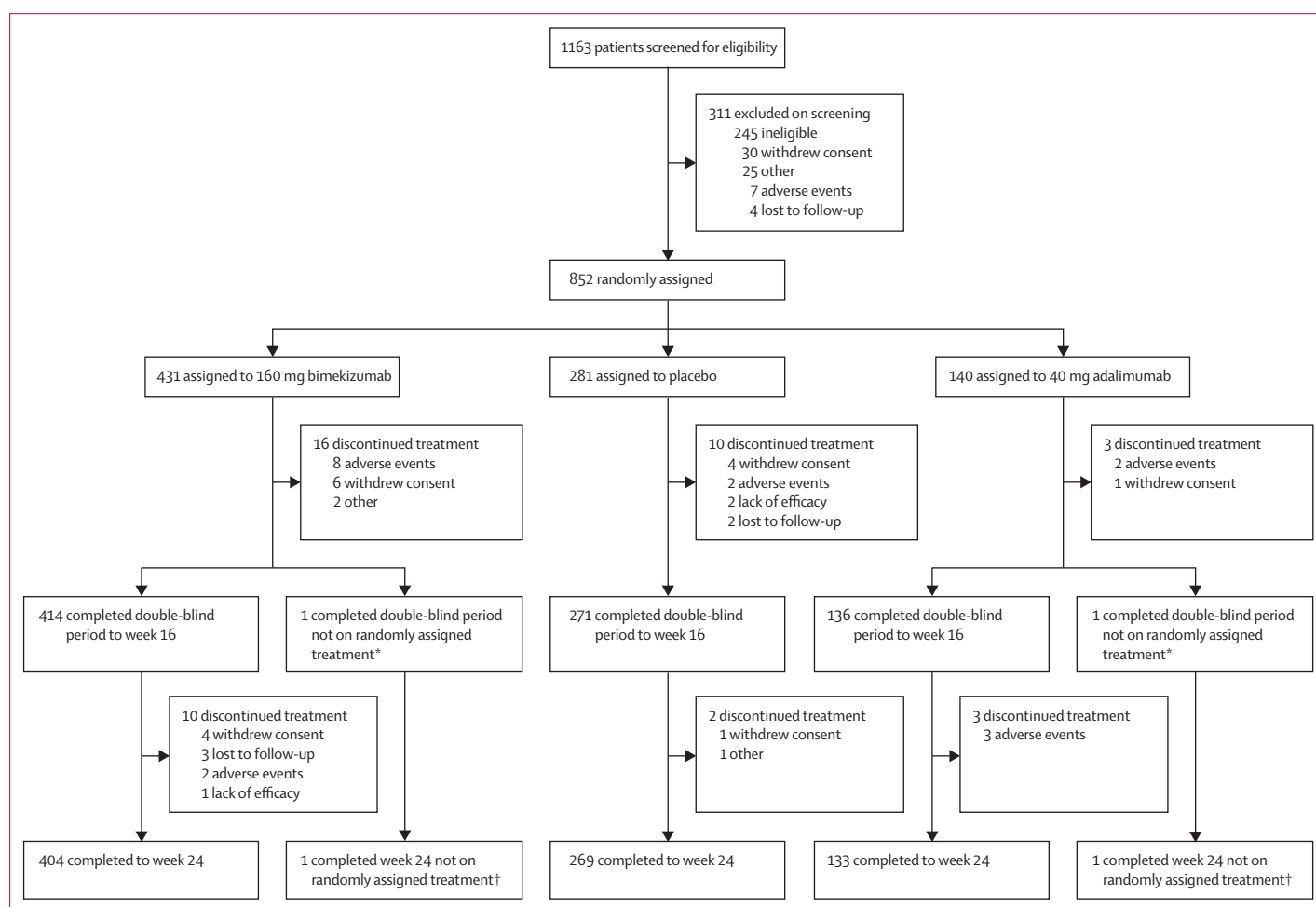


Figure 1: Trial profile

CONSORT diagram for BE OPTIMAL to week 24. *Patients who withdrew from study medication but returned for all scheduled visits up to week 16 were considered as completing week 16 not on the assigned treatment. †Patients who withdrew from study medication but returned for all scheduled visits up to week 24 were considered as completing week 24 not on the assigned treatment.

of 852 patients completed week 16 on the assigned treatment and 806 (95%) completed week 24 (figure 1). Important protocol deviations were reported for 104 (12%) patients to week 16 (appendix p 12). Minimal effect was seen from COVID-19 on study procedures and results and the OR for ACR50 in the COVID-19-free set was consistent with that for the overall population (appendix p 13).

	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*	All patients (n=852)
Age, years	48.7 (11.7)	48.5 (12.6)	49.0 (12.8)	48.7 (12.3)
Gender				
Male	127 (45%)	201 (47%)	71 (51%)	399 (47%)
Female	154 (55%)	230 (53%)	69 (49%)	453 (53%)
BMI, kg/m ²	29.6 (6.1)	29.2 (6.8)	28.4 (5.9)	29.2 (6.4)
Race, White†	270 (96%)	410 (95%)	133 (95%)	813 (95%)
Time since first psoriatic arthritis diagnosis, years‡	5.6 (6.5)	6.0 (7.3)	6.1 (6.8)	5.9 (7.0)
Any conventional synthetic DMARD at baseline	192 (68%)	301 (70%)	99 (71%)	592 (69%)
Methotrexate at baseline	162 (58%)	252 (58%)	82 (59%)	496 (58%)
TJC of 68 joints	17.1 (12.5)	16.8 (11.8)	17.5 (13.1)	17.0 (12.2)
SJC of 66 joints	9.5 (7.3)	9.0 (6.2)	9.6 (7.1)	9.2 (6.7)
High-sensitivity CRP ≥6 mg/L	121 (43%)	158 (37%)	44 (31%)	323 (38%)
Affected BSA ≥3%	140 (50%)	217 (50%)	68 (49%)	425 (50%)
PASI score§	7.9 (5.6)	8.2 (6.8)	8.5 (7.6)	8.1 (6.6)
Bone erosion ≥1 or high-sensitivity CRP ≥6 mg/L or both	236 (84%)	365 (85%)	116 (83%)	717 (84%)
Bone erosion ≥1	210 (75%)	341 (79%)	105 (75%)	656 (77%)
HAQ-DI score¶	0.89 (0.61)	0.82 (0.59)	0.86 (0.54)	0.85 (0.59)
PtAAP score¶	56.8 (23.2)	53.6 (24.3)	56.7 (23.9)	55.2 (23.9)
PhGA score	57.2 (15.1)	57.2 (16.3)	57.3 (17.5)	57.2 (16.1)
PGA score¶	58.6 (23.5)	54.4 (23.4)	57.1 (21.8)	56.2 (23.2)
SF-36 PCS score¶	36.9 (9.7)	38.1 (9.4)	37.6 (8.8)	37.6 (9.4)
Presence of enthesitis***††	70 (25%)	143 (33%)	36 (26%)	249 (29%)
LEI score	2.9 (1.5)	2.5 (1.5)	2.3 (1.6)	2.6 (1.5)
Presence of dactylitis‡‡§§	33 (12%)	56 (13%)	11 (8%)	100 (12%)
Dactylitic sites	1.5 (0.6)	1.4 (0.8)	1.4 (0.7)	1.4 (0.8)
LDI score	47.3 (41.1)	46.7 (54.3)	49.7 (31.9)	47.3 (47.8)

