

Bimekizumab treatment in biologic DMARD-naïve patients with active psoriatic arthritis: 52-week efficacy and safety results from the phase 3, randomised, placebo-controlled, active reference BE OPTIMAL study

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1 **ABSTRACT** (250/250)

2 **Objectives**

3 Bimekizumab (BKZ) is a monoclonal IgG1 antibody that selectively inhibits interleukin
4 (IL)-17F in addition to IL-17A. BKZ treatment has demonstrated superior efficacy
5 versus placebo (PBO) at Week 16 in biologic disease-modifying antirheumatic drug
6 (DMARD)-naïve patients with active psoriatic arthritis (PsA). Here, we report
7 longer-term efficacy and safety to Week 52.

8 **Methods**

9 BE OPTIMAL (NCT03895203) comprised a 16-week, double-blind, placebo-controlled
10 period, then 36 weeks treatment-blind. Patients were randomised 3:2:1 to
11 subcutaneous BKZ 160 mg every 4 weeks (Q4W), PBO with switch to BKZ at Week
12 16, or reference arm (adalimumab [ADA] 40 mg Q2W). Efficacy outcomes included
13 the American College of Rheumatology (ACR) response criteria 20/50/70, Psoriasis
14 Area and Severity Index (PASI) 75/90/100 in patients with baseline psoriasis
15 affecting $\geq 3\%$ body surface area, and minimal disease activity (MDA);
16 non-responder imputation.

17 **Results**

18 ACR20/50/70, PASI75/90/100 and MDA responses were sustained with BKZ to Week
19 52, consistent with results observed at Week 16. Patients who switched to BKZ at
20 Week 16 demonstrated improvements in efficacy with similar results to
21 BKZ-randomised patients by Week 52.

22 To Week 52, 555/702 (79.1%) patients had ≥ 1 treatment-emergent adverse event
23 (TEAE) during BKZ treatment; 113/140 (80.7%) on ADA. On BKZ, 46 (6.6%) patients
24 had serious TEAEs and 1 death (0.1%) occurred. 54 (7.7%) *Candida* infections
25 occurred during BKZ treatment and 1 (0.7%) during ADA; all cases were localised
26 and non-serious.

27 **Conclusions**

28 The efficacy of bimekizumab in bDMARD-naïve patients with PsA was sustained from
29 Week 16 to Week 52. BKZ was well tolerated with no new safety signals observed.

1 KEY MESSAGES

- 2 • **What is already known on this topic** – *summarise the state of scientific*
3 *knowledge on this subject before you did your study and why this study*
4 *needed to be done*

5 Psoriatic arthritis (PsA) is a chronic, inflammatory disease that is associated
6 with clinical manifestations across joint and skin domains that can negatively
7 impact quality of life. Bimekizumab (BKZ) is a monoclonal IgG1 antibody that
8 selectively inhibits interleukin (IL)-17F in addition to IL-17A. Primary results
9 from two phase 3 studies of BKZ treatment in patients with PsA who were
10 biologic disease-modifying antirheumatic drug-naïve (bDMARD; BE OPTIMAL)
11 or who had a previous inadequate response or intolerance to tumour necrosis
12 factor- α inhibitors (BE COMPLETE) demonstrated a similar magnitude of
13 response in both patient populations at Week 16. PsA is a chronic, long-term
14 disease, therefore it is important to assess the longer-term efficacy and
15 safety of new treatment options for PsA.

- 16 • **What this study adds** – *summarise what we now know as a result of this*
17 *study that we did not know before*

18 The 52-week randomised controlled trial BE OPTIMAL assessed the long-term
19 efficacy of BKZ across joint, skin, enthesitis, dactylitis and radiographic
20 outcomes. Improvements in joint, skin clearance and composite outcomes
21 observed at Week 16 were sustained to Week 52 in patients initially
22 randomised to BKZ, with over half of BKZ-treated patients achieving ACR50,
23 PASI100 or MDA by Week 52. For patients who switched from placebo to BKZ
24 at Week 16, improvements in efficacy were similar to those initially
25 randomised to BKZ across joint and skin outcomes at Week 52. The overall
26 safety profile was consistent with the known safety of BKZ, including higher
27 rates of mucocutaneous *Candida* infections when compared with adalimumab
28 (ADA).

- 1 • **How this study might affect research, practice or policy** – *summarise*
2 *the implications of this study*

3 Results to Week 52 from BE OPTIMAL suggest that BKZ is an effective
4 longer-term treatment option in bDMARD-naïve patients with active PsA. Data
5 from the ongoing open-label extension, BE VITAL, will assess the safety and
6 efficacy of BKZ treatment to three years.

1 INTRODUCTION

2 Psoriatic arthritis (PsA) is a chronic, inflammatory disease that develops in up to 30%
3 of patients with psoriasis, and is associated with a diverse range of clinical features
4 that result in a significant patient burden and reduced quality of life.(1-5)

5 Interleukins (IL)-17A and IL-17F have been identified as independent pivotal drivers
6 of joint and skin inflammation in PsA.(1, 2) IL-17A inhibitors, such as secukinumab
7 and ixekizumab, are currently available and are established therapies shown to be
8 effective treatment options for patients with PsA.(6, 7) However, inhibition of both
9 IL-17A and IL-17F could be a more effective treatment strategy, as *in vitro*, dual
10 neutralisation of IL-17A and IL-17F is more effective in reducing inflammation than
11 neutralising IL-17A alone.(8) Bimekizumab (BKZ) is a humanised monoclonal
12 immunoglobulin (Ig)G1 antibody that selectively inhibits IL-17F in addition to
13 IL-17A.(9) The benefits of dual neutralisation were demonstrated clinically in a phase
14 3b clinical trial in psoriasis, where skin clearance was significantly higher with BKZ
15 when compared with secukinumab.(6) This strategy may also achieve greater
16 disease control and alleviation of symptoms of inflammatory diseases like PsA, in
17 which both IL-17A and IL-17F are implicated as major effector cytokines.(8)

18 The efficacy and safety of BKZ was previously reported up to two years in multiple
19 phase 3 studies in patients with plaque psoriasis,(6, 10-12) and in patients with PsA
20 to Week 24 and Week 16 in two phase 3 studies: BE OPTIMAL and BE COMPLETE,
21 respectively.(13), (14) BE OPTIMAL included patients with active PsA who were
22 biologic disease-modifying antirheumatic drug (bDMARD)-naïve; BE COMPLETE
23 included patients with active PsA who had previous inadequate response or
24 intolerance to tumour necrosis factor- α inhibitors (TNFi-IR). BE OPTIMAL also
25 included an adalimumab (ADA) reference arm. BKZ demonstrated clinically
26 meaningful improvements across joint, skin clearance, composite and
27 patient-reported outcomes in the respective populations to Week 16 in both studies.
28 BKZ also demonstrated inhibition of structural progression to Week 16 in BE
29 OPTIMAL.(13) Safety results were similar to those reported in previous studies of
30 BKZ in psoriasis.(6, 10, 11)

31 PsA is a chronic, long-term disease,(15, 16) therefore treatment options that provide
32 inflammation control and long-term, durable efficacy and tolerability are needed.
33 Treatment should aim to achieve the lowest possible level of disease activity across
34 domains,(4) assessed using more stringent disease measures such as American

1 College of Rheumatology response criteria (ACR) 50% improvement, Psoriasis Area
2 and Severity Index (PASI) 100% improvement and minimal disease activity (MDA).
3 Data from BE OPTIMAL to Week 24 were reported in the primary manuscript.(13)
4 Here, we report the longer-term clinical efficacy and safety of subcutaneous BKZ 160
5 mg every four weeks (Q4W) in adult, bDMARD-naïve patients with active PsA to 52
6 weeks: the final results of the phase 3 BE OPTIMAL study.

