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Efficacy and Safety of the TYK2/JAK1 Inhibitor Brepocitinib for Active Psoriatic Arthritis: A Phase IIb Randomized Controlled Trial

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Objective. Brepocitinib is a TYK2/JAK1 inhibitor in development for the treatment of several immunologic diseases. The efficacy and safety of oral brepocitinib were assessed in participants with moderately-to-severely active psoriatic arthritis (PsA) for up to 52 weeks.

Methods. In this placebo-controlled, dose-ranging, phase IIb study, participants were randomized to receive 10 mg, 30 mg, or 60 mg of brepocitinib once daily or placebo, advancing to 30 mg or 60 mg of brepocitinib once daily at week 16. The primary endpoint was the response rate according to the American College of Rheumatology criteria for 20% improvement (ACR20) in disease activity at week 16. Secondary endpoints included response rates according to the ACR50/ACR70 response criteria, 75% and 90% improvement in the Psoriasis Area and Severity Index (PASI75/PASI90) score, and minimal disease activity (MDA) at weeks 16 and 52. Adverse events were monitored throughout the study.

Results. Overall, 218 participants were randomized and treated. At week 16, the brepocitinib 30 mg and 60 mg once daily groups had significantly greater ACR20 response rates (66.7% [$P = 0.0197$] and 74.6% [$P = 0.0006$], respectively), versus the placebo group (43.3%), and significantly higher ACR50/ACR70, PASI75/PASI90, and MDA response rates. Response rates were maintained or improved through week 52. Adverse events were mostly mild/moderate; serious adverse events (15) in 12 participants (5.5%) included infections in 6 participants (2.8%) in the brepocitinib 30 mg and 60 mg once daily groups. No major adverse cardiovascular events or deaths occurred.

Conclusion. Treatment with brepocitinib at dosages of 30 mg and 60 mg once daily was superior to placebo at reducing signs and symptoms of PsA. Brepocitinib was generally well tolerated throughout the 52-week study, with a safety profile consistent with those found in other brepocitinib clinical trials.

INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease with heterogeneous manifestations of peripheral arthritis, spondylitis, enthesitis, dactylitis, psoriasis, and nail disease (1,2). Approximately 30% of patients with psoriasis have PsA, making the estimated overall prevalence of PsA in the US 30–100 cases out of 10,000 (3).

There are a variety of approved treatment options for PsA, including nonbiologic conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), biologic therapies such as

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Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

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tumor necrosis factor (TNF), interleukin-17 (IL-17), IL-12/IL-23, and IL-23 inhibitors, and new targeted oral agents including a phosphodiesterase-4 inhibitor (apremilast) and Janus kinase inhibitors (JAKis) (4). In 2021, the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) determined that there is strong evidence for the use of JAKis to treat PsA across multiple domains of the disease (5). GRAPPA also recommends an individualized treatment approach, taking into careful consideration clinical and patient-reported signs and symptoms of PsA as well as patients' comorbidities. Further support for the use of JAKis in PsA comes from the pivotal phase III and open-label extension studies of tofacitinib (6–8) and upadacitinib (9–11), and from clinical studies of filgotinib (12,13).

Despite a variety of treatment options, the PsA treatment goals of decreasing disease activity, inducing remission, and improving health-related quality of life (HRQoL) and function, as well as preventing structural damage and complications (4), remain unmet needs. JAKis are a promising class of emerging treatment options for PsA due to their mechanism of action. Activation of the JAK family of tyrosine kinases (JAK1, JAK2, JAK3, and TYK2) induces inflammation in PsA. In particular, type I interferons, IL-22, and IL-23 signal via JAK1 and/or TYK2 (14). Although TNFα and IL-17 do not signal via JAKs, they are regulated by upstream cytokines such as IL-6 and IL-23, which are JAK-dependent (15). Through specific blockade of IL-23 signaling, TYK2 inhibitors also hold promise as a treatment for PsA, as demonstrated in a recent phase II study of the TYK2 inhibitor, deucravacitinib (16).

Brepocitinib is a JAKi with selectivity for TYK2 and JAK1 over JAK2 and JAK3 (17). TYK2 inhibition by brepocitinib provides greater blockade of IL-12 and IL-23 signaling compared with JAK1 inhibition alone; this reduces production of IL-17, one of the major effector cytokines in the pathogenesis of psoriatic disease (18).

Results from a previous phase IIa study demonstrated significant improvements in the Psoriasis Area and Severity Index (PASI) scores in participants with plaque psoriasis treated with brepocitinib compared with placebo (19). Safety results from phase IIa studies of brepocitinib in plaque psoriasis, alopecia areata, and ulcerative colitis demonstrated an acceptable safety and tolerability profile with brepocitinib, with few serious adverse events (SAEs), opportunistic infections, or major adverse cardiovascular events including vascular thrombosis (19–21).

The objective of the current study was to assess the efficacy, safety, and dose response of brepocitinib in participants with active PsA.

PARTICIPANTS AND METHODS

Study design and treatment. This was a phase IIb, randomized, double-blind, placebo-controlled, dose-ranging, parallel-treatment-group, efficacy, and safety study conducted across 11 countries in Europe between June 2019 and January 2021. The study consisted of a screening period of up to 5 weeks, a double-blind treatment period of 52 weeks, including a placebo-controlled phase from day 1 to week 16, and an extended active treatment phase from week 17 through week 52, with a safety follow-up period of 4 weeks from the last dose of the study drug to the last study visit. During the placebo-controlled phase, participants were randomized 2:2:1:2 to double-blinded treatment with brepocitinib 60 mg once daily, 30 mg once daily, 10 mg once daily, or placebo. At week 16, participants receiving brepocitinib at 60 mg or 30 mg once daily maintained the same dosage, while participants receiving brepocitinib at 10 mg once daily or placebo advanced to treatment with brepocitinib at either 60 mg or 30 mg once daily (Supplementary Figure 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.42519). Treatment allocations were predetermined at randomization through an interactive response technology system (interactive web-based response), with participants stratified by a single factor (prior TNF inhibitor [TNFi] exposure). The study was conducted in accordance with the International Conference on Harmonization Guideline for Good Clinical Practice and the principles of the Declaration of Helsinki, and was registered on ClinicalTrials.gov (NCT03963401). Study protocols, informed consent forms, and other appropriate study-related documents were reviewed and approved by local independent ethics committees and institutional review boards. All participants provided written informed consent.

