Bimekizumab for patients with moderate to severe plaque psoriasis: 60-week results from BE ABLE 2, a randomized, double-blinded, placebo-controlled, phase 2b extension study

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Background: Dual neutralization of both interleukin 17A and 17F with the monoclonal antibody bimekizumab may have greater efficacy in psoriasis than neutralization of interleukin 17A alone.

Objective: To provide longer-term efficacy and safety data for bimekizumab from a phase 2b extension study in patients with moderate to severe psoriasis (BE ABLE 2).

Methods: After the 12-week initial study (BE ABLE 1), patients who had a 90% improvement in Psoriasis Area and Severity Index (PASI 90) at week 12 received bimekizumab 64, 160, or 320 mg for an additional 48 weeks (60 weeks in total). The primary objective was safety.

Results: Across all dose groups (N = 217), initial PASI 90 responders generally maintained high levels of efficacy through week 60: PASI 90, 80% to 100%; 100% improvement in PASI, 69% to 83%; Investigator's Global Assessment score 0 or 1, 78% to 100% (all nonresponder imputation). Incidence of serious

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Funding sources: Supported by UCB Pharma.

Conflicts of interest: Dr Blauvelt has received consultant and investigator fees from AbbVie, Aclaris, Allergan, Almira, Athenex, Boehringer Ingelheim, Bristol-Myers Squibb, Dermavant, Dermira Inc, Eli Lilly, FLX Bio, Forte, Galderma, Janssen, LEO, Novartis, Ortho, Pfizer, Regeneron, Sandoz, Sanofi Genzyme, Sun Pharma, and UCB Pharma; and speaker fees from AbbVie. Dr Papp has received honoraria and grants from AbbVie, Akros, Amgen, Arcutis, Astellas, Baxalta, Boehringer Ingelheim, Bristol-Myers Squibb, Canfite, Celgene, Coherus, Dermira, Dow Pharma, Eli Lilly, Forward Pharma, Galderma, Genentech, Gilead, GlaxoSmithKline, Janssen, Kyowa Hakko Kirin, LEO, MedImmune, Merck (MSD), Merck-Serono, Mitsubishi Pharma, Moberg Pharma, Novartis, Pfizer, PRCL Research, Regeneron, Roche, Sanofi Aventis/Genzyme, Sun Pharma, Takeda, UCB Pharma, and Valeant/Bausch Health; and is a consultant (no compensation) for AstraZeneca and Meiji Seika Pharma. Dr Merola is a consultant or investigator for AbbVie, Aclaris, Almirall, Avotres, Biogen, Celgene, Dermavant, Eli Lilly, EMD Serono, Incyte, Janssen, Leo Pharma, Merck Research Laboratories, Novartis, Pfizer, Sanofi Regeneron, Sun Pharma, and UCB Pharma. Dr Gottlieb has received honoraria or grants from AbbVie, Avotres, Beiersdorf, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Eli Lilly, Incyte, Janssen, LEO, Novartis, Sun Pharma, UCB Pharma, and Xbiotech. Dr Cross is an employee of and holds stocks and stock options for UCB Pharma. Dr Madden is an employee of and holds stocks and stock options for UCB Pharma. Dr Cioffi is an employee of and holds stocks and stock options for UCB Pharma. Dr Griffiths has received honoraria or research grants from AbbVie, Almirall, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Janssen, LEO, Pfizer, Novartis, Sandoz, Sanofi Regeneron, and UCB Pharma, and is supported in part by the Manchester NIHR Biomedical Research Centre. Author Wang is an employee and stockholder of UCB Pharma.

IRB approval status: This study was approved by institutional review boards in the countries involved.

Accepted for publication May 12, 2020.

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Published online May 29, 2020.

0190-9622

https://doi.org/10.1016/j.jaad.2020.05.105

treatment-emergent adverse events was 15/217 (6.9%). No cases of inflammatory bowel disease, major adverse cardiovascular events, or suicidal ideation or behavior were reported.

Limitations: Low numbers in the bimekizumab 64 mg group (n = 15). The majority of 60-week data reported here are primarily for the week 12 PASI 90 responders only.