7 **METHODS**

8 **Study design and participants**

9 Complete methods details are reported in the primary manuscript.(13) In brief, BE
10 OPTIMAL (NCT03895203; ClinicalTrials.gov) was a 52-week, phase 3, multicentre,
11 randomised, double-blind, placebo (PBO)-controlled, active reference (ADA) study.
12 The study was conducted in Asia, Eastern Europe, Western Europe and North
13 America, and consisted of a 2–5-week screening period, a 16-week PBO-controlled,
14 double-blind treatment period and a 36-week active treatment-blind period. BE
15 OPTIMAL included an active reference (ADA) arm to provide a reference for the
16 benefit-risk profile of BKZ alongside a standard-of-care treatment. This arm was not
17 powered for statistical comparison to BKZ or PBO.

18 Patients completing Week 52 and meeting eligibility criteria were eligible for
19 enrolment in the ongoing open-label extension (OLE) study BE VITAL
20 (NCT04009499; ClinicalTrials.gov). A safety follow-up was conducted 20 weeks after
21 the last dose of BKZ for patients not entering the OLE, or who discontinued early
22 **(Supplementary Figure 1).**

23 **Patients**

24 Full inclusion and exclusion criteria were reported previously.(13) In brief, eligible
25 patients were ≥ 18 years and had a documented diagnosis of adult-onset PsA
26 meeting the Classification Criteria for Psoriatic Arthritis for ≥ 6 months prior to
27 screening. Patients had active PsA with a tender joint count (TJC) ≥ 3 (of 68),
28 swollen joint count (SJC) ≥ 3 (of 66) and ≥ 1 active psoriatic lesion and/or a
29 documented psoriasis history. Patients with current or prior exposure to any biologics
30 for the treatment of PsA or psoriasis were excluded.

31 The study was conducted in accordance with the Declaration of Helsinki and the
32 International Conference on Harmonisation guidance for Good Clinical Practice.
33 Ethical approval was obtained from the relevant institutional review boards at

1 participating sites, and all patients provided written informed consent in accordance
2 with local requirements.

3 **Randomisation and masking**

4 Patients were randomised 3:2:1 to receive subcutaneous BKZ 160 mg Q4W,
5 subcutaneous PBO every 2 weeks (Q2W), or the reference (subcutaneous ADA
6 40 mg Q2W). At Week 16, patients initially randomised to PBO were reallocated to
7 receive subcutaneous BKZ 160 mg Q4W through to Week 52 (PBO/BKZ); patients
8 initially randomised to BKZ or ADA continued their dosing to Week 52. Due to the
9 different dosing schedules, BKZ-treated patients received PBO between BKZ doses to
10 match the reference arm dosing schedule (double-dummy) and maintain treatment
11 blinding up to Week 52.

12 **Study procedures**

13 Study visits occurred every 2 weeks. Efficacy was assessed at baseline and Weeks 2,
14 4, 8, 12, 16, 20, 24, 36 and 52. Safety was assessed at baseline and each study visit
15 thereafter. Structural damage progression in the hands and feet was assessed on
16 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
18 radiographs were taken at screening, Week 16 and Week 52. These were read
19 centrally and independently by two experienced readers, who were blind to the
20 treatment assignment and time course of the films.

21 From Week 16 onwards, non-responder patients as per investigator assessment were
22 eligible for rescue therapy with prespecified background medications. Patients
23 requiring rescue therapy continued their assigned treatment. Further details in the
24 primary manuscript.(13)

25 **Outcomes**

26 Clinical efficacy outcomes assessed through Week 52 included ACR response criteria
27 20/50/70, PASI 75/90/100 (in patients with psoriasis affecting $\geq 3\%$ body surface
28 area [BSA] at baseline), MDA and very low disease activity (VLDA; achieved if 5/7 or
29 7/7 of the following criteria were fulfilled, respectively: tender joint count ≤ 1 ,
30 swollen joint count ≤ 1 , BSA $\leq 3\%$, patients' pain VAS ≤ 15 , patient's global
31 assessment of arthritis visual analogue scale [VAS] ≤ 20 , Health Assessment
32 Questionnaire-Disability Index [HAQ-DI] ≤ 0.5 , tender entheseal points ≤ 1),
33 ACR50+PASI100 (in patients with psoriasis affecting $\geq 3\%$ BSA at baseline),

1 radiographic endpoints (vdHmTSS, bone erosion, joint space narrowing and
2 proportion of patients with no radiographic inhibition [vdHmTSS change from
3 baseline (CfB) ≤ 0.5]; radiographic set), enthesitis (in patients with enthesitis at
4 baseline using the Leeds Enthesitis Index [LEI]), dactylitis (in patients with dactylitis
5 at baseline using the Leeds Dactylitis Index [LDI]), the modified Nail Psoriasis
6 Severity Index (mNAPSI; in patients with psoriatic nail disease at baseline; one
7 target nail was selected at baseline) and the Bath Ankylosing Spondylitis Disease
8 Activity Index (BASDAI; in patients with axial involvement [score ≥ 4] at baseline).
9 Patient-reported outcome measures reported include the Health Assessment
10 Questionnaire-Disability Index (HAQ-DI), Short Form 36-item health survey Physical
11 Component Summary (SF-36 PCS), Psoriatic Arthritic Impact of Disease-12 item
12 questionnaire (PsAID-12), Functional Assessment of Chronic Illness Therapy (FACIT)
13 Fatigue, and Patient Assessment of Arthritis Pain (PtAAP).

14 Safety is reported through Week 52, including incidence of treatment-emergent
15 adverse events (TEAEs), treatment-emergent serious adverse events (SAEs) and
16 TEAEs leading to study withdrawal. Where applicable, the exposure-adjusted
17 incidence rate (EAIR) per 100 patient-years (PY) is reported.

18 Prespecified safety topics of interest included infections (serious, opportunistic,
19 fungal and tuberculosis [TB]), neutropenia, hypersensitivity, suicidal ideation and
20 behaviour (SIB), major adverse cardiovascular events (MACE), liver function test
21 changes/enzyme elevations, malignancies and inflammatory bowel diseases (IBD).
22 SIB, MACE and IBD events were adjudicated by external adjudication committees. An
23 independent data monitoring committee periodically reviewed the safety data
24 collected during the study.

25 **Statistical analysis**

26 Statistical powering and sample size determination are reported in the BE OPTIMAL
27 primary manuscript.(13) The study was powered to show the statistical superiority of
28 BKZ compared with PBO for the primary endpoint of ACR50 at Week 16. The study
29 was not powered for statistical comparisons of ADA to BKZ or PBO. No statistical
30 comparisons were made between ADA and BKZ or PBO.