Participants. Male and female participants ages 18–75 years with a diagnosis of PsA for ≥6 months who fulfilled the Classification Criteria for Psoriatic Arthritis (CASPAR) were eligible for this study. Participants self-reported ethnicity and race. Study investigators reported the sex of participants based on their genetic composition. If a participant was transsexual or transgender, their original sex was reported, and any relevant surgical procedure or hormone treatment was recorded in the medical history and concomitant treatment sections of the case report form. Key inclusion criteria were as follows: at least 3 tender/painful joints on motion and 3 swollen joints at screening and baseline, active psoriasis at screening and baseline, negative test results for rheumatoid factor and cyclic citrullinated peptide antibodies, active PsA despite previous or current nonsteroidal antiinflammatory drug (NSAID) treatment of at least 4 weeks or intolerance, and/or csDMARD treatment of at least 3 months or intolerance.

Key exclusion criteria included the following: pregnancy or breastfeeding in female participants, history of infection requiring hospitalization (within 6 months of baseline), history of chronic or recurrent infection, history of pulmonary embolism or recurrent deep vein thrombosis, history of any lymphoproliferative disorder, history of disseminated herpes infection (either zoster or simplex) or a recurrent localized dermatomal herpes zoster, history of any

autoimmune rheumatic disease other than PsA, nonplaque psoriasis, risk factors for torsade de pointes, critical laboratory abnormalities, or electrocardiogram abnormalities indicative of underlying heart disease.

Details of prohibited prior and concomitant medications are outlined in Supplementary Table 1 (http://onlinelibrary.wiley.com/doi/10.1002/art.42519). Participants discontinued treatment with any csDMARDs except for methotrexate, leflunomide, or sulfasalazine ≥28 days prior to baseline. Participants could remain on stable doses of NSAIDs, cyclooxygenase 2 inhibitors, or prednisone/equivalent (≤10 mg/day). Up to 30% of participants could have previously received no more than 1 approved biologic TNFi with an inadequate response due to lack of efficacy (≥3 months duration) and/or intolerance (experience of a treatment-related adverse event).

Efficacy endpoints. The primary endpoint was the proportion of participants achieving a response according to the American College of Rheumatology criteria for 20% improvement (ACR20) in disease activity at week 16 (22). Secondary efficacy endpoints included the proportion of participants achieving an ACR20 response at all timepoints other than week 16, the proportion of participants achieving ACR50/ACR70 and PASI75/PASI90 responses at all timepoints, change from baseline in Dactylitis Severity Score (DSS) (23), Leeds Enthesitis Index (LEI) score (24), and Spondyloarthritis Research Consortium of Canada (SPARCC) Enthesitis Index (25) score at all timepoints, the proportion of participants with resolution of enthesitis and dactylitis at all timepoints, and the change from baseline in Psoriatic Arthritis Disease Activity Score (PASDAS) (26), Health Assessment Questionnaire–Disability Index (HAQ DI) (27), acute 36-item Short Form Health Survey Version 2 (SF-36) Physical Component Summary (PCS) and Mental Component Summary (MCS) (28), and Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) (29) over time. The proportion of participants achieving Minimal Disease Activity (MDA) at all timepoints except week 2 was assessed as a secondary endpoint, with MDA defined as meeting ≥5 of the following 7 criteria: tender/painful joint count ≤1, swollen joint count ≤1, PASI score ≤1 or psoriatic body surface area ≤3%, Patient's Assessment of Arthritis Pain (visual analog scale [VAS]) ≤15, Patient's Global Assessment of Arthritis (VAS) ≤20, HAQ DI score ≤0.5, and tender entheseal points (using LEI) ≤1 (30).

Safety endpoints. Incidence of treatment-emergent adverse events (TEAEs), SAEs, and serious infection events, withdrawals due to TEAEs and SAEs, and laboratory abnormalities, changes in vital signs, and electrocardiogram findings were assessed throughout the study.

Statistical analyses. Sample size was determined assuming an ACR20 response rate at week 16 (primary endpoint) of 25% for the placebo group and a 1-sided Type I error rate of 5%, using the normal approximation method. The study had over 90% power with a sample size of 50 participants per arm and 80% power with a sample size of 25 participants per arm to detect a treatment difference of 30% or greater without multiplicity adjustment.

Dunnett's multiple comparison test was used for the primary endpoint to adjust for multiplicity and serve as a gatekeeper for further testing of secondary endpoints. In cases where a brepocitinib dose regimen was superior to placebo under Dunnett's test, selected secondary endpoints at week 16 for that dose regimen were formally tested for superiority against placebo hierarchically in the following order: PASI75, ACR50, PASI90, PASI100, HAQ DI. The normal approximation method for the treatment differences in these endpoints was used to test superiority of brepocitinib against placebo. This testing strategy controlled the family-wise Type I error rate at an overall 1-sided 5% level. Change from baseline in HAQ DI response was analyzed using a repeated measure model. Safety endpoints were summarized descriptively.

For the analysis of efficacy endpoints and certain safety endpoints at week 52, the 3 groups treated with brepocitinib at 30 mg once daily after week 16 were combined, as were the 3 groups treated with brepocitinib at 60 mg once daily.

For all binary response-type endpoints (ACR20/ACR50/ACR70, PASI75/PASI90, and MDA), missing data due to participant withdrawal for any reason except COVID-19 were handled by nonresponder imputation at all timepoints. For the analysis of the presence of dactylitis/enthesitis, missing data were not imputed. Continuous endpoints were analyzed using a mixed model for repeated measures yielding unbiased estimates and valid inferences where data were missing at random. A multiple imputation approach was also used for the analysis of the change from baseline in HAQ DI response at week 16.

RESULTS

Participants. A total of 285 participants were screened from 47 sites in 11 countries, with the majority of participants enrolled from Eastern Europe; 218 participants were randomized and treated. One participant who was randomized to brepocitinib 30 mg once daily did not receive treatment and was not included in the analyses (Figure 1). Up to week 16, 15 participants discontinued the study; the most common reasons for discontinuation were withdrawal by participant (n = 7) and adverse events (AEs [n = 6]). Between weeks 20 and 52, 35 participants discontinued (n = 11 for brepocitinib 30 mg once daily; n = 24 for brepocitinib 60 mg once daily), with AEs being the most common reason for discontinuation.