Conclusion: Bimekizumab response rates were maintained through week 60. A substantial proportion of patients achieved complete skin clearance. Bimekizumab was generally well tolerated. (J Am Acad Dermatol 2020;83:1367-74.)

Key words: BE ABLE 2; bimekizumab; extension; IL-17A; IL-17F; PASI90; plaque psoriasis; randomized clinical trial.

INTRODUCTION

Alongside interleukin (IL)-17A, IL-17F is now recognized to play an important role in the pathophysiology of immune-mediated inflammatory diseases.[1-5] Recent evidence suggests that neutralizing both IL-17A and -17F may have greater efficacy in psoriasis than neutralizing IL-17A alone.[3,6,7] Bimekizumab is a humanized immunoglobulin G1 monoclonal antibody that selectively binds to and neutralizes the biologic functions of both IL-17A and -17F.

CAPSULE SUMMARY

- In the BE ABLE 2 study, bimekizumab demonstrated high response rates maintained through week 60, with a substantial proportion of patients achieving complete skin clearance, and was generally well tolerated.
- These data further support dual neutralization of interleukin 17A and 17F with bimekizumab as a novel therapeutic approach for patients with psoriasis.

In early clinical studies, bimekizumab proved efficacious, with no unexpected safety signals in patients with mild to moderate psoriasis[7] and psoriatic arthritis.[6] In BE ABLE 1, a phase 2b dose-ranging study, patients with moderate to severe psoriasis demonstrated a significant dose response, with 46.2% to 79.1% achieving a 90% improvement in Psoriasis Area and Severity Index (PASI 90) score at week 12, varying by dose received ($P < .001$ for all comparisons vs placebo).[8] Up to 60% of patients achieved complete skin clearance at week 12 (27.9%-60.0% bimekizumab vs 0% placebo; $P < .001$ for all doses). Here, we report results from the 48-week BE ABLE 2 extension study, which was conducted to provide longer-term efficacy and safety data for a total of 60 weeks' bimekizumab exposure.

MATERIALS AND METHODS

Study design and participants

BE ABLE 2 (NCT03010527) was conducted from December 14, 2016, to August 30, 2018. Study duration is provided from the start of BE ABLE 1 (NCT02905006). BE ABLE 2 baseline is therefore reported as week 12; the end of BE ABLE 2 (week 48) is week 60. Treatment depended on treatment received in BE ABLE 1 and week 12 PASI 90 response. Patients in BE ABLE 1 who were randomized to placebo, bimekizumab 64 mg, or bimekizumab 160 mg with or without a 320 mg loading dose (all every 4 weeks) who also achieved PASI 90 at week 12 received the same treatment in BE ABLE 2. Week 12 PASI 90 responders randomized to bimekizumab 320 and 480 mg (all every 4 weeks) in BE ABLE 1 received 320 mg every 4 weeks in BE ABLE 2. Patients who did not achieve PASI 90 at week 12 received bimekizumab 160 or 320 mg every 4 weeks in BE ABLE 2. Further details are provided in Supplemental Figure 1 (available via Mendeley at https://doi.org/10.17632/5ry2hmc2wm.1). Blinding was conducted as previously described;[8] in BE ABLE 2, blinded site personnel remained as such after BE ABLE 1 unblinding. Patients who did not achieve a 75% improvement in PASI (PASI 75) after at least 12 weeks of treatment were withdrawn from the study without receiving further treatment.

Patients who had completed BE ABLE 1 were eligible to enter BE ABLE 2 (ie, adults with a confirmed diagnosis of moderate to severe plaque psoriasis for ≥6 months, having PASI score ≥12, body surface area (BSA) affected ≥10%, and Investigator's Global Assessment (IGA) score ≥3 at BE ABLE 1 baseline). Exclusion criteria were previous treatment with an IL-17 inhibitor or withdrawal from BE ABLE 1 (details in the Supplemental Methods). The study was conducted according to the Declaration of Helsinki principles. Independent institutional review board approvals were obtained. All patients provided written informed consent before participation.