31 Missing data for binary endpoints were imputed using non-responder imputation
32 (NRI). P values for these endpoints were determined using logistic regression
33 adjusted for treatment, region and bone erosion at baseline (0 or ≥ 1). Observed

case data also reported for binary endpoints. Continuous outcomes are reported using multiple imputation (MI) for missing data. Bone erosion stratification for statistical analyses was based on actual erosion at baseline (assessed using centrally read radiographs, for which readings were more precise than the randomisation stratum for bone erosion). All analyses were done with SAS, Version 9.3 or higher.

RESULTS

Patient disposition and baseline characteristics

1158 patients were screened; of the 852 randomised patients, 770 (90.4%) completed Week 52 (**Figure 1**). Overall, 257/281 (91.5%) PBO/BKZ-treated patients, 388/431 (90.0%) BKZ-treated patients and 125/140 (89.3%) patients in the ADA group completed Week 52. 257 (94.8%) of the 271 patients who switched to BKZ from PBO at Week 16 completed Week 52. As per the protocol, patients withdrawn from study treatment could return for all remaining study visits; of the patients that remained in the study at Week 52, 9 (1.1%) were not on randomised treatment (2 [0.7%] PBO/BKZ-treated patients; 5 [1.2%] BKZ-treated patients; 2 [1.4%] patients in the ADA group).

The most common reasons for discontinuation in the active treatment-blind period were adverse events (PBO/BKZ: 6 [2.2%]; BKZ: 9 [2.2%]; ADA: 4 [2.9%]), withdrawal of consent (PBO/BKZ: 4 [1.5%]; BKZ: 9 [2.2%]; ADA: 2 [1.5%]) and lack of efficacy (PBO/BKZ: 1 [0.4%]; BKZ: 6 [1.4%]; ADA: 4 [2.9%]).

Important protocol deviations were reported for 29 (3.5%) patients from Week 16–52. No patients were excluded from the pharmacokinetic per protocol set. Important protocol deviations for the double-blind treatment period can be found in the BE OPTIMAL primary manuscript;(13) important protocol deviations for the active treatment-blind period are reported in **Supplementary Table 1**.

As previously reported, baseline patient demographics and disease characteristics were comparable between treatment groups (**Table 1**).⁽¹³⁾

1 **Table 1. Patient demographics and baseline disease characteristics**

	PBO N=281	BKZ 160 mg Q4W N=431	Reference arm (ADA 40 mg Q2W) N=140
Age, years, mean (SD)	48.7 (11.7)	48.5 (12.6)	49.0 (12.8)
Male, n (%)	127 (45.2)	201 (46.6)	71 (50.7)
BMI, kg/m ² , mean (SD)	29.6 (6.1)	29.2 (6.8)	28.4 (5.9)
Race, white, ^a n (%)	270 (96.1)	410 (95.1)	133 (95.0)
Time since PsA diagnosis, years, mean (SD)	5.6 (6.5)	6.0 (7.3)	6.1 (6.8)
cDMARDs at baseline, n (%)	194 (69.0)	301 (69.8)	99 (70.7)
Use of MTX at baseline, n (%)	163 (58.0)	252 (58.5)	82 (58.6)
BSA affected by PSO ≥3%, n (%)	140 (49.8)	217 (50.3)	68 (48.6)
PASI, ^b mean (SD)	7.9 (5.6)	8.2 (6.8)	8.6 (7.6)
TJC (of 68 joints), mean (SD)	17.1 (12.5)	16.8 (11.8)	17.5 (13.1)
SJC (of 66 joints), mean (SD)	9.5 (7.3)	9.0 (6.2)	9.7 (7.1)
Presence of enthesitis (LEI), ^{c,d} n (%)	70 (24.9)	143 (33.2)	36 (25.7)
Score, ^{d,e} mean (SD)	2.9 (1.5)	2.5 (1.5)	2.3 (1.6)
Presence of enthesitis (SPARCC), ^{d,f} n (%)	90 (32.0)	166 (38.5)	44 (31.4)
Score, ^{d,e} mean (SD)	4.7 (3.8)	4.6 (3.8)	4.4 (3.9)
Presence of dactylitis, ^{g,h} n (%)	33 (11.7)	56 (13.0)	11 (7.9)
Score, ^{h,i} mean (SD)	47.3 (41.1)	46.7 (54.3)	49.7 (31.9)
Nail psoriasis, ^{j,k} n (%)	156 (55.5)	244 (56.6)	75 (53.6)
Score, ^{k,l} mean (SD)	4.0 (2.1)	4.1 (2.5)	3.7 (2.3)
HAQ-DI score, ^m mean (SD)	0.89 (0.61)	0.82 (0.59)	0.86 (0.54)
hs-CRP ≥6 mg/L, n (%)	121 (43.1)	158 (36.7)	44 (31.4)
BASDAI score ≥4, ⁿ n (%)	213 (75.8)	311 (72.2)	107 (76.4)
PtAAP, ^m mean (SD)	56.8 (23.2)	53.6 (24.3)	56.7 (23.9)
Patient's global assessment score, ^m mean (SD)	58.6 (23.5)	54.4 (23.4)	57.1 (21.8)
Physician's global assessment score, ⁿ mean (SD)	57.2 (15.1)	57.2 (16.3)	57.3 (17.5)
SF-36 PCS score, mean (SD)	36.9 (0.6)	38.1 (0.5)	37.6 (0.7)
PsAID-12 score, mean (SE)	4.1 (0.1)	4.0 (0.1)	4.3 (0.2)
FACIT-Fatigue score, mean (SE)	36.0 (0.6)	37.7 (0.5)	36.4 (0.8)
Bone erosion ≥1 and/or high sensitivity CRP ≥6 mg/L, n (%)	236 (84.0)	365 (84.7)	116 (82.9)
vdHmTSS score, ^o mean (SD)	12.3 (22.5)	12.5 (30.0)	13.8 (26.5)
vdHmTSS score in at-risk set, ^p mean (SD)	14.5 (23.9)	14.4 (32.0)	16.5 (28.4)

2 The adalimumab 40 mg Q2W treatment arm served as an active reference. The study was not powered
3 for statistical comparisons of adalimumab to bimekizumab or placebo. [a] Race was reported by the
4 patient. Missing for patients enrolled in France (Data missing for 1 patient receiving BKZ and 2 patients
5 receiving ADA). PBO: 270; BKZ: 410; ADA: 133); [b] In patients with psoriasis affecting ≥3% BSA at
6 baseline; PBO/BKZ: n=140; BKZ: n=217; ADA: n=68; [c] LEI >0; [d] Data missing for 6 patients
7 receiving BKZ and 1 patient receiving ADA; [e] in patients with enthesitis at baseline; [f] SPARCC >0;
8 [g] LDI >0; [h] Data missing for 1 patient receiving PBO, 7 patients receiving BKZ and 1 patient
9 receiving ADA; [i] In patients with dactylitis at baseline; [j] mNAPSI >0; [k] Data missing for 7 patients
10 receiving BKZ; [l] In patients with nail psoriasis at baseline; [m] Data missing for 1 patient receiving
11 BKZ; [n] Data missing for 1 patient receiving PBO, 5 patients receiving BKZ and 1 patient receiving
12 ADA; [o] Radiographic set (patients with valid radiographs of hands and feet at baseline, as assessed by
13 ≥2 reviewers); PBO: n=269; BKZ: n=420; ADA: n=135; [p] At-risk subgroup defined as patients with

1 elevated hs-CRP and/or with at least one bone erosion at baseline; PBO: n=227; BKZ: n=361;
 2 ADA: n=112. ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index;
 3 BKZ: bimekizumab; BMI: body mass index; BSA: body surface area; cDMARD: conventional
 4 disease-modifying antirheumatic drugs; CRP: C-reactive protein; FACIT-Fatigue: Functional Assessment
 5 of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index;
 6 hs-CRP: high sensitivity C-reactive protein; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index;
 7 mNAPSI: modified Nail Psoriasis Severity Index; MTX: methotrexate; PASI: Psoriasis Area and Severity
 8 Index; PBO: placebo; PCS: Physical Component Summary; PsAID-12: Psoriatic Arthritic Impact of
 9 Disease-12; PSO: psoriasis; PtAAP: Patient's Assessment of Arthritis Pain; Q2W: every two weeks;
 10 Q4W: every four weeks; SD: standard deviation; SE: standard error; SF-36: Short-Form 36-item Health
 11 Survey; SJC: swollen joint count; SPARCC: Spondyloarthritis Research Consortium of Canada;
 12 TJC: tender joint count; vdHmTSS: van der Heijde modified Total Sharp Score.