Baseline demographics and disease characteristics were similar across treatment groups (Table 1). As defined in the protocol, only the csDMARDs methotrexate, leflunomide, and sulfasalazine were allowed along with the study drug, and use of concomitant csDMARDs occurred in 162 participants (74.3%),

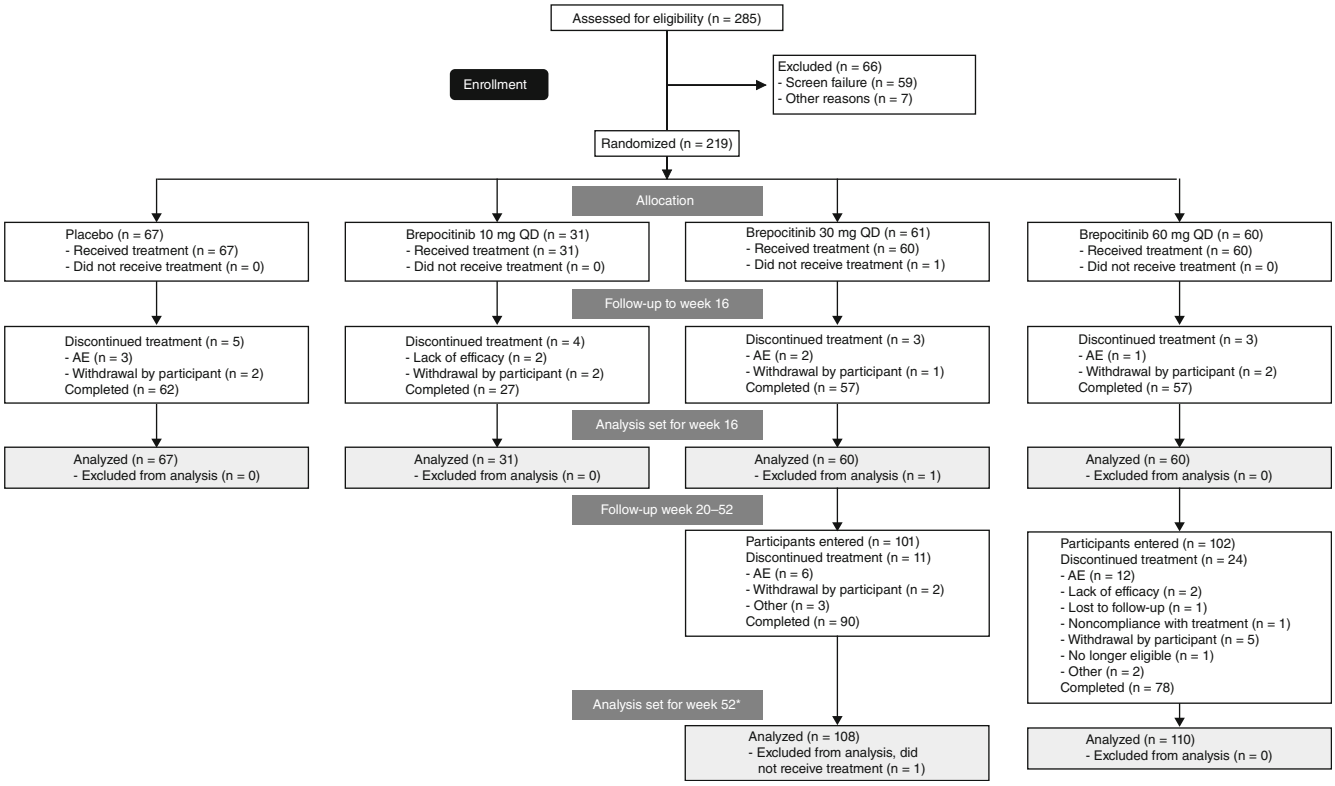

Figure 1. Description of participants in a study of the efficacy and safety of treatment with brepocitinib in individuals with active psoriatic arthritis. *Analysis set includes all participants who received at least 1 dose of the study treatment (brepocitinib or placebo) during the study. AE = adverse event; QD = once daily.

as shown in Table 1. The most frequently used csDMARDs were methotrexate (139 participants [63.8%]) and methotrexate sodium (16 participants [7.3%]; 1 participant in the brepocitinib 30 mg treatment group switched from methotrexate to methotrexate sodium during the study), which were administered at a mean dose of 16.39 mg/week at baseline (both methotrexate and methotrexate sodium doses included). Eighteen participants (8.3%) had prior TNFi exposure. The mean tender/painful and swollen joint counts for the overall population were 16.6 and 9.8, respectively, and the mean PASDAS and Disease Activity Index for PsA scores for the overall population were 5.6 and 38.2, respectively. These baseline characteristics were generally well balanced across the 4 treatment groups. A total of 141 participants (64.7%) had a PASI score >0 and ≥3% of their body surface area affected by psoriasis at baseline. The mean baseline PASI score ranged from 10.5 to 11.9 across the groups. There were 111 participants (50.9%) with high-sensitivity C-reactive protein levels >2.87 mg/liter (the upper limit of normal). At baseline, participants in the brepocitinib 60 mg once daily group had numerically higher SF-36 PCS and FACIT-F scores, indicating better HRQoL. These participants also had numerically lower Patient's Global Joint and Skin Assessment VAS scores and were more likely to be receiving csDMARDs and methotrexate, compared with participants in the other groups.

Efficacy endpoints. *Week 16.* At week 16, the proportions of participants achieving an ACR20 response were 43.3%, 64.5%, 66.7%, and 74.6% in the placebo, brepocitinib 10 mg once daily, 30 mg once daily, and 60 mg once daily groups, respectively. Compared with placebo, statistically significantly higher proportions of participants in the brepocitinib 30 mg once daily (P = 0.0197) and 60 mg once daily (P = 0.0006) groups achieved an ACR20 response (Figure 2A). As the brepocitinib 10 mg once daily group was not statistically significant versus placebo in the primary endpoint under the Dunnett's test, formal testing on PASI75, ACR50, PASI90, and HAQ DI was only performed for the brepocitinib 30 and 60 mg once daily groups, compared with placebo. As such, proportions of participants achieving PASI75 (Figure 3A), ACR50 (Figure 2B), and PASI90 (Figure 3B) and the change from baseline in HAQ DI response (Table 2) were statistically significantly greater in the brepocitinib 30 and 60 mg once daily groups, compared with placebo at week 16. Separations from placebo in PASI75/PASI90 responses were observed in the brepocitinib 30 and 60 mg once daily groups early at week 4 or week 8, respectively ($P < 0.1$ by 2-sided test; data not shown).