Abbreviations used:

IL: interleukin
PASI: Psoriasis Area and Severity Index

Procedures

Treatment was administered from week 12 (BE ABLE 2 baseline) and every 4 weeks through week 60. Safety data were monitored by independent data monitoring and cardiovascular adjudication committees.

Outcomes

The primary objective was safety and tolerability, and the primary variable was incidence of treatment-emergent adverse events adjusted by the duration of patient exposure to treatment, including the frequency and severity of adverse events according to the Common Terminology Criteria for Adverse Events, and serious adverse events. Other safety variables included clinical laboratory assessments, vital signs, physical examination, and 12-lead electrocardiogram results. Secondary efficacy variables were PASI 90 response and IGA response ("clear" or "almost clear," with at least a 2-category improvement) over time. Other efficacy variables included PASI 100 and PASI 75 responses, absolute and percentage change from baseline in PASI, BSA affected by psoriasis, and Dermatology Life Quality Index (DLQI) response, all assessed over time.

Statistical analyses

Safety analyses were evaluated in the safety set, which included all patients who received at least 1 dose of study drug in BE ABLE 2, and efficacy analyses were based on the full analysis set, comprising patients from the safety set who also had a valid PASI measurement at week 12 (BE ABLE 2 baseline). As an extension study, no sample size calculations were applied.

Descriptive statistics were used; no *P* values were calculated. Change from baseline and responder variables were defined relative to week 0 of BE ABLE 1 for PASI 90 responders and nonresponders. For the planned efficacy analyses, missing responder data were imputed with nonresponder imputation, and observed data are also presented. For continuous variables, missing data were imputed with last observation carried forward because of lack of convergence in multiple imputation; details are provided in the Supplemental Methods.

RESULTS

Two hundred seventeen patients entered the BE ABLE 2 extension study and were included in the full analysis set and safety set. According to response at week 12 in BE ABLE 1, 15 patients received bimekizumab 64 mg, 111 received bimekizumab 160 mg, and 91 received bimekizumab 320 mg (Supplemental Fig 1). Overall, 182 patients (83.9%) completed the study and 35 (16.1%) discontinued, most commonly because of protocol-mandated withdrawal for clinical laboratory values grade 3 or higher (or consistent grade 2 laboratory abnormality) in 10 patients (4.6%).

Baseline demographics and disease characteristics for the BE ABLE 1 population were previously reported[8] and remained generally well balanced among the 217 patients continuing into BE ABLE 2 (Supplemental Table I). The majority of patients were male (64.5%) and white (89.9%), with a mean age of 44.1 years (standard deviation 13.7 years) and median age of 43.0 years (range 18-75 years). Patients had a median duration of psoriasis of 15.0 years (range 0-58.7 years) and were representative of a population with moderate to severe psoriasis: mean PASI score was 19.4 (standard deviation 6.7), 76.5% of patients had an IGA score of 3 (moderate), 23.5% had an IGA score of 4 (severe), and median percentage of BSA involvement was 22.0% (range 10%-80%). Previous therapies included nonbiologic systemic therapy (38.7%), biologic therapy (23.0%), phototherapy or chemophototherapy (51.2%), and tumor necrosis factor-α inhibitors (12.9%).

Efficacy

For patients who had a PASI 90 response at week 12 and were treated with bimekizumab in BE ABLE 2, 80.0% to 100.0% maintained a PASI 90 response at week 60 (nonresponder imputation analysis) (Fig 1). In the observed data analysis, all patients who reached the end of the study achieved a PASI 90 response at week 60 (Supplemental Fig 2). The week 12 PASI 90 nonresponders who were reallocated to a higher bimekizumab dose in BE ABLE 2 (nonresponder imputation analysis) had a rapid increase in PASI 90 response rate across all treatment groups, which was maintained through week 60 (68.4%-91.9%) (Supplemental Fig 3).