13

1 **Efficacy**

2 The percentage of patients achieving ACR50 was sustained from Week 16 to Week
3 52 in patients receiving BKZ. At Week 16, 28/281 (10.0%), 189/431 (43.9%) and
4 64/140 (45.7%) patients treated with PBO, BKZ and ADA, respectively, achieved
5 ACR50 (NRI; **Table 2; Figure 2C**). At Week 52, approximately half of patients
6 continuing active treatment achieved ACR50 (BKZ: 235 [54.5%]; ADA: 70 [50.0%]).
7 In patients who switched from PBO to BKZ at Week 16, a similar proportion of
8 patients achieved ACR50 at Week 52 (149 [53.0%]; **Figure 2C**) compared to
9 patients initially randomised to BKZ.

1 **Table 2. Efficacy endpoints at Week 16 and Week 52**

Endpoint	PBO (Weeks 0–16) → N=281	BKZ 160 mg Q4W (Weeks 16–52) N=281	BKZ 160 mg Q4W (Weeks 0–52) N=431		Reference arm (ADA 40 mg Q2W; Weeks 0–52) N=140	
	Week 16	Week 52	Week 16	Week 52	Week 16	Week 52
ACR20 response, n (%)	67 (23.8)	191 (68.0)	268 (62.2)	307 (71.2)	96 (68.6)	102 (72.9)
ACR50 response, ^a n (%)	28 (10.0)	149 (53.0)	189 (43.9)	235 (54.5)	64 (45.7)	70 (50.0)
ACR70 response, n (%)	12 (4.3)	101 (35.9)	105 (24.4)	169 (39.2)	39 (27.9)	53 (37.9)
PASI75 response, ^b n/N (%)	18/140 (12.9)	119/140 (85.0)	168/217 (77.4)	177/217 (81.6)	45/68 (66.2)	45/68 (66.2)
PASI90 response, ^b n/N (%)	4/140 (2.9)	106/140 (75.7)	133/217 (61.3)	155/217 (71.4)	28/68 (41.2)	41/68 (60.3)
PASI100 response, ^b n/N (%)	3/140 (2.1)	91/140 (65.0)	103/217 (47.5)	132/217 (60.8)	14/68 (20.6)	33/68 (48.5)
MDA response, n (%)	37 (13.2)	151 (53.7)	194 (45.0)	237 (55.0)	63 (45.0)	74 (52.9)
VLDA response, n (%)	3 (1.1)	62 (22.1)	63 (14.6)	125 (29.0)	22 (15.7)	39 (27.9)
ACR50+PASI100 response, ^b n/N (%)	0/140 (0)	65/140 (46.4)	60/217 (27.6)	102/217 (47.0)	11/68 (16.2)	24/68 (35.3)
PASDAS category, ^c n (%)						
REM	6 (2.1)	64 (22.8)	85 (19.7)	109 (25.3)	27 (19.3)	37 (26.4)
REM+LDA	44 (15.7)	140 (49.8)	212 (49.2)	205 (47.6)	66 (47.1)	67 (47.9)
DAPSA state, ^d n (%)						
REM	4 (1.4)	46 (16.4)	47 (10.9)	100 (23.2)	27 (19.3)	41 (29.3)
REM+LDA	39 (13.9)	155 (55.2)	205 (47.6)	246 (57.1)	72 (51.4)	74 (52.9)

Endpoint	PBO (Weeks 0–16) → N=281	BKZ 160 mg Q4W (Weeks 16–52) N=281	BKZ 160 mg Q4W (Weeks 0–52) N=431		Reference arm (ADA 40 mg Q2W; Weeks 0–52) N=140	
	Week 16	Week 52	Week 16	Week 52	Week 16	Week 52
Change from baseline in vdHmTSS, ^e mean (SE)	0.25 (0.07)	0.17 (0.11)	0.03 (0.04)	0.10 (0.07)	−0.09 (0.08)	−0.12 (0.12)
Change from baseline in vdHmTSS (at-risk), ^f mean (SE)	0.29 (0.09)	0.19 (0.13)	0.03 (0.05)	0.10 (0.08)	−0.14 (0.10)	−0.17 (0.13)
Change from baseline in bone erosion subscore, ^e mean (SE)	0.16 (0.05)	0.06 (0.08)	0.02 (0.03)	0.06 (0.05)	−0.05 (0.06)	−0.16 (0.09)
Change from baseline in bone erosion subscore (at-risk), ^f mean (SE)	0.18 (0.06)	0.06 (0.10)	0.02 (0.04)	0.06 (0.06)	−0.07 (0.07)	−0.21 (0.10)
Change from baseline in joint space narrowing subscore, ^e mean (SE)	0.06 (0.03)	0.06 (0.04)	0.01 (0.02)	0.04 (0.03)	−0.03 (0.05)	0.04 (0.05)
Change from baseline in joint space narrowing subscore (at-risk), ^f mean (SE)	0.07 (0.03)	0.08 (0.05)	0.02 (0.02)	0.05 (0.03)	−0.06 (0.06)	0.03 (0.06)
Complete resolution of enthesitis (LEI), ^g n/N (%)	29/70 (41.4)	44/70 (62.9)	72/143 (50.3)	87/143 (60.8)	18/36 (50.0)	21/36 (58.3)
Complete resolution of enthesitis (SPARCC), ^h n/N (%)	32/90 (35.6)	55/90 (61.1)	83/166 (50.0)	94/166 (56.6)	23/44 (52.3)	25/44 (56.8)
Complete resolution of dactylitis, ⁱ n/N (%)	18/33 (54.5)	29/33 (87.9)	44/56 (78.6)	45/56 (80.4)	9/11 (81.8)	8/11 (72.7)
mNAPSI resolution, ^j n/N (%)	29/156 (18.6)	111/156 (71.2)	82/244 (33.6)	160/244 (65.6)	28/75 (37.3)	45/75 (60.0)
BASDAI change from baseline, ^k mean (SE)	−1.1 (0.1)	−3.0 (0.2)	−2.6 (0.1)	−3.2 (0.1)	−2.7 (0.2)	−3.1 (0.2)