Similar to ACR20/ACR50 and PASI75/PASI90 response rates, ACR70 (Figure 2C) and MDA (Figure 3C) response rates were higher in the brepocitinib 30 and 60 mg groups, as well as

Table 1. Participant baseline demographics and disease characteristics*

	Placebo (N = 67)	Brepocitinib 10 mg QD (N = 31)	Brepocitinib 30 mg QD (N = 60)	Brepocitinib 60 mg QD (N = 60)	Total (N = 218)
Age, mean (SD) years	48.2 (12.1)	47.8 (13.4)	45.9 (10.2)	48.7 (11.5)	47.6 (11.6)
Male, n (%)	31 (46.3)	17 (54.8)	28 (46.7)	26 (43.3)	102 (46.8)
Race, n (%)					
Asian	0 (0.0)	0 (0.0)	0 (0.0)	1 (1.7)	1 (0.5)
Black	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
White	67 (100)	31 (100)	60 (100)	59 (98.3)	217 (99.5)
BMI, mean (SD) kg/m^2	28.8 (5.2)	28.7 (6.0)	30.2 (6.5)	28.7 (5.6)	29.2 (5.9)
PsA duration, mean (SD) years	6.9 (7.5)	6.4 (6.6)	6.1 (7.2)	5.7 (4.9)	6.3 (6.6)
PASDAS, mean (SD)	5.7 (1.1)	5.7 (1.0)	5.7 (1.0)	5.4 (0.9)	5.6 (1.0)
DAPSA, mean (SD)	37.9 (16.4)	39.9 (20.4)	38.6 (17.2)	37.2 (15.0)	38.2 (16.8)
HAQ DI, mean (SD)	1.1 (0.6)	1.1 (0.7)	1.1 (0.6)	1.0 (0.6)	1.1 (0.6)
SPARCC enthesitis index >0, n (%)	40 (59.7)	20 (64.5)	34 (56.7)	38 (63.3)	132 (60.6)
Number of tender sites by SPARCC enthesitis, mean (SD)†	4.0 (2.9)	3.6 (2.4)	3.4 (2.3)	3.7 (2.9)	3.7 (2.7)
LEI >0, n (%)	35 (52.2)	18 (58.1)	28 (46.7)	29 (48.3)	110 (50.5)
Number of tender sites by LEI, mean (SD)‡	2.0 (1.4)	2.2 (1.0)	2.2 (1.3)	2.1 (1.3)	2.1 (1.3)
DSS >0, n (%)	21 (31.3)	9 (29.0)	19 (31.7)	14 (23.3)	63 (28.9)
DSS, mean (SD)§	6.8 (7.4)	4.3 (4.4)	5.4 (4.1)	5.0 (3.8)	5.6 (5.4)
Number of dactylitic digits, mean (SD)	1.0 (2.3)	0.6 (1.3)	1.0 (1.9)	0.7 (1.6)	0.8 (1.9)
Psoriatic BSA ≥3%, n (%)	42 (62.7)	21 (67.7)	39 (65.0)	40 (66.7)	142 (65.1)
Tender/painful joint count out of 68 joints, mean (SD)	16.0 (9.6)	16.5 (10.8)	16.6 (10.5)	17.3 (10.4)	16.6 (10.2)
Swollen joint count out of 66 joints, mean (SD)	9.8 (6.2)	11.1 (7.8)	9.6 (6.1)	9.3 (5.6)	9.8 (6.2)
PASI, mean (SD)¶	11.2 (9.5)	11.9 (10.5)	10.5 (9.4)	10.8 (7.3)	11.0 (9.0)
SF-36 PCS, mean (SD)	35.8 (7.9)	35.6 (7.8)	34.7 (7.3)	38.9 (7.3)	36.3 (7.7)
SF-36 MCS, mean (SD)	41.7 (10.4)	42.0 (12.7)	43.3 (12.2)	43.7 (11.9)	42.7 (11.6)
FACIT-F total score, mean (SD)	28.1 (10.1)	29.0 (11.7)	29.3 (9.4)	31.7 (9.8)	29.5 (10.1)
Prior TNFi exposure, n (%)	7 (10.4)	3 (9.7)	4 (6.7)	4 (6.7)	18 (8.3)
Medication use at baseline, n (%)					
csDMARDs	49 (73.1)	23 (74.2)	40 (66.7)	50 (83.3)	162 (74.3)
Methotrexate	48 (71.6)	21 (67.7)	38 (63.3)	46 (76.7)	153 (70.2)
NSAIDs	34 (50.7)	21 (67.7)	32 (53.3)	34 (56.7)	121 (55.5)
Oral steroids	11 (16.4)	5 (16.1)	6 (10.0)	9 (15.0)	31 (14.2)
Topical steroids	0 (0.0)	1 (3.2)	2 (3.3)	1 (1.7)	4 (1.8)
Methotrexate dose, mean mg/week#	16.8	16.4	15.5	16.7	16.4
Prednisone (or equivalent) dose, mean mg/day#	6.0	3.4	5.0	5.6	5.3
hsCRP >ULN, 2.87 mg/liter, n (%)	37 (55.2)	10 (32.3)	33 (55.0)	31 (51.7)	111 (50.9)
hsCRP, mean (SD) mg/liter	7.3 (10.2)	6.3 (17.0)	8.1 (14.4)	6.7 (11.0)	7.2 (12.7)
PAAP, mean (SD)	58.5 (21.1)	57.3 (23.3)	57.1 (22.5)	50.1 (18.8)	55.6 (21.4)
PGA-PsO, mean (SD)**	1.9 (0.8)	2.2 (0.8)	1.9 (0.8)	2.0 (0.9)	2.0 (0.8)
PGJS-VAS, mean (SD)	61.2 (20.7)	60.5 (19.3)	58.3 (19.7)	53.7 (20.3)	58.2 (20.2)

* QD = once daily; BMI = body mass index; PsA = psoriatic arthritis; PASDAS = Psoriatic Arthritis Disease Activity Score; DAPSA = Disease Activity Index for PsA; HAQ DI = Health Assessment Questionnaire–Disability Index; SPARCC = Spondyloarthritis Research Consortium of Canada; LEI = Leeds Enthesitis Index; DSS = Dactylitis Severity Score; BSA = body surface area; PASI = Psoriasis Area and Severity Index; SF-36 PCS = 36-Item Short Form Health Survey Physical Component Summary; SF-36 MCS = 36-Item Short Form Health Survey Mental Component Summary; FACIT-F = Functional Assessment of Chronic Illness Therapy–Fatigue; TNFi = tumor necrosis factor inhibitor; csDMARDs = conventional synthetic disease-modifying antirheumatic drugs; NSAIDs = nonsteroidal antiinflammatory drugs; hsCRP = high-sensitivity C-reactive protein; ULN = upper limit of normal; PAAP = Patient's Assessment of Arthritis Pain; PGA-PsO = Physician's Global Assessment of Psoriasis; PGJS-VAS = Patient's Global Joint and Skin Assessment-visual analog scale.
† Tender sites by SPARCC enthesitis reported for participants with SPARCC enthesitis >0 at baseline.
‡ Tender sites by LEI reported for participants with LEI >0 at baseline.
§ DSS score reported for participants with DSS >0 at baseline.
¶ PASI score reported for participants with BSA ≥3% and PASI >0 at baseline.
# Dose in participants receiving this medication.
** PGA-PsO reported for participants with PGA-PsO >0 at baseline (placebo, N = 65; 10 mg QD, N = 30; 30 mg QD, N = 58; 60 mg QD, N = 59).