Data are mean (SD) or n (%). BSA=body surface area. CRP=C-reactive protein. DMARD=disease-modifying antirheumatic drug. HAQ-DI=Health Assessment Questionnaire-Disability Index. LDI=Leeds Dactylitis Index. LEI=Leeds Enthesitis Index. PASI=Psoriasis Area and Severity Index. PGA=Patient Global Assessment. PhGA=Physician's Global Assessment. PTAAP=Patient's Assessment of Arthritis Pain. SF-36 PCS=Short-Form 36-item Health Survey Physical Component Summary. SJC=swollen joint count. TJC=tender joint count. *The adalimumab treatment group served as an active reference. †As reported by the patient; these data were missing for the three patients enrolled in France. ‡Data missing for two patients receiving placebo, eight receiving bimekizumab, and one in the reference group. §In patients with psoriasis affecting ≥3% of BSA at baseline (placebo n=140; bimekizumab 160 mg every 4 weeks n=217; reference group [adalimumab 40 mg every 2 weeks] n=68). ¶Data missing for one patient receiving bimekizumab. ||Data missing for one patient receiving placebo, five receiving bimekizumab, and one in the reference group. **Data missing for six patients receiving bimekizumab and one in the reference group. ††The presence of enthesitis was defined by a score greater than 0 on the LEI; the LEI score corresponds to the number of enthesitic sites. ‡‡Data missing for one patient receiving placebo, seven receiving bimekizumab, and one in the reference group. §§The presence of dactylitis was defined by a score greater than 0 on the LDI; dactylitic sites listed as digit eligible count for LDI.

Table 1: Baseline patient demographics and disease characteristics

Baseline patient demographics and disease characteristics were generally comparable between treatment groups, and representative of a patient population with active moderate-to-severe psoriatic arthritis (table 1). At baseline, 496 (58%) of 852 patients were receiving methotrexate, 425 (50%) had evaluable psoriasis BSA of 3% or more, and the mean PASI score for this subgroup was 8.1 (SD 6.6). 717 (84%) patients had one or more bone erosions or a high-sensitivity CRP concentration of 6 mg/L or more (or both). Additional baseline characteristics are presented in the appendix (p 14).

The study met the primary endpoint and all ranked secondary endpoints in the statistical hierarchy. A greater proportion of patients receiving bimekizumab reached the primary endpoint of ACR50 at week 16 than did those receiving placebo (189 [44%] of 431 vs 28 [10%] of 281, $p < 0.0001$; adalimumab 64 [46%] of 140; figure 2A; table 2). All prespecified supportive analyses were consistent with the primary analysis (p 13). All prespecified ranked secondary endpoints achieved statistical significance versus placebo at week 16 (table 2).

Greater proportions of patients receiving bimekizumab reached ACR20 and ACR70 responses at week 16 than did those receiving placebo (ACR20: 268 [62%] of 431 vs 67 [24%] of 281, adalimumab 96 [69%] of 140; ACR70: 105 [24%] of 431 vs 12 [4%] of 281, adalimumab 39 [28%] of 140; figure 2A; table 2). Differences in responder rates for bimekizumab versus placebo were observed as early as week 2 for ACR20, after a single dose of bimekizumab (ACR20: 117 [27%] of 431 vs 22 [8%] of 281), and at week 4 for all ACR criteria (ACR20: 182 [42%] of 431 vs 37 [13%] of 281; ACR50: 76 [18%] of 431 vs nine [3%] of 281; ACR70: 27 [6%] of 431 vs one [$<1\%$] of 281). At week 24, 282 (65%) of 431 patients receiving bimekizumab had ACR20, 196 (45%) of 431 had ACR50, and 126 (29%) of 431 had ACR70. Patients switching from placebo to bimekizumab at week 16 showed improved ACR20, ACR50, and ACR70 responses at week 24 (175 [62%] of 281, 101 [36%] of 281, and 53 [19%] of 281, respectively; figure 2A; table 2). 99 (71%) of 140 patients in the adalimumab group reached ACR20, 66 (47%) of 140 reached ACR50, and 42 (30%) of 140 reached ACR70 at week 24.