Endpoint	PBO (Weeks 0–16) N=281	BKZ 160 mg Q4W (Weeks 16–52) N=281	BKZ 160 mg Q4W (Weeks 0–52) N=431		Reference arm (ADA 40 mg Q2W; Weeks 0–52) N=140	
	Week 16	Week 52	Week 16	Week 52	Week 16	Week 52
HAQ-DI MCID response, ¹ n/N (%)	71/221 (32.1)	125/221 (56.6)	161/318 (50.6)	182/318 (57.2)	63/115 (54.8)	68/115 (59.1)
HAQ-DI score change from baseline, mean (SE)	−0.09 (0.03)	−0.38 (0.03)	−0.26 (0.02)	−0.34 (0.02)	−0.33 (0.04)	−0.41 (0.05)
FACIT-Fatigue score change from baseline, mean (SE)	1.5 (0.5)	5.5 (0.5)	3.9 (0.4)	5.3 (0.4)	5.0 (0.7)	5.5 (0.8)
PsAID-12 total score change from baseline, mean (SE)	−0.5 (0.1)	−2.2 (0.1)	−1.8 (0.1)	−2.3 (0.1)	−2.1 (0.2)	−2.5 (0.2)
SF-36 PCS score change from baseline, mean (SE)	2.3 (0.5)	8.4 (0.6)	6.3 (0.4)	8.1 (0.5)	6.8 (0.8)	9.0 (0.9)
PtAAP score change from baseline, mean (SE)	−6.2 (1.5)	−31.8 (1.8)	−23.6 (1.3)	−30.4 (1.4)	−25.7 (2.5)	−32.7 (2.5)

1 Randomised set. Previously reported data through Week 16 included for reference.(13) [a] ACR50 at Week 16 was the primary endpoint; [b] In patients with psoriasis
 2 affecting ≥3% BSA at baseline; [c] Patients achieved REM if PASDAS score was ≤1.9, and REM+LDA if PASDAS score was <3.2; [d] Patients achieved REM if DAPSA score was
 3 ≤4, and REM+LDA if DAPSA score was ≤14; [e] Radiographic set (patients with valid radiographs of hands and feet at baseline, as assessed by ≥2 reviewers); PBO/BKZ:
 4 n=269; BKZ: n=420; ADA: n=135); [f] At-risk subgroup defined as patients with elevated hs-CRP and/or with at least one bone erosion at baseline; PBO/BKZ: n=227; BKZ:
 5 n=361; ADA: n=112; [g] Patients with enthesitis at baseline (LEI >0). Patients achieved complete resolution when LEI=0; [h] Patients with enthesitis at baseline (SPARCC
 6 >0). Patients achieved complete resolution when SPARCC=0; [i] Patients with dactylitis at baseline (LDI >0). Patients achieved complete resolution when LDI=0; [j] Patients
 7 with psoriatic nail disease at baseline (mNAPSI score >0); [k] Patients with axial involvement at baseline (BASDAI ≥4); PBO/BKZ: n=213; BKZ: n=311; ADA: n=107; [l]
 8 Patients who had a HAQ-DI decrease from baseline of ≥0.35 in patients with HAQ-DI ≥0.35 at baseline. ACR 20/50/70: American College of Rheumatology 20%/50%/70%
 9 response criteria; ADA: adalimumab; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; BKZ: bimekizumab; BSA: body surface area; DAPSA: Disease Activity Index
 10 for Psoriatic Arthritis; FACIT-Fatigue: Functional Assessment of Chronic Illness Therapy-Fatigue; HAQ-DI: Health Assessment Questionnaire-Disability Index; hs-CRP: high

1 sensitivity C-reactive protein; LDA: low disease activity; LDI: Leeds Dactylitis Index; LEI: Leeds Enthesitis Index; MCID: meaningful clinically important difference;
2 MDA: minimal disease activity; mNAPSI: modified Nail Psoriasis Severity Index; PASDAS: Psoriatic Arthritis Disease Activity Score; PASI 75/90/100: Psoriasis Area and Severity
3 Index 75%/90%/100% improvement; PBO: placebo; PCS: Physical Component Summary; PsAID-12: Psoriatic Arthritis Impact of Disease 12-item questionnaire;
4 PtAAP: Patients' Assessment of Arthritis Pain; Q2W: every two weeks; Q4W: every four weeks; REM: remission; SE: standard error; SF-36: Short-Form 36-item Health Survey;
5 SPARCC: Spondyloarthritis Research Consortium of Canada; vdHmTSS: van der Heijde modified Total Sharp Score; VLDA: very low disease activity.

6

7

1 ACR20 and ACR70 responses were also sustained to Week 52 in BKZ-treated patients
2 (ACR20: 191 [68.0%] PBO/BKZ, 307 [71.2%] BKZ, 102 [72.9%] ADA; ACR70: 101
3 [35.9%] PBO/BKZ, 169 [39.2%] BKZ, 53 [37.9%] ADA; NRI; **Figure 2A; Figure**
4 **2E**). Observed case data are also shown in **Figure 2**. A consistent trend was seen
5 across the individual components of the ACR response criteria with BKZ treatment
6 (**Supplementary Table 2**).

7 Improvements in skin, including complete clearance, were sustained from Week 16
8 to Week 52 in patients with $\geq 3\%$ BSA affected by psoriasis at baseline. At Week 16,
9 4/140 (2.9%), 133/217 (61.3%) and 28/68 (41.2%) patients treated with PBO, BKZ
10 and ADA, respectively, achieved PASI90. At Week 52, 155 (71.4%) BKZ-treated
11 patients and 41 (60.3%) ADA-treated patients achieved PASI90 at Week 52 (NRI;
12 **Figure 3C; Table 2**). Compared to patients initially randomised to BKZ, a similar
13 proportion of patients who switched from PBO to BKZ at Week 16 achieved PASI90
14 response at Week 52 (106 [75.7%]). At Week 52, 91 (65.0%) PBO/BKZ-treated
15 patients and 132 (60.8%) BKZ-treated patients achieved complete skin clearance
16 (PASI100; NRI; **Figure 3E**). In total, 33 (48.5%) ADA-treated patients achieved
17 PASI100. PASI75 responder rates are shown in **Figure 3A** (NRI). Observed case
18 data are also shown in **Figure 3**.

19 The percentage of patients achieving MDA improved from Week 16 to Week 52 in
20 patients initially randomised to BKZ at baseline. At Week 16, 37 (13.2%), 194
21 (45.0%) and 63 (45.0%) patients treated with PBO, BKZ and ADA, respectively,
22 achieved MDA (NRI; **Table 2**). At Week 52, 237 (55.0%) BKZ-treated patients and
23 74 (52.9%) ADA-treated patients achieved MDA. Compared to patients initially
24 randomised to BKZ, a similar proportion of patients who switched from PBO to BKZ
25 at Week 16 achieved MDA response at Week 52 (151 [53.7%]; NRI; **Figure 4A**).

26 Responder rates were sustained from Week 16 to Week 52 for VLDA (Week 16: 3
27 [1.1%] PBO, 63 [14.6%] BKZ, 22 [15.7%] ADA; Week 52: 62 [22.1%] PBO/BKZ,
28 125 [29.0%] BKZ, 39 [27.9%] ADA; NRI; **Figure 4C**) and ACR50+PASI100 (Week
29 16: 0/140 PBO, 60/217 [27.6%] BKZ and 11/68 [16.2%] ADA; Week 52: 65 [46.4%]
30 PBO/BKZ, 102 [47.0%] BKZ, 24 [35.3%] ADA; NRI; **Figure 4E**). Observed case data
31 are also shown in **Figure 4**.