Complete skin clearance was achieved by 53.3% to 70.0% of PASI 90 responders at week 12 and maintained in BE ABLE 2 through week 60 (69.1%-83.3%) (Fig 2). Similar to PASI 90, the observed data analysis for PASI 100 exhibited higher response rates (80.0%-96.2%) than the nonresponder imputation

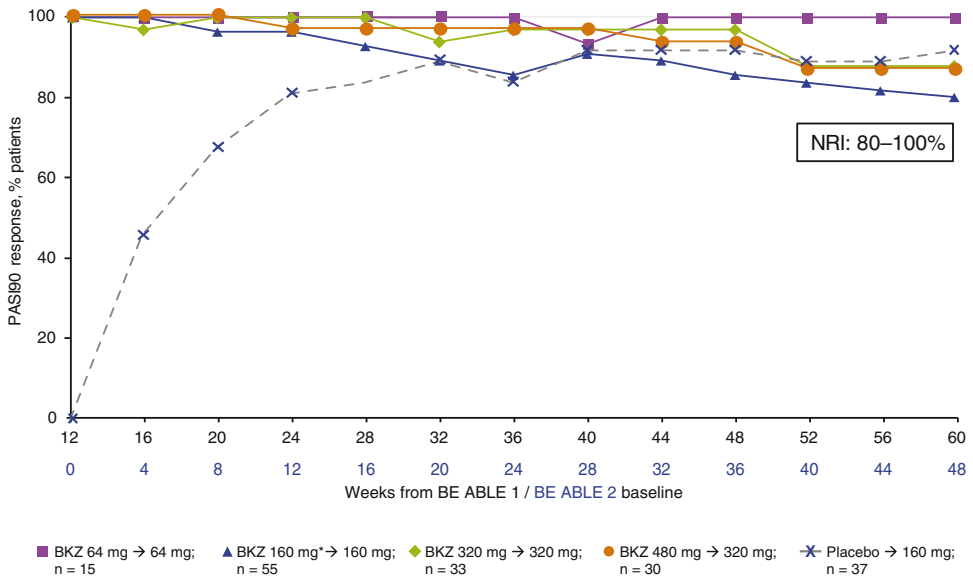

Fig 1. Psoriasis. PASI 90 response rates over time in PASI 90 responders and patients switching from placebo to bimekizumab 160 mg (nonresponder imputation; full analysis set). Arrows indicate treatment reallocation at week 12. *BKZ*, Bimekizumab; *NRI*, nonresponder imputation; *PASI*, Psoriasis Area and Severity Index. *The bimekizumab 160 mg group includes patients randomized to both bimekizumab 160 mg and 160 mg with 320 mg loading dose in BE ABLE 1.

(Supplemental Fig 4). Among PASI 90 nonresponders (nonresponder imputation), PASI 100 increased rapidly in all treatment groups and was achieved by 33.3% to 75.7% of patients at week 60.

In PASI 90 responders, IGA 0 or 1 responses were higher than in nonresponders and also maintained through week 60, with 78.2% to 100.0% of patients across dose groups achieving "clear" or "almost clear" skin at week 60 (Table I). The majority of PASI 90 responders also maintained IGA 0 response through week 60 (Table I): 69.1% to 83.3% of patients achieved "clear" skin. In addition, the PASI 90 nonresponders demonstrated a rapid increase in IGA 0 or 1 response rate, which was maintained to week 60 (62.5%-89.2%), and a high proportion also achieved "clear" skin by week 60 (33.3%-75.7%).

Absolute PASI score decreased to less than or equal to 2 in the majority of patients in all treatment groups at week 60 (80.0%-100.0% and 66.7%-91.9% for PASI 90 responders and nonresponders, respectively). High proportions of patients also achieved absolute PASI score less than or equal to 1 at week 60 (78.2%-93.3% and 50.0%-86.5%, respectively). Individual data for patients receiving continuous bimekizumab 320 mg every 4 weeks are shown in Fig 3. Similarly, high proportions of patients achieved an absolute BSA affected less than or equal to 1% at week 60 (76.4%-86.7% of PASI 90 responders and 50.0%-83.8% of PASI 90 nonresponders). Proportions of patients achieving a DLQI 0 or 1 response, indicating little or no effect of psoriasis on quality of life, were likewise maintained at week 60 in PASI 90 responders and nonresponders (76.4%-93.3% and 63.2%-83.8%, respectively) (Table I).