Almost half of all bimekizumab-treated patients with baseline psoriasis affecting 3% or more BSA had complete skin clearance (PASI100) at week 16 (103 [47%] of 217 vs three [2%] of 140; adalimumab 14 [21%] of 68; figure 2B; table 2). Improvements in PASI90 were significantly greater with bimekizumab versus placebo at week 16 (133 [61%] of 217 vs four [3%] of 140, $p < 0.0001$; adalimumab 28 [41%] of 68) and numerically greater for PASI75 (168 [77%] of 217 vs 18 [13%] of 140; adalimumab 45 [66%] of 68; figure 2B; table 2). Greater PASI75, PASI90, and PASI100 responses were observed in the bimekizumab group compared with placebo at week 4 (PASI75:

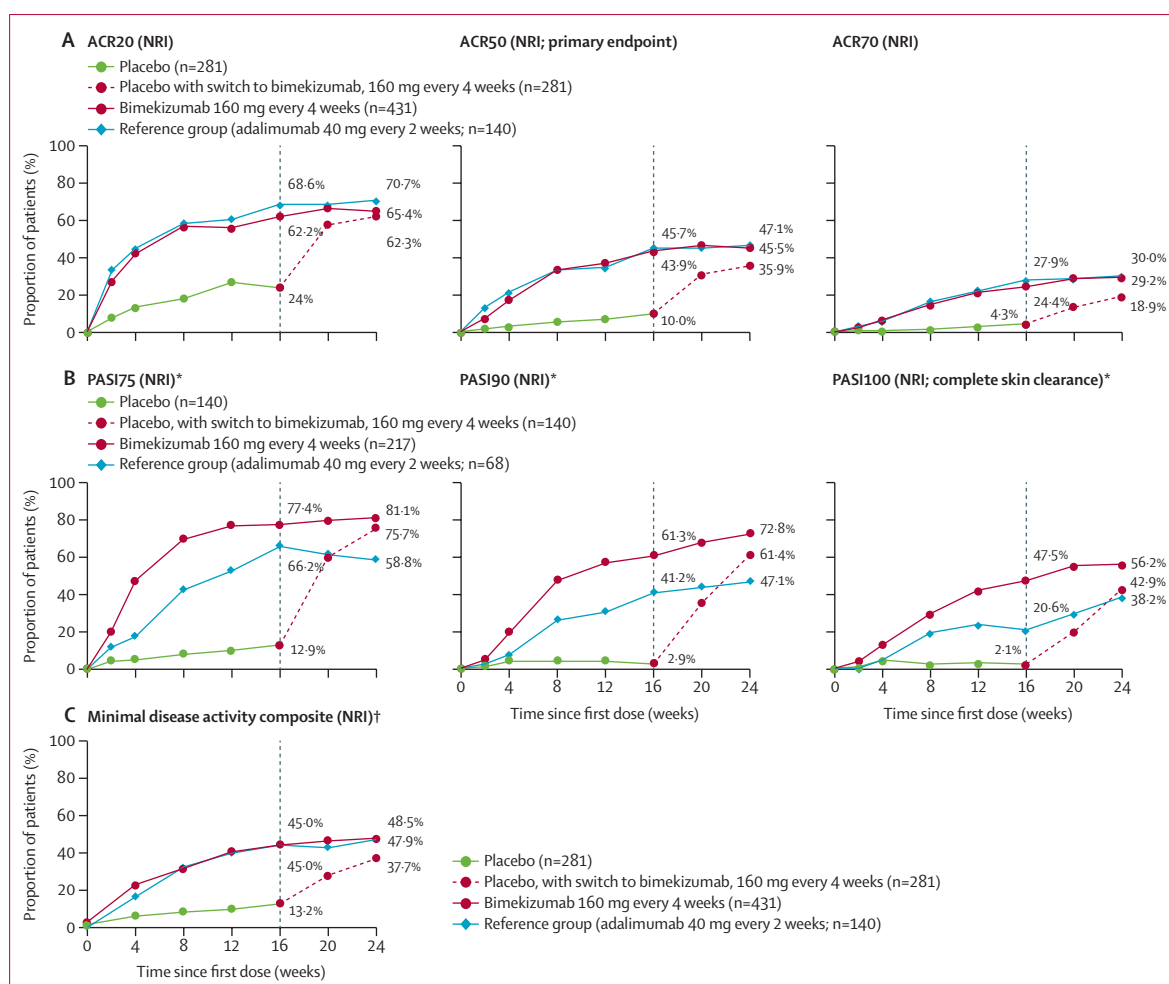


Figure 2: ACR (A), PASI (B), and minimal disease activity (C) data from weeks 0 to 24

ACR=American College of Rheumatology. BSA=body surface area. HAQ-DI=Health Assessment Questionnaire-Disability Index. NRI=non-responder imputation. PASI=Psoriasis Area and Severity Index. *In patients with psoriasis involving 3% or more BSA at baseline. †If a patient achieves five or more of the following criteria: tender joint count of one or less, swollen joint count of one or less, PASI ≤ 1 , or BSA $\leq 3\%$, patients' pain visual analogue scale 15 or less, Patient Global Assessment for psoriatic arthritis 20 or less, HAQ-DI 0.5 or less, and tender enthesal points 1 or less.

103 [47%] of 217 vs seven [5%] of 140; PASI90: 43 [20%] of 217 vs six [4%] of 140; PASI100: 28 [13%] of 217 vs six [4%] of 140). At week 24, 176 (81%) of 217 patients receiving bimekizumab reached PASI75, 158 (73%) of 217 reached PASI90, and 122 (56%) of 217 reached PASI100. Patients switching from placebo to bimekizumab at week 16 showed improvements at week 24 (PASI75: 106 [76%] of 140; PASI90: 86 [61%] of 140; PASI100: 60 [43%] of 140; figure 2B). At week 24, 40 (59%) of 68 patients in the adalimumab group reached PASI75, 32 (47%) of 68 reached PASI90, and 26 (38%) of 68 reached PASI100. Responses to the ACR50 and PASI100 outcome are reported in the appendix (p 15).

At week 16, MDA was reached by a significantly greater proportion of patients receiving bimekizumab than those receiving placebo (194 [45%] of 431 vs 37 [13%] of 281, $p < 0.0001$; adalimumab 63 [45%] of 140; figure 2C; table 2).