32 Improvements in enthesitis and dactylitis in patients with enthesitis or dactylitis at
33 baseline were sustained from Week 16 to Week 52 (complete resolution of enthesitis

1 at Week 52 [LEI]: 44/70 [62.9%] PBO/BKZ, 87/143 [60.8%] BKZ, 21/36 [58.3%]
2 ADA; complete resolution of dactylitis at Week 52 [LDI]: 29/33 [87.9%] PBO/BKZ,
3 45/56 [80.4%] BKZ, 8/11 [72.7%] ADA; **Table 2**). The percentage of patients
4 achieving complete resolution of nail psoriasis, as measured by mNAPSI, improved
5 from Week 16 to Week 52 (complete resolution of nail psoriasis at Week 52: 111/156
6 [71.2%] PBO/BKZ, 160/244 [65.6%] BKZ, 45/75 [60.0%] ADA).

7 Radiographic progression in the radiographic set was minimal to Week 16 (mean CfB
8 [SE] in vdHmTSS; 0.25 [0.07] PBO, 0.03 [0.04] BKZ and -0.09 [0.08] ADA) and to
9 Week 52 (0.17 [0.11] PBO/BKZ, 0.10 [0.07] BKZ and -0.12 [0.12] ADA). The
10 majority of patients experienced no radiographic progression to Week 16 (222/250
11 [88.8%] PBO, 356/390 [91.3%] BKZ and 109/116 [94.0%] ADA) or to Week 52
12 (207/237 [87.3%] PBO/BKZ, 326/365 [89.3%] BKZ, 111/118 [94.1%] ADA; OC data;
13 **Supplementary Figure 2A**). Cumulative probability plots of radiographic inhibition
14 for Week 0–16 and Week 0–52 can be found in **Supplementary Figure 2B**. Bone
15 erosion and joint space narrowing sub-scores are reported in **Table 2**.

16 Improvements in patient-reported physical functioning with BKZ were sustained from
17 Week 16 to Week 52 (**Table 2**); mean (SE) HAQ-DI CfB was -0.38 (0.03) for
18 PBO/BKZ, -0.34 (0.02) for BKZ and -0.41 (0.05) for ADA at Week 52.

19 Improvements in pain and fatigue with BKZ treatment were also sustained from
20 Week 16 to Week 52 (mean [SE] PtAAP CfB: -31.8 [1.8] PBO/BKZ, -30.4 [1.4] BKZ,
21 -32.7 [2.5] ADA; mean [SE] FACIT-Fatigue CfB: 5.5 [0.5] PBO/BKZ, 5.3 [0.4] BKZ,
22 5.5 [0.8] ADA; **Table 2**). Similar results showing sustained improvement from Week
23 16 to Week 52 were observed across other health-related quality of life (HRQoL)
24 outcomes such as BASDAI, PsAID-12 and SF-36 PCS (**Table 2**).

25 **Safety**

26 Up to Week 52, 555/702 (79.1%; EAIR/100 PY: 222.5) patients reported ≥1 TEAE
27 whilst receiving BKZ treatment, including patients who switched from PBO to BKZ at
28 Week 16; 113/140 (80.7%; EAIR/100 PY: 209.4) ADA-treated patients reported ≥1
29 TEAE to Week 52. Up to Week 52, 46 (6.6%; EAIR/100 PY: 7.9) patients receiving
30 BKZ treatment and 10 (7.1%; EAIR/100 PY: 7.5) patients receiving ADA treatment
31 reported a SAE. In total, 21 (3.0%; EAIR/100 PY: 3.5) patients receiving BKZ and 7
32 (5.0%; EAIR/100 PY: 5.2) patients receiving ADA discontinued the study. One death
33 occurred, in a BKZ-treated patient, unrelated to treatment (motorcycle accident;
34 **Table 3**). Week 16–52 safety data are reported in **Supplementary Table 4**.

1 **Table 3. Safety data to Week 52**

	Up to Week 16, n (%)			Up to Week 52, n (%) [EAIR/100 PY]	
	PBO N=281 (PYAR: 87.3)	BKZ 160 mg Q4W N=431 (PYAR: 134.2)	Reference Arm (ADA 40 mg Q2W) N=140 (PYAR: 43.4)	BKZ 160 mg Q4W Total N=702 ^a (PYAR: 603.4)	Reference Arm (ADA 40 mg Q2W) N=140 (PYAR: 136.8)
Any TEAE	139 (49.5)	257 (59.6)	83 (59.3)	555 (79.1) [222.5]	113 (80.7) [209.4]
Severe adverse events	0	4 (0.9)	3 (2.1)	23 (3.3)	9 (6.4)
Serious TEAEs	3 (1.1)	8 (1.9)	2 (1.4)	46 (6.6) [7.9]	10 (7.1) [7.5]
Study discontinuation due to adverse event	3 (1.1)	8 (1.9)	3 (2.1)	21 (3.0) [3.5]	7 (5.0) [5.2]
Drug-related adverse event	35 (12.5)	100 (23.2)	34 (24.3)	224 (31.9)	54 (38.6)
Deaths	0	0	0	1 (0.1) ^b	0
Most frequent adverse events ^c					
Nasopharyngitis	13 (4.6)	40 (9.3)	7 (5.0)	84 (12.0) [15.2]	12 (8.6) [9.4]
Upper respiratory tract infection	18 (6.4)	22 (5.1)	3 (2.1)	50 (7.1) [8.7]	8 (5.7) [6.1]
Urinary tract infection	4 (1.4)	9 (2.1)	3 (2.1)	43 (6.1) [7.3]	5 (3.6) [3.7]
Headache	7 (2.5)	19 (4.4)	2 (1.4)	41 (5.8) [7.1]	6 (4.3) [4.5]
Oral candidiasis ^d	0	9 (2.1)	0	38 (5.4) [6.5]	1 (0.7) [0.7]
Diarrhoea	7 (2.5)	16 (3.7)	5 (3.6)	36 (5.1) [6.2]	7 (5.0) [5.3]
Hypertension	11 (3.9)	12 (2.8)	4 (2.9)	29 (4.1) [4.9]	9 (6.4) [6.8]
ALT elevation	2 (0.7)	3 (0.7)	7 (5.0)	16 (2.3) [2.7]	11 (7.9) [8.5]
AST elevation	2 (0.7)	1 (0.2)	4 (2.9)	14 (2.0) [2.3]	7 (5.0) [5.3]
Injection site erythema	0	1 (0.2)	4 (2.9)	6 (0.9) [1.0]	7 (5.0) [5.3]
Uveitis	0	0	0	0	0