Safety

The incidence of treatment-emergent adverse events was similar between patients in the bimekizumab 160 mg group (98/111; 88.3%) and 320 mg group (76/91; 83.5%), and lower in the bimekizumab 64 mg group (10/15; 66.7%) (Table II). The majority of treatment-emergent adverse events were mild or moderate, with no apparent relationship between dose and severity or incidence. The most common treatment-emergent adverse events (≥5%) were oral candidiasis (13.4%) and nasopharyngitis (12.9%) (Table II). All cases of oral candidiasis were nonserious, localized, superficial infections of mild or moderate intensity, and did not lead to discontinuation, except for 1 case of esophageal candidiasis. No cases of suicidal ideation or behavior, major adverse cardiovascular events, or inflammatory bowel disease were reported during the study.

Overall, 15 patients (6.9%) reported serious adverse events, with a similar incidence across the 160 mg and 320 mg treatment groups (Supplemental Table II). No individual serious adverse event was reported by more than 1 patient. One serious adverse event was considered related to bimekizumab (hepatic enzyme increased in a patient receiving bimekizumab 160 mg).

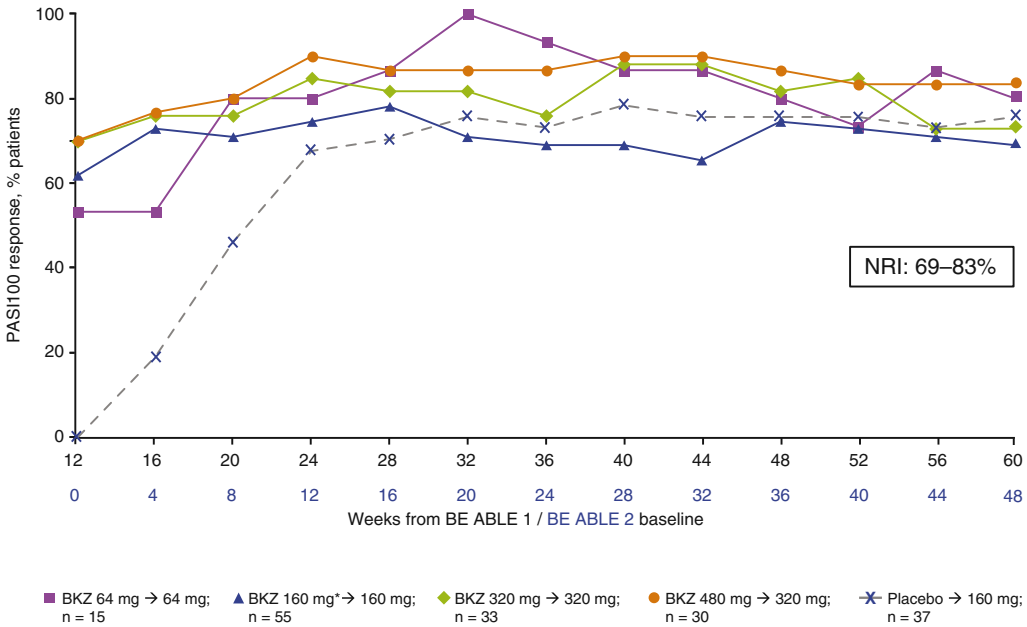

Fig 2. Psoriasis. PASI 100 response rates over time in PASI 90 responders (nonresponder imputation analysis; full analysis set). Arrows indicate treatment reallocation at week 12. *BKZ*, Bimekizumab; *NRI*, nonresponder imputation; *PASI*, Psoriasis Area and Severity Index. *The bimekizumab 160 mg group includes patients randomized to both bimekizumab 160 mg and 160 mg with 320 mg loading dose in BE ABLE 1.