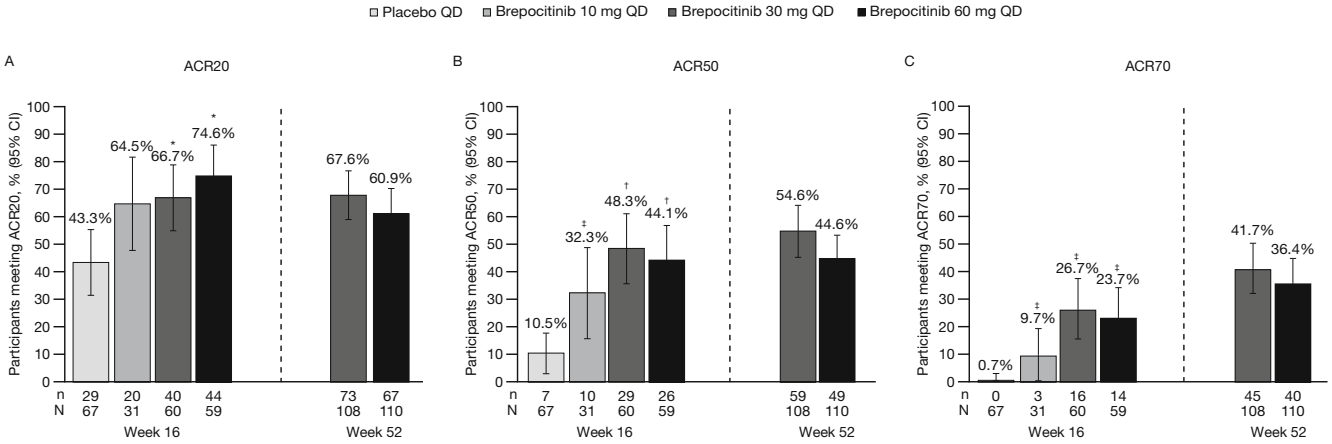

Figure 2. Efficacy of brepocitinib versus placebo by response rate according to the American College of Rheumatology criteria for 20%, 50%, and 70% improvement (ACR20/50/70) at weeks 16 and 52. As the brepocitinib 10 mg once daily (QD) group was not tested as statistically significant versus placebo in the primary endpoint of ACR20 at week 16 under the Dunnett's method, formal testing on ACR50 was only performed for the brepocitinib 30 and 60 mg groups, compared with placebo. * = statistical significance versus placebo using a 2-sided adjusted $P < 0.1$ based on Dunnett's method for ACR20 at week 16 (primary endpoint). † = statistical significance versus placebo using formal testing for secondary endpoints with overall family-wise Type I error rate controlled, 2-sided $P < 0.1$ based on the normal approximation for binomial proportions. ‡ = statistical significance versus placebo using informal testing for secondary endpoints without overall family-wise Type I error rate controlled, 2-sided $P < 0.1$ based on the normal approximation for binomial proportions. 95% CI = 95% confidence interval; QD = once daily.

in the 10 mg once daily group, compared with placebo at week 16. Change from baseline in disease activity, as measured by PASDAS, was also greater in all brepocitinib groups, compared with placebo at week 16 (Table 2).

Participants in the brepocitinib 30 and 60 mg once daily groups generally experienced numerical improvements in enthesitis and dactylitis assessments up to week 16, compared with placebo. The brepocitinib 60 mg once daily group had a higher proportion of participants with resolution of enthesitis and dactylitis at week 16, compared with placebo, as measured by SPARCC enthesitis index, LEI, and DSS (Figure 3D–F).

Regarding patient-reported outcomes, all brepocitinib groups experienced improvements in arthritis pain and SF-36 PCS at week 16, compared with placebo (Table 2). Improvements in fatigue were greatest in the brepocitinib 30 mg once daily group, and improvements in SF-36 MCS were similar between the brepocitinib groups and placebo group up to week 16 (Table 2).

Week 52. ACR20/ACR50/ACR70 response rates (Figure 2), PASI75/PASI90 response rates (Figures 3A and B), HAQ DI response (Table 2), and disease activity (as measured using MDA response rate and PASDAS; Figure 3C and Table 2, respectively) were generally sustained or continued to improve out to week 52 in both the brepocitinib 30 and 60 mg once daily groups. Changes from baseline in enthesitis and dactylitis assessments were also generally maintained to week 52, accompanied by general increases in the proportion of participants achieving resolution (Figures 3D–F). Fatigue, SF-36 PCS and MCS, and arthritis pain also continued to improve from week 16 to week 52 in both the brepocitinib 30 and 60 mg once daily groups (Table 1 and Table 2).

Safety endpoints. TEAEs, SAEs, and AEs of special interest are listed in Table 3. The majority of TEAEs both up to week 16 and week 52 were mild or moderate in severity. Overall, 469 TEAEs were reported during the study; 108 of which were characterized as being treatment related.

Up to week 16, 257 TEAEs were reported in 119 participants, with higher proportions of participants in the brepocitinib 30 and 60 mg once daily groups experiencing all-causality TEAEs, compared with placebo; 65 TEAEs were characterized as treatment related. Five participants reported 6 SAEs through week 16; 1 SAE was reported in the placebo group, 3 SAEs in the brepocitinib 30 mg once daily group, and 2 SAEs (in 1 participant) in the brepocitinib 60 mg once daily group. Only 1 SAE in the brepocitinib 30 mg once daily group (acute otitis media onset on day 12) was considered treatment related. One other participant in the brepocitinib 30 mg once daily group experienced a serious infection (appendicitis onset on day 8); however, adjudication criteria were not met, and this was not considered treatment related. Up to week 16, infections and infestations (system organ class) were the most common group of AEs experienced by participants across treatment groups, and the frequency increased slightly with higher doses of brepocitinib (Table 3).