	Up to Week 16, n (%)			Up to Week 52, n (%) [EAIR/100 PY]	
	PBO N=281 (PYAR: 87.3)	BKZ 160 mg Q4W N=431 (PYAR: 134.2)	Reference Arm (ADA 40 mg Q2W) N=140 (PYAR: 43.4)	BKZ 160 mg Q4W Total N=702 ^a (PYAR: 603.4)	Reference Arm (ADA 40 mg Q2W) N=140 (PYAR: 136.8)
Adjudicated MACE	0	0	0	4 (0.6) [0.7] ^e	0
Neutropenia	1 (0.4)	5 (1.2)	1 (0.7)	11 (1.6) [1.8]	2 (1.4) [1.5]
Infections					
Serious	0	1 (0.2)	1 (0.7)	6 (0.9) [1.0] ^f	2 (1.4) [1.5] ^f
Opportunistic	0	0	1 (0.7) ^g	9 (1.3) [1.5]	1 (0.7) [0.7]
Active TB	0	0	0	0	0
Hypersensitivity	6 (2.1)	18 (4.2)	3 (2.1)	59 (8.4) [10.3]	7 (5.0) [5.3]
Injection site reactions	3 (1.1)	5 (1.2)	7 (5.0)	15 (2.1) [2.5]	13 (9.3) [10.2]
Adjudicated SIB	0	0	0	0	0
Liver function test changes/enzyme elevations					
ALT >3 × ULN	0 ^h	5 (1.2)	2 (1.4) ⁱ	15 (2.1) ⁱ	7 (5.0) ⁱ
AST or ALT >3 × ULN	0 ^h	5 (1.2)	3 (2.2) ⁱ	24 (3.4) ⁱ	9 (6.5) ⁱ
Adjudicated IBD	0	0	0	2 (0.3) [0.3] ^j	0
Malignancies excluding nonmelanoma skin cancer					
Breast cancer stage 1	1 (0.4)	0	0	0	0
Colon cancer	0	0	0	1 (0.1) [0.2]	0
Chronic lymphocytic leukaemia stage 0	0	0	0	1 (0.1) [0.2]	0
Papillary thyroid cancer	0	0	0	1 (0.1) [0.2]	0

	Up to Week 16, n (%)			Up to Week 52, n (%) [EAIR/100 PY]	
	PBO N=281 (PYAR: 87.3)	BKZ 160 mg Q4W N=431 (PYAR: 134.2)	Reference Arm (ADA 40 mg Q2W) N=140 (PYAR: 43.4)	BKZ 160 mg Q4W Total N=702 ^a (PYAR: 603.4)	Reference Arm (ADA 40 mg Q2W) N=140 (PYAR: 136.8)
Nonmelanoma skin cancer					
Squamous cell carcinoma	0	0	0	1 (0.1) [0.2]	0
Basal cell carcinoma	0	1 (0.2)	0	3 (0.4) [0.5]	0

1 Safety set (Week 16) and active medication set for the overall study period (Week 52). TEAEs are reported for all study groups for Weeks 0–16 and Weeks 0–52. For Weeks
 2 0–52, only TEAEs occurring whilst receiving BKZ are reported; for patients initially randomised to PBO, only events after switching to BKZ at Week 16 are included. [a] Includes
 3 patients who switched from placebo to BKZ (events after switch only); [b] Motorcycle accident; [c] Most frequent adverse events are those occurring in ≥5% of patients in any
 4 study arm; [d] All infections were mild or moderate and none were serious, 1 BKZ-treated patient discontinued; [e] 1 case each of myocardial infarction, cerebrovascular
 5 accident, ischaemic stroke and thrombotic cerebral infarction. The case of ischaemic stroke was deemed by the investigator to be related to study medication; [f] 6 serious
 6 infections were reported on the BKZ treatment arm: 1 cellulitis, 1 gangrene, 1 pneumonia, 1 upper respiratory tract infection, 1 cystitis and 1 urinary tract infection. 2
 7 ADA-treated patients reported serious infections: 1 otitis media and 1 reported both herpes zoster and atypical pneumonia; [g] 1 opportunistic infection event of herpes zoster
 8 was reported for the ADA treatment arm during the double-blind period; [h] Data missing for 2 patients; [i] Data missing for 1 patient; [j] Both ulcerative colitis; one in a
 9 patient with a prior history of IBD and the other de novo. ADA: adalimumab; ALT: alanine aminotransferase; AST: aspartate aminotransferase; BKZ: bimekizumab;
 10 EAIR: exposure-adjusted incident rate; IBD: inflammatory bowel disease; MACE: major adverse cardiovascular event; PBO: placebo; PY: patient-years; PYAR: patient-years at
 11 risk; Q2W: every two weeks; Q4W: every four weeks; SIB: suicidal ideation and behaviour; TB: tuberculosis; TEAE: treatment-emergent adverse event; ULN: upper limit of
 12 normal.

1 The three most common TEAEs to Week 52 in patients receiving BKZ were
 2 nasopharyngitis (84 [12.0%]; EAIR/100 PY: 15.2), upper respiratory tract infection
 3 (50 [7.1%]; EAIR/100 PY: 8.7) and urinary tract infection (43 [6.1%]; EAIR/100
 4 PY: 7.3; **Table 3**). In patients treated with ADA, the three most common TEAEs
 5 were nasopharyngitis (12 [8.6%]; EAIR/100 PY: 9.4), ALT elevation (11 [7.9%];
 6 EAIR/100 PY: 8.5) and hypertension (9 [6.4%]; EAIR/100 PY: 6.8).

7 In patients receiving BKZ to Week 52, six (0.9%; EAIR/100 PY: 1.0) patients had
 8 serious infections: one case each of cellulitis, gangrene of the oral cavity base,
 9 pneumonia, upper respiratory tract infection, cystitis and urinary tract infection.
 10 Overall, two (1.4%; EAIR/100 PY: 1.5) ADA-treated patients had serious infections,
 11 one patient with a case of otitis media, and one patient with a case each of herpes
 12 zoster and atypical pneumonia. There were no cases of active TB.

13 Fungal infections were reported by the investigators for 82 (11.7%; EAIR/100
 14 PY: 14.6; **Supplementary Table 3**) patients receiving BKZ and two (1.4%;
 15 EAIR/100 PY: 1.5) ADA-treated patients. Of patients receiving BKZ, 54 (7.7%;
 16 EAIR/100 PY: 9.3) had a *Candida* infection, the majority of which were oral
 17 candidiasis (38 patients [5.4%]; EAIR/100 PY: 6.5). Of ADA-treated patients, one
 18 (0.7%; EAIR/100 PY: 0.7) had a *Candida* infection (oral candidiasis). There were no
 19 serious or systemic *Candida* infections in either treatment arm. One *Candida* infection
 20 (oral candidiasis; 0.1% of BKZ-treated patients; EAIR/100 PY: 0.2) that resulted in
 21 study discontinuation occurred in a patient receiving BKZ. Cases of *Candida* were
 22 managed using standard antifungal treatment, with the majority of patients receiving
 23 nystatin or fluconazole. In BKZ-treated patients, 12 (1.7%) patients had recurrent
 24 candidiasis, as reported by the investigators.

25 To Week 52, nine (1.3%; EAIR/100 PY: 1.5) patients receiving BKZ and one (0.7%;
 26 EAIR/100 PY: 0.7) receiving ADA had an infection defined as opportunistic (definition
 27 provided in **Supplementary Appendix 1**). No serious or systemic opportunistic
 28 infections were reported in patients treated with BKZ. In BKZ-treated patients, all
 29 opportunistic infections were localised, mucocutaneous and fungal in nature; four
 30 oesophageal candidiasis, two oropharyngeal candidiasis, one fungal oesophagitis,
 31 one fungal laryngitis and one upper respiratory tract fungal infection were reported
 32 (**Supplementary Table 3**). The ADA-treated patient had a serious case of herpes
 33 zoster.