VLDA was also reached by a greater proportion of patients in the bimekizumab group than in the placebo group at week 16 (63 [15%] of 431 vs three [1%] of 281; adalimumab 22 [16%] of 140; table 2; appendix p 16). At week 24, 209 (48%) of 431 patients receiving bimekizumab had MDA and 96 (22%) of 431 had VLDA. Patients switching from placebo to bimekizumab at week 16 showed improvements at week 24 (MDA: 106 [38%] of 281; VLDA: 33 [12%] of 281). 67 (48%) of 140 and 28 (20%) of 140 patients in the adalimumab group had MDA and VLDA at week 24.

Patients receiving bimekizumab had significantly less structural progression at week 16 than did those receiving placebo (at-risk population [patients with high-sensitivity CRP ≥ 6 mg/L or one or more baseline bone erosions, or both]; change from baseline in vHmTSS: 0.01 [SE 0.04] vs 0.36 [0.10], $p = 0.0012$; adalimumab -0.06 [0.08]) and in the overall population

	Week 16			Reference group (adalimumab 40 mg every 2 weeks; n=140)*	Week 24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Bimekizumab vs placebo, OR or least squares mean difference (95% CI)		Placebo to bimekizumab 160 mg every 4 weeks (n=281)†	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)*
Primary efficacy endpoint							
ACR50 response	28 (10%)	189 (44%)	OR 7.1 (4.6 to 10.9); p<0.0001	64 (46%)	101 (36%)	196 (45%)	66 (47%)
Ranked secondary endpoints							
HAQ-DI score change from baseline	-0.09 (0.03)	-0.26 (0.02)	Least squares mean difference -0.19 (-0.26 to -0.13); p<0.0001	-0.33 (0.04)	-0.28 (0.03)	-0.30 (0.02)	-0.34 (0.05)
PASI90 response‡	4 (3%) of 140	133 (61%) of 217	OR 63.0 (22.2 to 178.9); p<0.0001	28 (41%) of 68	86 (61%) of 140	158 (73%) of 217	32 (47%) of 68
SF-36 PCS change from baseline	2.3 (0.5)	6.3 (0.4)	Least squares mean difference 4.3 (3.2 to 5.4); p<0.0001	6.8 (0.8)	6.2 (0.5)	7.3 (0.4)	7.3 (0.8)
MDA response	37 (13%)	194 (45%)	OR 5.4 (3.7 to 8.1); p<0.0001	63 (45%)	106 (38%)	209 (48%)	67 (48%)
vdHmTSS change from baseline (subgroup); number of patients, n	0.36 (0.10); 227	0.01 (0.04); 361	Least squares mean difference -0.33 (-0.52 to -0.13); p=0.0012	-0.06 (0.08); 112
Complete resolution of enthesitis (pooled)§	37 (35%) of 106	124 (50%) of 249	OR 1.9 (1.2 to 3.1); p=0.0083	18 (50%) of 36
Complete resolution of dactylitis (pooled)§	24 (51%) of 47	68 (76%) of 90	OR 3.4 (1.6 to 7.6); p=0.0022	9 (82%) of 11
vdHmTSS change from baseline (overall); number of patients, n	0.31 (0.09); 269	0.01 (0.04); 420	Least squares mean difference -0.28 (-0.45 to -0.11); p=0.0012	-0.03 (0.07); 135
Additional efficacy outcomes							
ACR20 response	67 (24%)	268 (62%)	..	96 (69%)	175 (62%)	282 (65%)	99 (71%)
ACR70 response	12 (4%)	105 (24%)	..	39 (28%)	53 (19%)	126 (29%)	42 (30%)
PASI75 response‡	18 (13%) of 140	168 (77%) of 217	..	45 (66%) of 68	106 (76%) of 140	176 (81%) of 217	40 (59%) of 68
PASI100 response‡	3 (2%) of 140	103 (47%) of 217	..	14 (21%) of 68	60 (43%) of 140	122 (56%) of 217	26 (38%) of 68
VLDA	3 (1%)	63 (15%)	..	22 (16%)	33 (12%)	96 (22%)	28 (20%)
IGA 0 or 1 response¶	5 (4%) of 129	103 (50%) of 204	..	21 (34%) of 62	62 (48%) of 129	120 (59%) of 204	27 (44%) of 62
HAQ-DI MCID	71 (32%) of 221	161 (51%) of 318	..	63 (55%) of 115	106 (48%) of 221	170 (53%) of 318	64 (56%) of 115
PsAID-12 change from baseline	-0.5 (0.1)	-1.8 (0.1)	..	-2.1 (0.2)	-1.8 (0.1)	-2.0 (0.1)	-2.2 (0.2)
PtAAP change from baseline	-6.2 (1.5)	-23.6 (1.3)	..	-25.7 (2.5)	-22.7 (1.6)	-27.0 (1.4)	-27.2 (2.7)
FACIT-Fatigue change from baseline	1.5 (0.5)	3.9 (0.4)	..	5.0 (0.7)	4.5 (0.5)	4.5 (0.4)	5.2 (0.8)

Data are n (%) or mean change from baseline (SE) unless indicated. For binary variables, ORs, CIs, and p values were generated using logistic regression with treatment, bone erosion at baseline, and region as factors. For enthesitis and dactylitis resolution, where data were pooled from BE OPTIMAL and BE COMPLETE, the study was also included as a factor in the model, and bone erosion at baseline was excluded. For continuous variables, least squares mean, SE, difference in least squares means, and p values were generated using ANCOVA with treatment, bone erosion at baseline, and region as fixed effects, and the baseline value as covariate. Continuous variables were calculated using multiple imputation. Reference-based multiple imputation was used in hierarchical testing. Proportions were calculated using NRI. ACR=American College of Rheumatology. ANCOVA=analysis of covariance. BSA=body surface area. FACIT-Fatigue=Functional Assessment of Chronic Illness Therapy-Fatigue. HAQ-DI=Health Assessment Questionnaire-Disability Index. IGA=Investigator's Global Assessment. MCID=minimal clinically important difference. MDA=minimal disease activity. NRI=non-responder imputation. OR=odds ratio. PASI=Psoriasis Area and Severity Index. PsAID-12=Psoriatic Arthritis Impact of Disease-12. PtAAP=Patient's Assessment of Arthritis Pain. SF-36 PCS=Short-Form 36-item Health Survey Physical Component Summary. vdHmTSS=van der Heijde-modified Total Sharp Score. VLDA=very low disease activity. *The adalimumab 40 mg every 2 weeks treatment group served as an active reference and the study was not powered for statistical comparisons of adalimumab to bimekizumab or placebo. †Patients switching from placebo to bimekizumab 160 mg every 4 weeks received 8 weeks of bimekizumab treatment to week 24. ‡In patients with psoriasis affecting 3% or more BSA at baseline. §Resolution of enthesitis and dactylitis data are reported for patients with enthesitis or dactylitis at baseline. Data for the placebo and bimekizumab groups are pooled from the BE OPTIMAL and BE COMPLETE trials; data for patients in the reference group are reported from BE OPTIMAL only. ¶IGA score of 0 or 1 and at least a two-grade reduction from baseline in patients with psoriatic skin lesions at baseline and psoriasis BSA of 3% or more. ||In patients with HAQ-DI 0.35 or greater at baseline.

