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Bimekizumab Safety in Patients With Moderate to Severe Plaque Psoriasis

Pooled Results From Phase 2 and Phase 3 Randomized Clinical Trials

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IMPORTANCE Psoriasis is a chronic disease requiring long-term management; understanding the long-term safety profiles of psoriasis treatments, such as bimekizumab, is important.

OBJECTIVE To evaluate the 2-year safety profile of bimekizumab in patients with moderate to severe plaque psoriasis.

DESIGN, SETTING, AND PARTICIPANTS Safety data were pooled from a cohort of patients from 4 phase 2 randomized clinical trials (BE ABLE 1, BE ABLE 2, PS0016, and PS0018) and 4 phase 3 randomized clinical trials (BE VIVID, BE READY, BE SURE, and BE BRIGHT) to include 2 years of study treatment. Data were obtained on adults with moderate to severe plaque psoriasis (Psoriasis Area and Severity Index level ≥ 12 , $\geq 10\%$ body surface area affected by psoriasis, and an Investigator's Global Assessment score ≥ 3 on a 5-point scale) who were eligible for systemic psoriasis therapy and/or phototherapy.

INTERVENTIONS Included patients received 1 or more doses of bimekizumab during the phase 2 or phase 3 trials.

MAIN OUTCOMES AND MEASURES Treatment-emergent adverse events (TEAEs), serious TEAEs, and TEAEs leading to treatment discontinuation are reported using exposure-adjusted incidence rates (EAIRs) per 100 person-years.

RESULTS A total of 1789 patients (1252 [70.0%] men; mean [SD] age, 45.2 [13.5] years) were treated with 1 or more doses of bimekizumab across the phase 2/3 trials and were included in these analyses; total bimekizumab exposure was 3109.7 person-years. TEAEs occurred at an EAIR of 202.4 per 100 person-years and did not increase with longer duration of bimekizumab exposure. The 3 most frequently reported TEAEs were nasopharyngitis (19.1 per 100 person-years; 95% CI, 17.4-20.9 per 100 person-years), oral candidiasis (12.6 per 100 person-years; 95% CI, 11.3-14.0 per 100 person-years), and upper respiratory tract infection (8.9 per 100 person-years; 95% CI, 7.8-10.1 per 100 person-years). Most oral candidiasis events were mild or moderate; 3 events led to discontinuation. The EAIRs of inflammatory bowel disease (0.1 per 100 person-years; 95% CI, 0.0-0.3 per 100 person-years), adjudicated suicidal ideation and behavior (0.0 per 100 person-years; 95% CI, 0.0-0.2 per 100 person-years), and adjudicated major adverse cardiac events (0.5 per 100 person-years; 95% CI, 0.3-0.8 per 100 person-years) were low.

CONCLUSIONS AND RELEVANCE In these pooled analyses of data from a cohort of patients from 8 randomized clinical trials, bimekizumab was well tolerated aside from an increased incidence of mild to moderate oral candidiasis. No safety signals were observed compared with previous reports, and there was no increased risk of AEs with longer duration of bimekizumab exposure.

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The chronic nature of psoriasis can place a substantial burden on patients' health and quality of life.¹⁻⁴ Long-term clinical trial data are valuable for evaluating the safety profiles of psoriasis treatments.⁵ Biologic therapies that inhibit key cytokines involved in psoriasis pathogenesis, such as interleukin (IL)-23, tumor necrosis factor, and IL-17A, are mainstays of treatment for patients with moderate to severe plaque psoriasis, and have well-established safety profiles.⁶⁻¹³

Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits both IL-17A and IL-17F.¹⁴⁻¹⁶ Bimekizumab has previously demonstrated superior efficacy vs placebo, ustekinumab (anti-IL-12/23), adalimumab (anti-tumor necrosis factor), and secukinumab (anti-IL-17A) for the treatment of patients with moderate to severe plaque psoriasis.¹⁷⁻²⁰

Safety data reported from the first year of clinical trials in the bimekizumab treatment for plaque psoriasis clinical program demonstrated that bimekizumab is well tolerated, with a safety profile in line with other anti-IL-17 biologics, aside from an increased incidence of mild to moderate oral candidiasis,¹⁷⁻²² as a result of the protective roles of IL-17A and IL-17F against fungal infections at the oral mucosa.^{20,23,24}

We report safety data from 4 phase 2 randomized clinical trials and 4 phase 3 randomized clinical trials in the bimekizumab plaque psoriasis clinical program, pooled to include 2 years of study treatment, to assess the longer-term safety profile of bimekizumab in patients with moderate to severe plaque psoriasis.