Table I. Secondary and other efficacy outcomes in PASI 90 responders by bimekizumab dose (full analysis set; nonresponder imputation)

Efficacy outcomes, no. (%)	BKZ 64 mg → BKZ 64 mg, n = 15	BKZ 160 mg → BKZ 160 mg, n = 55	BKZ 320 mg → BKZ 320 mg, n = 33	BKZ 480 mg → BKZ 320 mg, n = 30
IGA 0/1 (clear/almost clear) response*				
Wk 12	15 (100)	53 (96.4)	33 (100)	30 (100)
Wk 60	15 (100)	43 (78.2)	29 (87.9)	26 (86.7)
IGA 0 (clear) response†				
Wk 12	8 (53.3)	34 (61.8)	23 (69.7)	21 (70.0)
Wk 60	12 (80.0)	38 (69.1)	24 (72.7)	25 (83.3)
DLQI response (achieving a 0 or 1)				
Wk 12	10 (66.7)	47 (85.5)	23 (69.7)	24 (80.0)
Wk 60	14 (93.3)	42 (76.4)	26 (78.8)	26 (86.7)
Absolute BSA ≤1% at wk 60	13 (86.7)	42 (76.4)	26 (78.8)	26 (86.7)

BKZ, Bimekizumab; *BSA*, body surface area affected by psoriasis; *DLQI*, Dermatology Life Quality Index; *IGA*, Investigator's Global Assessment; *Wk*, week.

Weeks are counted from baseline in BE ABLE 1 so that week 12 is baseline of BE ABLE 2 and week 60 is week 48 in BE ABLE 2. Arrows in column headers indicate treatment reallocation at week 12.

*IGA 0/1 response defined as clear (0) or almost clear (1), with at least a 2-category improvement from baseline.

†IGA 0 response defined as clear (0) with at least a 2-category improvement from baseline.

Discontinuations because of treatment-emergent adverse events were reported in similar numbers of patients in the bimekizumab 160 mg and 320 mg groups (7/111 patients [6.3%] and 7/91 patients [7.7%], respectively), with no apparent dose relationship; 0 of 15 patients receiving bimekizumab 64 mg discontinued because of treatment-emergent adverse events. Treatment-emergent adverse events leading to discontinuation were acute myeloid leukemia, γ-glutamyltransferase increase, hepatic enzyme increase, hypermagnesemia, IgA nephropathy, nasopharyngitis, nonalcoholic fatty liver, and

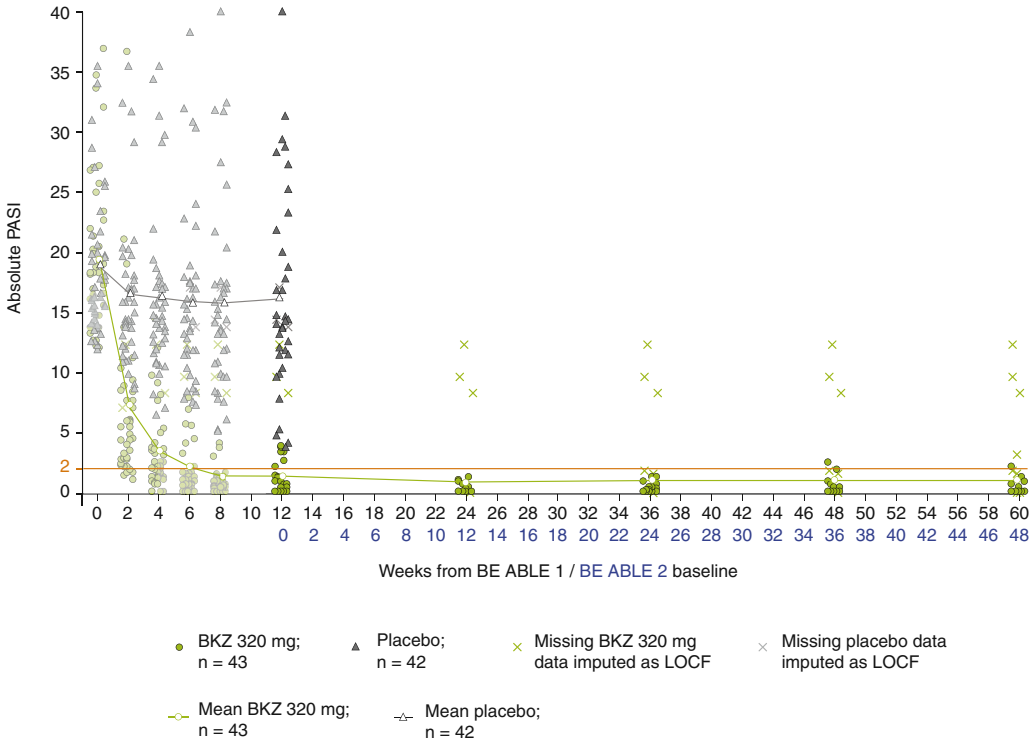

Fig 3. Psoriasis. Absolute PASI over time in individual patients who received bimekizumab 320 mg continuously; observed data. *BKZ*, Bimekizumab; *PASI*, Psoriasis Area and Severity Index.