Table 2: Efficacy outcomes at weeks 16 and 24

(0.01 [0.04] vs 0.31 [0.09], p=0.0012; adalimumab -0.03 [0.07]; table 2). The proportion of patients with no structural progression is presented in the appendix (p 17).

Pooled BE OPTIMAL and BE COMPLETE data showed that a significantly greater proportion of patients with

baseline enthesitis receiving bimekizumab reached complete resolution at week 16 compared with those receiving placebo (124 [50%] of 249 vs 37 [35%] of 106, p=0.0083; adalimumab 18 [50%] of 36). In patients with baseline dactylitis, a significantly greater proportion of those receiving bimekizumab had complete resolution at

week 16 versus those receiving placebo (68 [76%] of 90 vs 24 [51%] of 47, $p=0.0022$; adalimumab nine [82%] of 11; table 2).

Improvements in patient-reported physical functioning and symptoms were observed at week 16. Statistically significant improvements in HAQ-DI and SF-36 PCS scores were reported by patients receiving bimekizumab compared with those receiving placebo (HAQ-DI change from baseline: -0.26 [SE 0.02] vs -0.09 [0.03], $p<0.0001$; adalimumab -0.33 [0.04]; SF-36 PCS change from baseline: 6.3 [0.4] vs 2.3 [0.5], $p<0.0001$; adalimumab 6.8 [0.8]; table 2). Patients receiving bimekizumab also had numerically greater improvements (change from baseline) in pain and fatigue compared with those receiving placebo (PtAAP: -23.6 [1.3] vs -6.2 [1.5]; adalimumab -25.7 [2.5]; FACIT-Fatigue: 3.9 [0.4] vs 1.5 [0.5]; adalimumab 5.0 [0.7]).

During the double-blind period to week 16, 258 (60%) of 431 patients receiving bimekizumab and 139 (49%) of 281 patients receiving placebo reported at least one TEAE (table 3). By week 16, 83 (59%) of 140 patients receiving adalimumab had at least one TEAE. SAEs were recorded for seven (2%) patients receiving bimekizumab, three (1%) receiving placebo, and two (1%) receiving adalimumab. Discontinuations due to TEAEs were low (bimekizumab: eight [2%]; placebo: three [1%]; adalimumab: three [2%]).

To week 24, in the safety set, TEAEs were reported for 300 (70%) of 431 patients who were assigned to bimekizumab, and 96 (69%) of 140 patients assigned to adalimumab. SAEs occurred in 17 (4%) patients assigned to bimekizumab at baseline and five (4%) patients assigned to adalimumab. Three (1%) patients who switched to bimekizumab at week 16 had an SAE to week 24. Up to and including week 24, 12 (3%) patients who received bimekizumab from week 0 discontinued due to TEAEs. In the adalimumab group, seven (5%) patients discontinued due to TEAEs (table 3). No deaths occurred up to week 24.

The most common TEAEs reported in patients who received bimekizumab from week 0 to week 24 were nasopharyngitis, upper respiratory tract infections, headache, and diarrhoea (table 3). The most common TEAEs reported in the adalimumab group to week 24 included nasopharyngitis, increased alanine aminotransferase concentration, oral herpes, upper respiratory tract infections, injection site erythema, and diarrhoea.

There was one serious infection in each of the bimekizumab and adalimumab groups (pneumonia and herpes zoster, respectively) to week 16. Two additional serious infections occurred in the bimekizumab group from weeks 16 to 24 (cellulitis and upper respiratory tract infection) and one additional serious infection in the adalimumab group (otitis media).

Between week 16 and week 24, four (1%) patients receiving bimekizumab, including those randomly assigned and those who switched from placebo, had an opportunistic infection (two oesophageal candidiasis

cases, one case each of fungal oesophagitis and laryngitis fungal); three patients were in the group that switched to bimekizumab at week 16. None of the events led to discontinuation and all resolved with appropriate treatment. The herpes zoster SAE was the only opportunistic event in the adalimumab group to week 24, resolving after hospitalisation.

By week 16, 20 (5%) patients receiving bimekizumab had a fungal infection; 11 (3%) were reported as *Candida* infections. Four (1%) patients had a fungal infection while receiving placebo, two (1%) of which were reported specifically as vulvovaginal candidiasis and the others as vulvovaginal mycotic infections. By week 24, 33 (8%) patients assigned to bimekizumab had a fungal infection and 18 (4%) were reported as *Candida* infections; the majority (15 [3%] patients) were oral candidiasis.

By week 24, 15 (3%) patients assigned to bimekizumab had fungal infections not elsewhere classified. One case of moderate oral candidiasis, reported during the double-blind period, led to study discontinuation. By week 24, one (1%) patient had a fungal infection in the adalimumab group (tinea versicolor).