Methods

Patient Population

Safety data were pooled from 4 phase 3 randomized clinical trials (BE VIVID [NCT03370133], BE READY [NCT03410992], BE SURE [NCT03412747], and BE BRIGHT [NCT03598790])¹⁷⁻¹⁹ and 4 phase 2 randomized clinical trials (BE ABLE 1 [NCT02905006], BE ABLE 2 [NCT03010527], PS0016 [NCT03025542], and PS0018 [NCT03230292]).^{21,22,25,26} The data cutoff for the ongoing BE BRIGHT trial was November 9, 2020; the last ongoing patient in BE BRIGHT reached 2 years of study treatment on this date. All other trials included herein were completed.

Full inclusion and exclusion criteria have been described.^{17-19,21,22,26} Eligible patients for all trials were adults with moderate to severe plaque psoriasis, with a baseline Psoriasis Area and Severity Index (PASI) score greater than or equal to 12, 10% or more of body surface area affected by psoriasis, and an Investigator's Global Assessment score greater than or equal to 3 on a 5-point scale, who were eligible for systemic psoriasis therapy and/or phototherapy. Patients with active symptomatic inflammatory bowel disease (IBD), a recent (<6 months before screening) myocardial infarction or stroke, an active tuberculosis (TB) infection, or a high risk of acquiring a TB infection were excluded. For phase 2 trials, patients with suicidal ideation less than 6 months before screening or a lifetime history of suicide attempts were excluded. For phase 3 trials, patients with active suicidal ideation less than 1 month

Key Points

Question What is the 2-year safety profile of bimekizumab in patients with moderate to severe plaque psoriasis?

Findings In this cohort study including 1789 patients receiving bimekizumab, pooled data on 2 years of study treatment from 4 phase 2 randomized clinical trials and 4 phase 3 randomized clinical trials identified no safety signals. The incidence of adverse events did not increase with longer duration of exposure to bimekizumab.

Meaning These results, pooled to include 2 years of treatment, suggest that bimekizumab is well tolerated among patients with moderate to severe plaque psoriasis.

or a suicide attempt less than 5 years before screening were excluded.

Study Designs

The trials were conducted in accordance with the principles of the Declaration of Helsinki²⁷ and approved by an independent review board and independent ethics committee. All participants provided informed written consent. Reporting in this study followed the applicable portions of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline.

Trials included in these analyses are summarized in eTable 1 in the Supplement. Study designs for BE VIVID, BE READY, and BE SURE were published previously.¹⁷⁻¹⁹ The BE VIVID 52-week, randomized, double-blind, multicenter trial randomized patients to bimekizumab, 320 mg, every 4 weeks (Q4W), ustekinumab (per labeled dosing), or placebo to week 16 followed by bimekizumab, 320 mg, Q4W to week 52. The BE READY 56-week, randomized withdrawal, double-blind, multicenter trial randomized patients to bimekizumab, 320 mg, Q4W or placebo to week 16. At week 16, bimekizumab-treated patients who achieved a 90% or greater reduction from baseline in their PASI (PASI 90) score were rerandomized to bimekizumab, 320 mg, Q4W, bimekizumab, 320 mg, every 8 weeks (Q8W), or placebo to week 56. Week 16 PASI 90 nonresponders entered a 12-week bimekizumab, 320 mg, Q4W open-label escape group. The BE SURE 56-week, randomized, double-blind, multicenter trial randomized patients to bimekizumab, 320 mg, Q4W, bimekizumab, 320 mg, Q4W to week 16 then Q8W to week 56, or adalimumab (per labeled dosing) to week 24 followed by bimekizumab, 320 mg, Q4W to week 56. Patients completing each phase 3 trial were eligible to enroll in the BE BRIGHT open-label extension and received bimekizumab, 320 mg, Q4W or Q8W, depending on treatment, dose, and PASI response on feeder trial completion.