Table II. Overview and incidence of treatment-emergent adverse events reported (safety set)

No. (%) (incidence per 100 patient-years)	BKZ 64 mg, n = 15	BKZ 160 mg, n = 111	BKZ 320 mg, n = 91	All BKZ, N = 217
Any TEAE	10 (66.7) [110.7]	98 (88.3) [225.3]	76 (83.5) [206.8]	184 (84.8) [206.1]
SAEs	1 (6.7) [5.5]	7 (6.3) [5.7]	7 (7.7) [7.0]	15 (6.9) [6.2]
Discontinuation because of TEAEs	0	7 (6.3)	7 (7.7)	14 (6.5)
Treatment-related TEAEs	3 (20.0)	29 (26.1)	27 (29.7)	59 (27.2)
Deaths	0	0	2 (2.2)	2 (0.9)
Most common TEAEs (≥5% of patients in any group)				
Oral candidiasis	1 (6.7) [5.7]	13 (11.7) [11.1]	15 (16.5) [16.1]	29 (13.4) [12.7]
Nasopharyngitis	2 (13.3) [11.9]	15 (13.5) [12.9]	11 (12.1) [11.5]	28 (12.9) [12.2]
Upper respiratory tract infection	1 (6.7) [5.6]	10 (9.0) [8.3]	9 (9.9) [9.1]	20 (9.2) [8.4]
Hypertension	2 (13.3) [11.5]	8 (7.2) [6.6]	4 (4.4) [4.0]	14 (6.5) [5.9]
Oropharyngeal pain	0	6 (5.4) [4.9]	6 (6.6) [6.0]	12 (5.5) [5.0]
Psoriasis	2 (13.3) [10.9]	5 (4.5) [3.9]	5 (5.5) [4.9]	12 (5.5) [4.8]

BKZ, Bimekizumab; *SAE*, serious treatment-emergent adverse event; *TEAE*, treatment-emergent adverse event.

pustular rash (all in 1 patient each in the 160 mg group), alanine aminotransferase increase, blood bilirubin level increase, esophageal candidiasis, purpura, hypovolemic shock, and transaminases increase (all in 1 patient each in the 320 mg group), and γ-glutamyltransferase increase (in 2 patients in the 320 mg group).

Two deaths occurred, neither of which were considered related to study drug; both patients were receiving bimekizumab 320 mg. A 50-year-old man experienced hypovolemic shock during the treatment period, which was fatal. He had a history of alcohol dependence, gastrointestinal bleeding, and esophageal varices, and a recent episode of

alcohol abuse. A 67-year-old man experienced dyspnea, respiratory failure, and circulatory collapse during the safety follow-up period, which were fatal. He had a history of type 2 diabetes, asthma, and myocardial infarction. Overall, no clinically relevant patterns of change or dose-related trends were observed for hematology, biochemistry values, vital signs, or electrocardiogram findings.

DISCUSSION

In this phase 2b 48-week extension study in patients with moderate to severe psoriasis, bimekizumab treatment resulted in a substantial proportion of patients achieving durable complete or almost complete skin clearance. PASI 90 responses were maintained for the entire study period in the majority of PASI 90 responders. PASI 90 nonresponders who were originally randomized to placebo and switched to bimekizumab 160 mg at week 12 achieved PASI 90 responses similar to those initially randomized to bimekizumab. Nineteen of 34 patients receiving bimekizumab 64 mg in BE ABLE 1 did not achieve PASI 90 response at week 12 and were assigned to bimekizumab 160 mg. PASI 90 responders also continued to improve, and achieved and maintained PASI 100 response rates with bimekizumab during the BE ABLE 2 study period; between 69% and 83% maintained complete skin clearance. This finding is clinically relevant because achieving complete skin clearance is associated with substantial improvements in patients' health-related quality of life, including emotional and psychosocial well-being.[9] High PASI 100 response rates were also achieved by PASI 90 nonresponders after reallocation to higher doses of bimekizumab (160 or 320 mg) and were maintained through the end of the study. The observed data analyses for PASI 90 and 100 improvement demonstrated higher responder rates than the nonresponder imputation analyses.