Two malignancies occurred by week 16, one (<1%) in a patient receiving bimekizumab (basal cell carcinoma) and one (<1%) in a patient receiving placebo (breast cancer stage I, which led to study discontinuation). Between weeks 16 and 24, a case of non-melanoma skin cancer was reported in both the bimekizumab-assigned group (squamous cell carcinoma) and the group switching from placebo (basal cell carcinoma); these did not lead to discontinuation. No malignancies were reported in the adalimumab group.

One adjudicated major adverse cardiovascular event (myocardial infarction) was recorded in a patient randomised to bimekizumab from week 0 and was not deemed treatment-related. This patient had a previous medical history of atherosclerosis, hypertension, abdominal aortic aneurysm, and nicotine addiction. Between weeks 16 and 24, one case of probable inflammatory bowel disease was reported in the bimekizumab-assigned group in a patient with no previous history of the condition. By week 24, seven (2%) of 431 patients assigned to bimekizumab, and six (4%) of 139 patients in the adalimumab group had aspartate or alanine aminotransferase levels of more than three-times the upper limit of normal. One case of alanine aminotransferase elevation, which was considered unrelated to bimekizumab by the investigator, resulted in study discontinuation. No cases of suicidal ideation and behaviour were reported. Among patients receiving bimekizumab from week 0 to week 24, incidences of neutropenia and injection site reactions were low, with cases recorded in five (1%) and six (1%) patients, respectively.

Discussion

Dual inhibition of IL-17A and IL-17F with bimekizumab showed superior efficacy compared with placebo across

	Week 0–16			Week 0–24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)	Placebo to bimekizumab 160 mg every 4 weeks (week 16–24; n=271)*	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)
Any TEAE	139 (49%)	258 (60%)	83 (59%)	95 (35%)	300 (70%)	96 (69%)
Serious TEAE	3 (1%)	7 (2%)	2 (1%)	3 (1%)	17 (4%)	5 (4%)
Discontinuation due to TEAE	3 (1%)	8 (2%)	3 (2%)	0	12 (3%)	7 (5%)
Drug-related TEAE	35 (12%)	101 (23%)	34 (24%)	27 (10%)	122 (28%)	43 (31%)
Severe TEAE	0	4 (1%)	3 (2%)	1 (<1%)	9 (2%)	3 (2%)
Deaths	0	0	0	0	0	0
Most frequent TEAEs†						
Nasopharyngitis	13 (5%)	40 (9%)	7 (5%)	8 (3%)	50 (12%)	12 (9%)
Upper respiratory tract infection	18 (6%)	21 (5%)	3 (2%)	5 (2%)	26 (6%)	5 (4%)
Headache	7 (2%)	20 (5%)	2 (1%)	6 (2%)	20 (5%)	3 (2%)
Diarrhoea	7 (2%)	16 (4%)	5 (4%)	1 (<1%)	20 (5%)	5 (4%)
Oral candidiasis	0	9 (2%)	0	1 (<1%)	15 (3%)	0
Pharyngitis	4 (1%)	11 (3%)	2 (1%)	3 (1%)	15 (3%)	2 (1%)
Hypertension	11 (4%)	12 (3%)	4 (3%)	5 (2%)	14 (3%)	4 (3%)
Urinary tract infection	4 (1%)	9 (2%)	3 (2%)	4 (1%)	14 (3%)	3 (2%)
Oral herpes	3 (1%)	5 (1%)	3 (2%)	0	7 (2%)	6 (4%)
Increased alanine aminotransferase	2 (1%)	3 (1%)	7 (5%)	1 (<1%)	4 (1%)	8 (6%)
Injection site erythema	0	1 (<1%)	4 (3%)	0	2 (<1%)	5 (4%)
Infections	56 (20%)	131 (30%)	35 (25%)	41 (15%)	170 (39%)	41 (29%)
Serious	0	1 (<1%)	1 (1%)	0	3 (1%)	2 (1%)
Opportunistic	0	0	1 (1%)	3 (1%)	1 (<1%)	1 (1%)
Active tuberculosis	0	0	0	0	0	0
SARS-CoV-2 infections	0	0	0	1 (<1%)	1 (<1%)	0
Neutropenia	1 (<1%)	5 (1%)	1 (1%)	1 (<1%)	5 (1%)	2 (1%)
Serious hypersensitivity	0	0	0	0	0	0
Injection site reactions	3 (1%)	5 (1%)	7 (5%)	1 (<1%)	6 (1%)	11 (8%)
Adjudicated suicidal ideation and behaviour	0	0	0	0	0	0
Adjudicated major adverse cardiovascular event	0	0	0	0	1 (<1%)	0
Liver function test changes or enzyme concentration increases‡						
Alanine aminotransferase more than three times upper limit of normal	0	5 (1%)	2 (1%)	0	6 (1%)	5 (4%)
Aspartate aminotransferase or alanine aminotransferase more than three times upper limit of normal	0	5 (1%)	3 (2%)	0	7 (2%)	6 (4%)
Adjudicated inflammatory bowel disease	0	0	0	0§	1 (<1%)¶	0
Malignancies	1 (<1%)	1 (<1%)	0	1 (<1%)	2 (<1%)	0
Breast cancer stage I	1 (<1%)	0	0	0	0	0
Non-melanoma skin cancers	0	1 (<1%)	0	1 (<1%)	2 (<1%)	0
Fungal infections	4 (1%)	20 (5%)	1 (1%)	7 (3%)	33 (8%)	1 (1%)
Candida infections	2 (1%)	11 (3%)	0	4 (1%)	18 (4%)	0
Oral candidiasis	0	9 (2%)	0	1 (<1%)	15 (3%)	0
Vulvovaginal candidiasis	2 (1%)	1 (<1%)	0	2 (1%)	1 (<1%)	0
Oesophageal candidiasis	0	0	0	1 (<1%)	1 (<1%)	0
Skin candida	0	1 (<1%)	0	0	2 (<1%)	0

(Table 3 continues on next page)