Study designs for BE ABLE 1 and BE ABLE 2 phase 2b trials have also been published.^{21,22} The 12-week BE ABLE 1 randomized, double-blind, dose-ranging trial randomized patients to placebo or bimekizumab Q4W at doses of 64 mg, 160 mg, 160 mg with a 320-mg loading dose at baseline, 320 mg, or 480 mg. On BE ABLE 1 completion, patients could enroll in the BE ABLE 2 48-week open-label extension. Treatment allocation in BE ABLE 2 depended on dosing in BE ABLE 1 and week

12 PASI response. PS0016 was a 28-week, phase 2a, randomized, double-blind, multicenter trial. Randomized patients received bimekizumab, 320 mg, at baseline and week 4 then placebo at week 16, or bimekizumab, 320 mg, at baseline, week 4, and week 16.²⁶ On completion, eligible patients could enroll in the 48-week PS0018 open-label extension, in which patients received bimekizumab, 160 mg, Q4W and, at the investigators' discretion, could increase the dose to 320 mg Q4W if PASI 50 to less than PASI 75 was achieved at week 12 or later.

Safety Evaluations

Treatment-emergent adverse events (TEAEs), serious AEs, and TEAEs leading to discontinuation are reported. TEAEs were defined as AEs that occurred during exposure to treatment including less than or equal to 140 days after the last dose. Serious AEs were defined as any AE that led to 1 or more of the following: death, life-threatening event, substantial or persistent disability or incapacity, congenital anomaly or birth defect (including any occurring in a fetus), important medical event, and initial or prolongation of hospitalization. TEAEs were coded according to the Medical Dictionary for Regulatory Activities (MedDRA), version 19.0. The intensity of AEs was assessed by the investigators as mild, moderate, or severe, independently from the seriousness.

Safety topics of interest were infections (serious, opportunistic, TB, and fungal), malignant neoplasms, major adverse cardiac events, neutropenia, suicidal ideation and behavior (SIB), IBD, hypersensitivity (including anaphylactic, hypersensitivity, and injection site reactions), and elevated liver enzyme/liver function test results.

Cardiovascular TEAEs were reviewed and adjudicated by an independent cardiovascular clinical event adjudication committee. Predefined neuropsychiatric TEAEs and prespecified questionnaire scores were assessed by an independent neuropsychiatric adjudication committee to determine events that met SIB criteria. Assessments and monitoring of SIB were performed using the Columbia Suicide Severity Rating Scale.²⁸

Opportunistic infections were predefined using company conventions. During the trials, patients were screened to evaluate TB signs, symptoms, and possible exposure (eTable 2 in the Supplement). If a patient developed evidence of active or latent TB, study treatment was stopped immediately and patients would be referred to a TB specialist for further evaluation.

Statistical Analysis

Pooled safety data were assessed for all patients who received 1 or more bimekizumab doses in the phase 2/3 trials (phase 2/3 total) and in the phase 3 trials only (phase 3 total). For patients who switched to bimekizumab from placebo, ustekinumab, or adalimumab, only TEAEs that occurred during exposure to bimekizumab are reported. Safety data were also analyzed for patients who received bimekizumab, 320 mg, Q4W or Q8W in the phase 3 trials. TEAEs were attributed to the dose most recently received before the TEAE date of onset.

All TEAEs were evaluated based on exposure-adjusted incidence rates (EAIRs), defined as the number of patients with

a specific AE adjusted for the duration of exposure. EAIRs are reported per 100 person-years with associated 95% CIs. Data analysis was conducted using SAS, version 9.4 (SAS Institute LLC).

Results

Patient Population

Of the 1789 patients who received 1 or more doses of bimekizumab in the phase 2/3 trials (eFigure in the Supplement), 1252 were men (70.0%) and 537 were women (30.0%); mean (SD) age was 45.2 (13.5) years. Baseline demographic and other characteristics were similar between bimekizumab dose groups and were representative of patients with plaque psoriasis eligible for biologic therapy (eTable 3 in the Supplement).

In total, 1789 patients received 1 or more doses of bimekizumab across the phase 2/3 trials (eFigure in the Supplement); total bimekizumab exposure was 3109.7 person-years and median bimekizumab duration was 673.0 days (range, 1-1037). Of these patients, 1495 were treated with 1 or more doses of bimekizumab in the phase 3 trials; total bimekizumab exposure was 2740.8 person-years and median bimekizumab duration was 730.0 days (range, 23-1037) (Table 1).