A dose-dependent decrease was observed in mean hemoglobin values, and dose-dependent increases were observed in mean alanine aminotransferase (ALT) and aspartate aminotransferase (AST) values up to week 16. These changes were continuously observed throughout the study. The increases in ALT and AST levels were not associated with evidence of drug-induced liver injury or Hy's Law. The decrease in hemoglobin levels was most pronounced in the brepocitinib 60 mg once daily group,

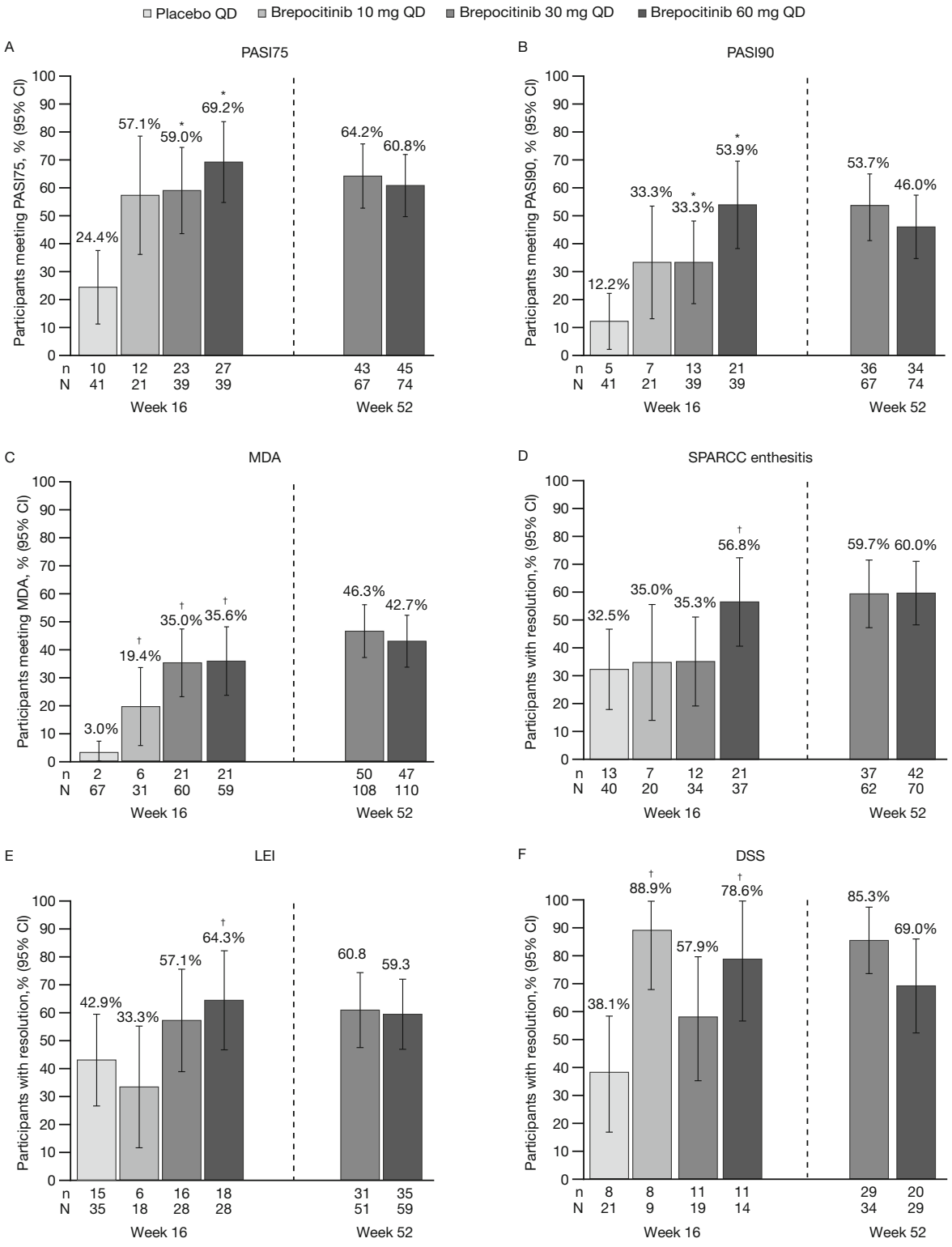

Figure 3. Improvement in psoriatic arthritis (PsA) signs and symptoms with brepocitinib treatment versus placebo at weeks 16 and 52. Psoriasis Area and Severity Index 75 (PASI75)/PASI90 evaluated in participants with baseline body surface area (BSA) ≥3% and PASI >0. Spondyloarthritis Research Consortium of Canada (SPARCC) enthesitis, Leeds Enthesitis Index (LEI), and Dactylitis Severity Score (DSS) resolution assessed in evaluable participants with respective score values >0 at baseline. As the brepocitinib 10 mg once daily (QD) group was not tested as statistically significant versus placebo in the primary endpoint under the Dunnett's method, formal testing on PASI75 and PASI90 was only performed for the brepocitinib 30 and 60 mg QD groups, versus placebo. Statistical significance versus placebo, 2-sided $P < 0.1$ based on the normal approximation for binomial proportions, using formal testing (indicated by *) with, or informal testing (indicated by †) without, overall family-wise Type I error rate controlled. 95% CI = 95% confidence interval; QD = once daily.

Table 2. PsA secondary efficacy endpoints at week 16 and week 52

Secondary efficacy endpoints	Week 16†				Week 52†	
		Brepocitinib			Brepocitinib	
	Placebo (N = 67)	10 mg QD (N = 31)	30 mg QD (N = 60)	60 mg QD (N = 59)	30 mg QD (N = 108)	60 mg QD (N = 110)
Change from baseline in PASDAS	−0.9 (−1.2, −0.6)	−1.9 (−2.3, −1.5)‡	−2.2 (−2.5, −1.9)‡	−2.4 (−2.6, −2.1)‡	−3.0 (1.6)	−3.0 (1.4)
Change from baseline in FACIT-F total score	3.8 (2.0, 5.7)	4.6 (1.9, 7.3)	7.1 (5.2, 9.0)‡	5.9 (4.0, 7.8)	10.7 (10.4)	8.9 (8.7)
Change from baseline in SF-36 PCS	1.7 (0.1, 3.4)	5.0 (2.6, 7.5)‡	6.8 (5.0, 8.5)‡	6.6 (4.8, 8.3)‡	9.5 (9.0)	7.1 (9.2)
Change from baseline in SF-36 MCS	2.1 (−0.1, 4.3)	1.9 (−1.3, 5.1)	2.6 (0.3, 4.8)	2.2 (−0.1, 4.4)	4.9 (13.0)	4.5 (9.6)
Change from baseline in HAQ DI	−0.18 (−0.28, −0.08)	−0.32 (−0.47, −0.17)	−0.50 (−0.61, −0.39)‡	−0.50 (−0.61, −0.40)‡	−0.55 (0.51)	−0.47 (0.52)
Change from baseline in PAAP	−13.1 (−18.0, −8.23)	−23.4 (−30.7, −16.1)‡	−24.9 (−30.1, −19.8)‡	−30.5 (−35.6, −25.3)‡	−36.3 (27.4)	−34.6 (24.8)