	Week 0–16			Week 0–24		
	Placebo (n=281)	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)	Placebo to bimekizumab 160 mg every 4 weeks (week 16–24; n=271)*	Bimekizumab 160 mg every 4 weeks (n=431)	Reference group (adalimumab 40 mg every 2 weeks; n=140)
(Continued from previous page)						
Fungal infections not elsewhere classified	2 (1%)	9 (2%)	0	2 (1%)	15 (3%)	0
Fungal skin infection	0	3 (1%)	0	0	5 (1%)	0
Tongue fungal infection	0	3 (1%)	0	0	3 (1%)	0
Oral fungal infection	0	2 (<1%)	0	0	4 (1%)	0
Onychomycosis	0	1 (<1%)	0	0	1 (<1%)	0
Fungal oesophagitis	0	0	0	1 (<1%)	0	0
Laryngitis fungal	0	0	0	1 (<1%)	0	0
Vulvovaginal mycotic infection	2 (1%)	0	0	0	3 (1%)	0
Tinea infections	0	0	1 (1%)	1 (<1%)	1 (<1%)	1 (1%)
Tinea pedis	0	0	0	0	1 (<1%)	0
Tinea versicolour	0	0	1 (1%)	1 (<1%)	0	1 (1%)
Serious <i>Candida</i> infections	0	0	0	0	0	0
Systemic fungal infections	0	0	0	0	0	0
<i>Candida</i> infections leading to study discontinuation	0	1 (<1%)	0	0	1 (<1%)	0

Data are n (%). Events were coded according to the Medical Dictionary for Regulatory Activities, version 19.0. A safety follow-up was conducted 20 weeks after the last dose of bimekizumab for those not entering the open-label extension, or who discontinued early. TEAE=treatment-emergent adverse event. *Patients who switched at week 16 from placebo to bimekizumab 160 mg every 4 weeks (for these patients, events are reported after the switch only and for 8 weeks of bimekizumab treatment). †Most frequent adverse events are those occurring in 3% or more patients in any study group. ‡Data were not available for all patients; proportions are based on the following: to week 16, placebo n=279, bimekizumab n=431, and adalimumab n=139; and to week 24, placebo to bimekizumab n=262, bimekizumab n=431, and adalimumab n=139. §One possible inflammatory bowel disease. ¶One probable inflammatory bowel disease.

Table 3: Safety outcomes to weeks 16 and 24

the signs and symptoms of psoriatic arthritis, and inhibition of structural damage progression in patients with psoriatic arthritis who were naive to biologic DMARD treatment. All primary and ranked secondary endpoints were achieved at week 16.

Bimekizumab improved outcomes across several key psoriatic arthritis disease domains; responses were durable through the 24-week timeframe and outcomes were improved or sustained from week 16 to week 24. Joint and skin outcomes, assessed by ACR and PASI responses, were significantly improved versus the placebo group, in which responses remained low at week 16. More than 70% of patients with psoriatic arthritis and concomitant psoriasis reached PASI90 and more than 50% had complete skin clearance (PASI100) by week 24. A superior response in the MDA composite measure assessing multiple psoriatic arthritis disease domains was also observed versus placebo, showing efficacy across disease manifestations. Pooled data showed that bimekizumab treatment was associated with resolution of dactylitis and enthesitis in high proportions of patients with these symptoms. Additionally, inhibition of structural progression, assessed using vdHmTSS, was demonstrated as early as week 16 for patients receiving bimekizumab and was superior to placebo.

Improvements in efficacy measures to week 16 resulting from bimekizumab treatment in this biologic DMARD-naive population showed a similar magnitude of response to those reported in the BE COMPLETE study of patients with psoriatic arthritis, who had inadequate response or intolerance to TNF α inhibitors.¹⁵

The results provide evidence for the efficacy of bimekizumab in reducing psoriatic arthritis disease state severity, as well as the prevention of structural damage, within the study timeframe. Improved physical function and reductions in the key symptoms of pain and fatigue accompanied the improvements in clinical outcomes, reducing patient-reported disease burden; pain and fatigue have both been identified by patients as important to how they experience their disease.²² Therefore, bimekizumab addresses the key treatment goals outlined in international guidelines and might provide a suitable treatment option for psoriatic arthritis.^{3,4} Although the study was not powered for statistical comparisons of adalimumab and bimekizumab, results from the adalimumab reference group, a current standard of care for psoriatic arthritis, contextualise the benefit–risk profile observed with bimekizumab treatment.

Clinical responses were rapid, with separation between the bimekizumab and placebo groups observed as early as week 2 for ACR20, after a single dose of bimekizumab,

and at week 4 for PASI75, PASI90, and PASI100 responses. Switchers from placebo to bimekizumab at week 16 also showed improvement in the clinical outcomes as early as week 20, 4 weeks after their first bimekizumab dose, demonstrating the speed of response.

To week 24, bimekizumab was well tolerated and the overall safety profile was consistent with previous studies for this indication.^{13,14} Incidence of SAEs and discontinuations were low and similar to placebo at week 16, providing additional support for tolerability. As with previous studies, and consistent with the role of IL-17A and IL-17F in antifungal mucosal immunity,²³ *Candida* infections were commonly reported for patients receiving bimekizumab. In addition, some cases might not have been specified as *Candida* given the hesitancy of investigators to classify this without the appropriate diagnostic tests; thus, these events might be reported as fungal events not elsewhere classified. Despite higher fungal infection occurrence in the bimekizumab group than the placebo group, all reported cases were mild or moderate, none were systemic, and most resolved with appropriate antifungal treatment without leading to treatment or study discontinuation. One patient receiving bimekizumab discontinued due to a moderate case of oral candidiasis.

Limitations of this study include that there were higher proportions of patients with polyarticular versus oligoarticular psoriatic arthritis than might be observed in clinical practice, as well as the exclusion of patients with severe forms of comorbidities from the study population. These demographics and characteristics, along with the limited study diversity, might result in differences between the study population and patients presenting in clinical practice. The inclusion of an active reference group goes some way to alleviating potential differences by allowing numerical comparisons of bimekizumab with a commonly used standard-of-care treatment. However, the absence of a formal, statistical comparison between treatments in this study prevents direct comparison. As such, future head-to-head studies will be advantageous to rheumatologists to formally compare treatment options for psoriatic arthritis.