Four (0.6%; EAIR/100 PY: 0.7; **Table 3**) patients had an event adjudicated as MACE up to Week 52 whilst receiving BKZ, three cases of stroke (two of which were thrombotic) and one case of myocardial infarction. Each of these patients had a history of cardiovascular events. No events adjudicated as MACE were reported in the reference treatment arm.

Of patients receiving BKZ, there were four cases of nonmelanoma skin cancer (three basal cell carcinoma and one squamous cell carcinoma) and one case each of colon cancer, chronic lymphocytic leukaemia (stage 0) and papillary thyroid cancer (**Table 3**). No malignancies were reported in the ADA group.

In total, 15 (2.1%; EAIR/100 PY: 2.5) patients receiving BKZ and 13 (9.3%; EAIR/100 PY: 10.2) ADA-treated patients had injection site reactions (**Table 3**). There were two (0.3%; EAIR/100 PY: 0.3) cases of IBD in patients receiving BKZ; no cases of IBD were reported in patients receiving ADA. There were no cases of adjudicated SIB in any treatment arm.

DISCUSSION

BE OPTIMAL demonstrated long-term efficacy of BKZ up to Week 52 in patients with active PsA who were bDMARD-naïve across a range of PsA domains, including joints, skin, enthesitis, dactylitis, and nails, as well as the inhibition of structural progression. Improvements in efficacy as assessed by stringent outcome measures were sustained from Week 16 to Week 52 with BKZ treatment, with a low rate of patient drop-out. Furthermore, safety was as expected with no new safety signals observed.

PsA is a chronic, long-term disease, and treatment goals include achievement of more stringent efficacy outcomes that are sustained over time. Improvements seen with BKZ in the BE OPTIMAL study indicate a long-term, sustained depth of response. Improvements in ACR50 and PASI100 observed at Week 16 continued to improve to Week 52 in patients initially randomised to BKZ. Patients who switched from PBO to BKZ at Week 16 had similar ACR50 and PASI100 responder rates at Week 52 to those initially randomised to BKZ. ACR50 responder rates in all treatment groups were 50% or greater, and PASI100 responder rates for BKZ-treated patients were greater than 60% at Week 52.

A similar trend of improvements sustained from Week 16 to Week 52 was observed for the composite endpoints MDA, VLDA and ACR50+PASI100, demonstrating the

1 efficacy of BKZ treatment across multiple domains of PsA.(4) This is particularly
2 important as international guidelines emphasise the need to reduce disease activity
3 across all active domains of the disease, as this is associated with better
4 outcomes.(4) A positive trend in the individual components of ACR indicate that no
5 single component drove the overall response. For patients who switched from PBO to
6 BKZ at Week 16, improvements in composite outcomes were observed to Week 52.

7 Prevention of structural joint damage is a key goal of treatment.(4) Persistent
8 inflammation in patients with PsA can lead to structural damage,(17) but the
9 majority of patients treated with BKZ experienced minimal changes in radiographic
10 progression to Week 52. This is especially notable, as BE OPTIMAL did not include
11 joint erosion or elevated C-reactive protein as inclusion criteria. Thus, it was more
12 difficult to demonstrate inhibition of radiographic progression compared to other
13 studies on biologics.

14 Improvements in efficacy were accompanied by improvements in physical function
15 (HAQ-DI), HRQoL (SF-36 PCS, PsAID-12) and patient-reported pain and fatigue
16 (PtAAP, FACIT-Fatigue), which have been identified by patients as important to
17 address in managing their disease.(18)

18 BKZ was well tolerated and the safety profile was similar to previous studies in PsA
19 and consistent with the known safety profile of BKZ.(13, 14, 19) Numerical
20 differences were observed between the safety profile of BKZ and the ADA reference
21 arm. In line with the mechanism of action of bimekizumab and the contribution of
22 IL-17 in host protection against mucosal fungal infection,(20) increased incidence of
23 fungal infections was observed in BKZ-treated patients compared with ADA-treated
24 patients. In the BKZ group, all fungal infections were mucocutaneous and localised.
25 All cases of *Candida* were mild or moderate in severity and the majority were
26 assessed as treatment related by the investigator. There were no cases of systemic
27 candidiasis and the vast majority of cases did not lead to patients discontinuing
28 treatment. The rate of *Candida* infections observed with BKZ treatment to Week 52
29 in BE OPTIMAL was consistent with those reported to Week 52 in the BE COMPLETE
30 sister study and its OLE, BE VITAL, and the phase 2b trial of BKZ in PsA to 3
31 years.(19, 21) Rates were also similar to those reported in axSpA,(22) and lower
32 than those reported in psoriasis.(23)

1 In BKZ-treated patients, there were four cases of MACE and three malignancies
2 excluding non-melanoma skin cancers. None were observed in the reference arm.
3 Numerically higher rates of injection site reactions and liver enzyme elevations were
4 observed in the ADA treatment group than the BKZ treatment group.

5 A limitation of this study is the small size of the subgroups of patients with enthesitis
6 or dactylitis at baseline. In the primary analysis described in the previously, these
7 subgroups were pooled with the BE COMPLETE study as part of the statistical
8 hierarchy, to ensure adequate power for statistical analysis.(13) In this manuscript,
9 enthesitis and dactylitis subgroups were reported for BE OPTIMAL only. Despite this,
10 a numerical difference was observed between BKZ and PBO at Week 16, and
11 PBO/BKZ patients demonstrated similar resolution of both enthesitis and dactylitis at
12 Week 52. Another limitation is that the study was not powered for statistical
13 comparisons of ADA to BKZ, therefore no such comparisons between treatments can
14 be made.

15 BKZ has demonstrated efficacy and tolerability to 52 weeks in bDMARD-naïve
16 patients with active PsA. Data are reported to Week 52, which was the duration of
17 the BE OPTIMAL study. However, PsA is a chronic, lifelong disease, therefore
18 longer-term data are needed to further assess the long-term safety and efficacy
19 profile of BKZ; longer treatment exposure is still required. Data from the OLE, BE
20 VITAL, will assess BKZ treatment in patients with active PsA over three years to
21 further assess long-term efficacy and tolerability. The long-term safety profile of BKZ,
22 particularly the increased risk of fungal infections, will be important to further
23 characterise and consider in context with the mechanistic benefits of dual inhibition
24 of IL-17A and IL-17F in achieving complete skin clearance and will be particularly
25 relevant for treatment decisions in clinical practice.(13, 14, 24) In addition to the
26 OLE, further observational research on outcomes in real-world data sets would aid
27 extrapolation of these results to routine clinical populations.

28 In conclusion, dual inhibition of IL-17A and IL-17F with BKZ in bDMARD-naïve
29 patients with active PsA resulted in sustained long-term, clinically meaningful
30 improvements across the PsA disease domains, determined using stringent efficacy
31 measures. Efficacy on BKZ treatment was sustained from Week 16 to Week 52 in
32 patients initially randomised to BKZ; patients who switched from PBO to BKZ at
33 Week 16 achieved similar levels of efficacy at Week 52 to patients initially

- 1 randomised to BKZ. BKZ was well tolerated and the safety profile was consistent with
- 2 prior studies. Longer-term safety and efficacy data will be assessed in the ongoing
- 3 OLE study, BE VITAL.

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DATA SHARING

Data from this manuscript may be requested by qualified researchers six months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymised individual patient data and redacted study documents which may 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. Prior to 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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Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

AUTHORS' CONTRIBUTIONS

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2 All the results presented in this article are in aggregate form, and no personally
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4

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