* As the brepocitinib 10 mg QD group was not tested as statistically significant versus placebo in the primary endpoint under the Dunnett's method, formal testing on HAQ DI was only performed for the brepocitinib 30 and 60 mg groups, compared with placebo. See Table 1 for definitions.
† Week 16 values represent least squares means and 95% confidence intervals; Week 52 values represent the mean (SD).
‡ Indicates statistical significance versus placebo using a 2-sided $P < 0.1$ based on a mixed model for repeated measures containing fixed factors of treatment, visit, treatment by visit interactions, and baseline value.

but there was no associated increase in the incidence of hemoglobin-related AEs (i.e., anemia) reported during the study. There were more participants with increased creatine kinase levels (>2.0 × upper limit of normal) in the brepocitinib 30 and 60 mg groups compared to the placebo group up to week 16 with a dose-related trend. However, there were no events of rhabdomyolysis during the study.

Between weeks 16 and 52, there were 11 SAEs in 7 participants, with the following 3 SAEs in 2 participants considered to be treatment related: coronavirus infection and pneumonia (1 case with 2 events) in 1 participant in the brepocitinib 60 mg once daily group (onset on day 176) and viral pneumonia in 1 participant in the brepocitinib 30 mg once daily group (onset on day 287). There were 4 participants who developed the following serious

Table 3. All-causality TEAEs and AEs of special interest up to week 16, and through week 52*

	Week 0–16 (initial dose)					Week 0–52	
		Brepocitinib				Brepocitinib	
	Placebo (N = 67)	10 mg QD (N = 31)	30 mg QD (N = 60)	60 mg QD (N = 60)	Total (N = 151)	30 mg QD (N = 108)	60 mg QD (N = 110)
Number of TEAEs	61	24	68	104	196	206	263
Number of treatment-related TEAEs	11	8	19	27	54	42	66
Number (%) of participants							
Any TEAEs	32 (47.8)	14 (45.2)	33 (55.0)	40 (66.7)	87 (57.6)	80 (74.1)	80 (72.7)
Treatment-related TEAEs	9 (13.4)	6 (19.4)	12 (20.0)	15 (25.0)	33 (21.9)	27(25.0)	34 (30.9)
SAEs	1 (1.5)	0 (0.0)	3 (5.0)	1 (1.7)	4 (2.6)	10 (9.3)	2 (1.8)
Severe AEs	1 (1.5)	0 (0.0)	2 (3.3)	1 (1.7)	3 (2.0)	8 (7.4)	2 (1.8)
TEAEs leading to discontinuation of study drug	3 (4.5)	0 (0.0)	2 (3.3)	3 (5.0)	5 (3.3)	9 (8.3)	14 (12.7)
Infections and infestations (SOC)	16 (23.9)	9 (29.0)	21 (35.0)	21 (35.0)	51 (33.8)	54 (50.0)	44 (40.0)
COVID-19 infection	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (4.6)	4 (3.6)
Serious infection	0 (0.0)	0 (0.0)	2 (3.3)	0 (0.0)	2 (1.3)	5 (4.6)	1 (0.9)
Herpes zoster/varicella	0 (0.0)	1 (3.2)	1 (1.7)	0 (0.0)	2 (1.3)	2 (1.9)	2 (1.8)
Active tuberculosis	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms, benign, malignant, and unspecified (SOC)	0 (0.0)	0 (0.0)	0 (0.0)	2 (3.3)	2 (1.3)	1 (0.9)	2 (1.8)
MACEs including DVT and PE	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrointestinal perforation	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Death	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

* Week 0–52 data are cumulative, including all data collected since the first dose of study drug. TEAE = treatment-emergent adverse event; AE = adverse event; QD = once daily; SAE = serious adverse event; SOC = system organ class; MACE = major adverse cardiovascular event; DVT = deep vein thrombosis; PE = pulmonary embolism.

infections between weeks 16 and 52: viral pneumonia, pneumonia, varicella (1 participant each in the brepocitinib 30 mg once daily group), and COVID-19 pneumonia (1 participant in the brepocitinib 60 mg once daily group).

Over the 52-week study period, herpes zoster/varicella occurred in 4 participants (2 participants treated with brepocitinib 30 mg once daily and 2 with brepocitinib 60 mg once daily). Neoplasm TEAEs included anogenital warts (1 participant in the brepocitinib 30 mg once daily group), basal cell carcinoma (1 participant in the brepocitinib 60 mg once daily group), and uterine leiomyoma (1 participant in the brepocitinib 60 mg once daily group). Neoplasm AEs were not considered to be treatment related by the investigator.

A total of 9 participants were diagnosed as having COVID-19 during the 52-week study period (Table 3). The incidence was generally similar across treatment groups. Seven participants had mild-to-moderate COVID-19 and 1 participant treated with brepocitinib 30 mg once daily was discontinued from the study. COVID-19 pneumonia was reported in 2 participants treated with brepocitinib 60 mg once daily, both of whom were discontinued from the study. All participants with COVID-19 recovered.

There were no major adverse cardiovascular events (MACEs), embolic or thrombotic events, cases of tuberculosis, or deaths during the study.

DISCUSSION

This dose-ranging phase II study investigated the effect of brepocitinib on participants with active PsA with regards to disease activity, physical functioning, and safety. Compared with placebo, treatment with brepocitinib 30 or 60 mg once daily was significantly more effective at reducing the signs and symptoms of PsA and improving function and HRQoL at 16 weeks, including significant improvements in the primary endpoint of ACR20 response rate. Measurable improvements in disease activity were seen in the brepocitinib 30 and 60 mg groups as early as week 4 (data not shown). Brepocitinib significantly improved peripheral arthritis, enthesitis, and psoriasis, and also improved overall PsA disease control (as measured by PASDAS and fulfillment of MDA response criteria). Beneficial effects on the patient-reported outcomes of physical functioning, fatigue, and pain were also noted, with significant improvements in HAQ DI, Patient's Assessment of Arthritis Pain, and SF-36 PCS at week 16, compared with participants receiving placebo.