In summary, this study showed that bimekizumab treatment resulted in clinically meaningful and consistent improvements across joint, skin, radiographic, and patient-reported outcomes in biologic DMARD-naïve patients with active psoriatic arthritis. Long-term data will be reported to week 52, as well as from the open-label extension study, to assess the safety and efficacy of bimekizumab in psoriatic arthritis.

Contributors

IBM, AA, LCC, RL, JFM, CTR, YT, LG, ABG, RBW, BI, DA, RB, VS, JC, and PJM made substantial contributions to study conception and design; IBM, AA, LCC, RL, JFM, CTR, YT, LG, ABG, RBW, BI, DA, RB, VS, JC, and PJM made substantial contributions to analysis and interpretation of the data; IBM, AA, LCC, RL, JFM, CTR, YT, LG, ABG, RBW, BI, DA, RB, VS, JC, and PJM drafted the article or revised it critically for important intellectual content; IBM, AA, LCC, RL, JFM, CTR, YT, LG,

ABG, RBW, BI, DA, RB, VS, JC, and PJM gave final approval of the version of the article to be published; IBM, BI, DA, RB, VS, and JC accessed and verified the data. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

IBM reports consulting fees and honoraria from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Cabaletta, Causeway Therapeutics, Celgene, Evelo, Janssen, Novartis, Lilly, Moonlake, and UCB Pharma; and research support from BMS, Boehringer Ingelheim, Celgene, Janssen, Novartis, and UCB Pharma. AA reports honoraria or research grants from AbbVie, Amgen, BMS, Boehringer Ingelheim, Eisai, Eli Lilly, Janssen, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe Pharma, Pfizer, Sun Pharma, Taiho Pharma, Torii Pharmaceutical, and UCB Pharma. LCC reports grants or research support from AbbVie, Amgen, Celgene, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, and UCB Pharma; paid consultant work for AbbVie, Amgen, BMS, Boehringer Ingelheim, Celgene, Domain, Eli Lilly, Gilead, Galapagos, Janssen, Moonlake, Novartis, Pfizer, and UCB Pharma; and paid speaker work for AbbVie, Amgen, Biogen, Celgene, Eli Lilly, Galapagos, Gilead, GSK, Janssen, Medac, Novartis, Pfizer, and UCB Pharma. RL reports consultancy fees from AbbVie, AstraZeneca, BMS, Eli Lilly, Novartis, Pfizer, and UCB Pharma; research grants from AbbVie, Novartis, Pfizer, and UCB Pharma; and is an owner of Rheumatology Consultancy, an AMS company under Dutch law. JFM reports consultant or investigator work for AbbVie, Amgen, Biogen, BMS, Dermavant, Eli Lilly, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, Sun Pharma, and UCB Pharma. CTR reports research for AbbVie, Amgen, and UCB Pharma; and consultancy for Amgen, AbbVie, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, and UCB Pharma. YT reports speaking fees or honoraria from AbbVie, AstraZeneca, BMS, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eisai, Eli Lilly, Gilead, GSK, Mitsubishi-Tanabe, and Pfizer; and research grants from AbbVie, Asahi-Kasei, Boehringer Ingelheim, Chugai, Daiichi-Sankyo, Eisai, and Takeda. LG reports non-financial support from UCB Pharma, during the conduct of the study; grants from Amgen, Galapagos, Lilly, Pfizer, Sandoz, and UCB Pharma; personal fees from AbbVie, Amgen, BMS, Celltrion, Galapagos, Gilead, Janssen, Lilly, MSD, Novartis, Pfizer, Sandoz, and UCB Pharma; and non-financial support from AbbVie, Janssen, Novartis, Pfizer, and UCB Pharma, outside the submitted work. ABG reports honoraria as an advisory board member, non-promotional speaker, or consultant for Amgen, AnaptysBio, Avotres Therapeutics, BMS, Boehringer Ingelheim, Dermavant, Eli Lilly, Janssen, Novartis, Pfizer, Sanofi, Sun Pharma, UCB Pharma, and Xbiotech (stock options); and research or educational grants from AnaptysBio, BMS, Janssen, Novartis, Ortho Dermatologics, Sun Pharma, and UCB Pharma (all funds go to the Icahn School of Medicine at Mount Sinai). RBW reports consulting fees from AbbVie, Almirall, Amgen, Arena, Astellas, Avillion, Biogen, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, GSK, Janssen, LEO Pharma, Novartis, Pfizer, Sanofi, and UCB Pharma; research grants to his institution from AbbVie, Almirall, Janssen, LEO Pharma, Novartis, and UCB Pharma; and honoraria from Astellas, DiCE, GSK, and Union. BI is an employee and stockholder of UCB Pharma and a stockholder of GSK and AbbVie. DA, RB, VS, and JC are all employees and stockholders of UCB Pharma. PJM reports research grants from AbbVie, Amgen, BMS, Eli Lilly, Galapagos, Gilead, Janssen, Novartis, Pfizer, Sun Pharma, and UCB Pharma; consultancy fees from AbbVie, Acelyrin, Aclaris, Amgen, BMS, Boehringer Ingelheim, Eli Lilly, Galapagos, Gilead, GSK, Inmagene, Janssen, Moonlake Pharma, Novartis, Pfizer, Sun Pharma, and UCB Pharma; and speakers' bureau fees from AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, and UCB Pharma.

Data sharing

Data from this manuscript can be requested by qualified researchers 6 months after product approval in the USA or Europe, or global development is discontinued, and 18 months after trial completion. Investigators can request access to anonymised individual patient data and redacted study documents, which can include: raw datasets, analysis-ready datasets, study protocol, blank case report form, annotated

case report form, statistical analysis plan, dataset specifications, and clinical study report. Before the use of the data, proposals need to be approved by an independent review panel at www.vivli.org and a signed data sharing agreement will need to be executed. All documents are available in English only, for a prespecified time, typically 12 months, on a password protected portal.

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