Improvements were maintained through week 60 in disease severity, measured by IGA response rates, and extent of disease, measured by absolute BSA affected by psoriasis. Between 50% and 84% of patients achieved a BSA affected less than or equal to 1% and maintained this to week 60. There was rapid improvement in the proportion of patients achieving a DLQI of 0 or 1, representing minimal or no effect of psoriasis on quality of life, which was maintained through week 60 and consistent with improvements in skin clearance, disease severity, and extent of psoriasis observed throughout the study. Taken together, these results are promising in the context of other IL-17 inhibitors.[10-16] These results are from a phase 2b study, whereas phase 3 studies of bimekizumab have recently been completed to further characterize its efficacy in treatment of moderate to severe psoriasis, including comparison with active controls.

Bimekizumab treatment was generally well tolerated, with a safety profile consistent with that of previous reports and no new safety findings observed.[6-8] Incidences of treatment-emergent adverse events were similar between bimekizumab 160 mg and 320 mg treatment groups, although a numerically greater proportion of patients receiving bimekizumab 320 mg (15/91; 16.5%) reported oral candidiasis than in the bimekizumab 160 mg group (13/111; 11.7%). All cases were nonserious, of mild to moderate intensity, and were localized, superficial infections. With the exception of 1 case of esophageal candidiasis, oral candidiasis did not lead to discontinuation. The observation of oral candidiasis was expected for the mechanism of action for IL-17A and -17F inhibition.[17,18] No cases of inflammatory bowel disease, major adverse cardiovascular events, or suicidal ideation or behavior were reported in this study. The safety profile of bimekizumab is being further assessed in phase 3 studies.

These 60-week data for bimekizumab in patients with moderate to severe psoriasis build on the encouraging outcomes and improvements noted in patients with other immune-mediated inflammatory diseases, including psoriatic arthritis and ankylosing spondylitis.[6,19,20] The data presented add to the growing body of evidence supporting dual neutralization of IL-17A and -17F with bimekizumab as a novel therapeutic approach for patients with psoriasis.

Limitations included a relatively short duration of observation for a chronic disease and a small number of patients overall, with a very small number of patients in the bimekizumab 64 mg group (n = 15); results from this treatment group should be interpreted with caution. The results need to be confirmed in larger phase 3 studies, and eventually in real-world studies. In addition, patients who did not achieve PASI 75 after 12 weeks' treatment in BE ABLE 2 were withdrawn from the study, leading to some selection bias (ie, enrichment for responders). However, the majority of patients (88%-100%) who enrolled into BE ABLE 2 achieved this efficacy level by 12 weeks, limiting this effect.

CONCLUSIONS

The results of this phase 2b extension study demonstrated that bimekizumab provides a high level of efficacy, with complete skin clearance achieved in a substantial proportion of patients, which was maintained over 1 year. The drug was also generally well tolerated. Bimekizumab is being

further evaluated across a comprehensive phase 3 clinical development program (BE VIVID, NCT03370133; BE SURE, NCT03412747; BE RADIANT, NCT03536884; and BE READY, NCT03410992).

The authors thank the patients, the investigators, and their teams who took part in this study; Susanne Wiegratz, MSc, of UCB Pharma, for publication coordination and critical review; and Sally Cotterill, PhD, of iMed Comms, an Ashfield Company, part of UDG Healthcare PLC, for medical writing support in preparing this manuscript for publication according to the authors' input and direction.

Data sharing statement Underlying 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 study completion. Investigators may request access to anonymized IPD 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.clinicalstudydatarequest.com and a signed data sharing agreement will need to be executed. All documents are available in English only, for a pre-specified time, typically 12 months, on a password protected portal.

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