Efficacy outcomes were generally dose-dependent up to week 16, particularly in dermatologic outcomes, as measured by PASI responses. When participants advanced to either brepocitinib 30 or 60 mg once daily after the 16-week placebo-controlled period, efficacy outcomes generally continued to improve to week 52, but the dose-dependence observed up to week 16 was not evident at week 52, possibly due to a ceiling effect or participant withdrawals at the higher 60 mg once daily dose level. Placebo response was high for the primary endpoint, with 43.3% of participants achieving an ACR20 response versus the assumption of a 25% placebo response, which formed the basis of the sample size calculation. However, a consistent response was generally observed across primary and secondary endpoints at week 16, with statistically significant differences in ACR20, PASI75, ACR50, PASI90, and HAQ DI in the brepocitinib 30 and 60 mg once daily groups versus placebo, suggesting that the study was sufficiently powered and that the high placebo response did not meaningfully affect the statistical analysis.

The gene that encodes TYK2 is a psoriasis susceptibility gene (31), making TYK2 a prime target in the treatment of rheumatic skin diseases. TYK2 signaling is required for the key proinflammatory cytokines IL-12 and IL-23, which influence Th1 and Th17 cell activation, respectively. Th17 cell activation in turn drives pathologic inflammation in autoimmune diseases, most notably in psoriasis and spondyloarthritis (32). In a previous phase II study of brepocitinib in participants with plaque psoriasis, high proportions of participants achieved PASI75 and PASI90 responses over 12 weeks of treatment (86.2% and 51.7%, respectively), with the highest dose in that study being 30 mg once daily for 12 weeks (19). These results are generally consistent with those observed for the brepocitinib 60 mg once daily group after 16 weeks of treatment in the current study, providing added support for the beneficial effects of brepocitinib on psoriasis. Notably, in the current study, the effects of the lower 30 mg brepocitinib dose matched those of the higher dose over the course of 52 weeks, including in the skin, but also for musculoskeletal disease, enthesitis, and dactylitis.

JAK1 inhibition by brepocitinib attenuates signaling by a number of cytokines, including IL-6, which plays a role in Th22 cell activation in the inflammation of the synovium (33–35). However, with inhibition of TYK2, greater blockade of IL-12 signaling and of IL-23 signaling leads to a reduction in IL-17 (35), a major effector cytokine with effects on multiple cell types driving the pathogenesis of psoriatic disease (18). Therefore, the paired TYK2 and JAK1 inhibitory capacity of brepocitinib may offer an advantage over other JAKis, increasing the likelihood of improvements across the dermatologic, musculoskeletal, and axial components of PsA. Although no direct comparisons can be made with studies of other JAKis, the efficacy of brepocitinib in terms of ACR20 (6,7) and ACR and PASI (9) responses at week 16 was similar to that of approved JAKis. However, further confirmatory data and head-to-head studies are required.

Consistent with findings from previous studies in patients with alopecia areata (21) and plaque psoriasis (19), brepocitinib was generally well tolerated at all doses. The 60 mg once daily group experienced the most AEs and study discontinuations during the extension period, but the majority of AEs were mild or moderate in severity. The overall 52-week safety profile of brepocitinib was consistent with that previously observed with brepocitinib in other clinical trials (19,21,36), and was consistent

with that of approved JAKis (6–9,37), with a small number of participants in the brepocitinib 30 and 60 mg once daily groups who developed serious infections, including herpes zoster/varicella. A higher risk of interferon-mediated infections is a known concern with JAKis due to the suppression of the interferon-mediated pathways required for immunity to viruses (17,38). However, there did not appear to be any dose-related increases in serious infections in the current study. Similarly, among a total of 9 participants diagnosed with COVID-19 during the study, incidence was similar across treatment groups.

In addition to warnings around serious infections for all approved JAKis (39–41), the Food and Drug Administration recently issued new and updated warnings around malignancy, thrombosis (39–41), and MACEs including death (39), based on a post-approval safety study with tofacitinib in patients with rheumatoid arthritis at elevated risk for cardiovascular events (42). Although studies are still ongoing to fully elucidate the potential association between currently approved JAKis and MACEs, malignancy, and venous thromboembolism, the current study of brepocitinib in participants with active PsA and the previous phase II study in plaque psoriasis (19) reported no instances of MACEs or embolic or thrombotic events after 52 and 12 weeks of treatment, respectively. Neoplasms were reported for 3 participants over 52 weeks in the current study. However, none were considered to be treatment related. No new safety signals emerged over this 1-year study that included daily doses of brepocitinib at 60 mg. The laboratory abnormalities in ALT/AST, creatine kinase, and hemoglobin observed with brepocitinib are generally consistent with changes seen within the JAKi class (6–9) and, based on studies so far, the additional TYK2 inhibition has not demonstrated additional safety concerns. However, longer durations of placebo control and larger confirmatory studies are needed.

This study has some limitations, including the restricted geographic location and the predominantly White analysis population. There was a relatively large placebo effect in some endpoints, as has been seen in more recent studies in participants with PsA (43). However, the consistent response noted across the primary and secondary endpoints at week 16 suggests that high placebo response did not meaningfully affect the statistical analysis. Further limitations include the lack of an extended placebo-controlled period past 16 weeks, which may have hindered interpretation of safety signals during the extension period, and the small sample size and relatively limited treatment duration that may have limited the detection of rare safety events.

This study also had numerous strengths, including a robust hierarchical statistical testing method, which could control for the overall Type I error rate for prespecified endpoints. The significance level used in the current study ($P < 0.1$ by 2-sided test) was not as stringent as in registrational phase III trials but was appropriate for phase II dose-ranging proof-of-concept trials.

In conclusion, TYK2/JAK1 inhibition with brepocitinib treatment at 30 and 60 mg once daily significantly improved the signs and symptoms of PsA. These clinical benefits across multiple domains of PsA disease activity were observed over 16 weeks, with sustained or further improvements in disease measures out to week 52. Overall, the safety profile of brepocitinib was consistent with that previously observed in other clinical trials of brepocitinib and with that of approved JAKis, and no new safety signals were identified.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Martin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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