Overall Safety

TEAEs occurred at an EAIR of 202.4 per 100 person-years in the phase 2/3 trials (Table 1) and did not increase with longer duration of bimekizumab exposure (weeks 0-16: 324.7 per 100 person-years; 95% CI, 305.6-344.7 per 100 person-years; weeks 16-52: 225.5 per 100 person-years; 95% CI, 212.8-238.7 per 100 person-years; weeks 52-104: 149.1 per 100 person-years; 95% CI, 139.4-159.3 per 100 person-years) (Figure 1A). In the phase 3 trials, the overall EAIR of TEAEs was lower in patients treated with bimekizumab, 320 mg, Q8W (141.4 per 100 person-years; 95% CI, 129.6-153.9 per 100 person-years) than with bimekizumab, 320 mg, Q4W (219.6 per 100 person-years; 95% CI, 207.3-232.3 per 100 person-years) (Table 1).

In the phase 2/3 trials, serious TEAEs occurred at a rate of 5.9 per 100 person-years (95% CI, 5.1-6.9 per 100 person-years) and EAIRs were consistent throughout the observed treatment period (weeks 0-16: 6.1 per 100 person-years; 95% CI, 4.2-8.6 per 100 person-years; weeks 16-52: 6.8 per 100 person-years; 95% CI, 5.3-8.6 per 100 person-years; weeks 52-104: 5.6 per 100 person-years; 95% CI, 4.3-7.1 per 100 person-years) (Figure 1B). The EAIR of discontinuations due to a TEAE was 3.8 per 100 person-years and was lower during the second year of treatment compared with the first. EAIRs decreased over the observed treatment period (weeks 0-16: 6.9 per 100 person-years; 95% CI, 4.8-9.5 per 100 person-years; weeks 16-52: 4.9 per 100 person-years; 95% CI, 3.6-6.4 per 100 person-years; weeks 52-104: 2.1 per 100 person-years; 95% CI, 1.4-3.1 per 100 person-years). (Figure 1C). Most TEAEs were mild or moderate; severe TEAEs occurred at a rate of 5.4 per 100 person-years. The EAIRs of severe TEAEs did not increase with longer duration of bimekizumab exposure (weeks 0-16: 6.3 per 100 person-years; 95% CI, 4.4-8.8 per 100 person-years; weeks 16-52: 6.6 per 100 person-years; 95% CI, 5.2-8.4 per 100 person-

Table 1. Summary of Treatment Exposure and TEAEs in Bimekizumab-Treated Patients in the Phase 2 and Phase 3 Trials^a

Variable	EAIR per 100 person-years (95% CI)					
	Phase 3 (wk 0-16) ^b		Phase 3			Phase 2/3, bimekizumab, total (n = 1789)
	Placebo (n = 169)	Bimekizumab, 320 mg, Q4W (n = 670)	Bimekizumab, 320 mg, Q4W (n = 1456)	Bimekizumab, 320 mg, Q8W (n = 930)	Bimekizumab, total (n = 1495)	
Total exposure, person-years	51.6	207.7	1863.6	879.8	2740.8	3109.7
Exposure, d						
Mean (SD)	107.4 (16.8)	110.6 (7.3)	456.3 (262.5)	342.2 (236.1)	659.0 (213.6)	608.5 (232.6)
Median (range)	112.0 (28-120)	112.0 (28-122)	455.5 (23-1037)	293.0 (1-869)	730.0 (23-1037)	673.0 (1-1037)
Any TEAE	205.0 (161.0-257.4)	305.8 (276.4-337.6)	219.6 (207.3-232.3)	141.4 (129.6-153.9)	192.7 (182.5-203.3)	202.4 (192.6-212.6)
Severe TEAEs	7.8 (2.1-19.9)	3.9 (1.7-7.6)	5.3 (4.3-6.5)	4.8 (3.4-6.5)	5.0 (4.2-5.9)	5.4 (4.6-6.3)
TEAEs leading to discontinuation	13.8 (5.6-28.5)	5.3 (2.7-9.5)	3.6 (2.8-4.5)	2.7 (1.8-4.1)	3.3 (2.7-4.1)	3.8 (3.1-4.6)
Treatment-related TEAEs ^c	30.7 (17.2-50.7)	80.0 (67.5-94.2)	43.4 (39.8-47.1)	28.9 (25.0-33.2)	35.5 (32.8-38.3)	35.4 (32.9-38.0)
Serious TEAEs	7.8 (2.1-20.0)	5.3 (2.7-9.5)	6.2 (5.1-7.4)	5.3 (3.8-7.0)	5.9 (5.0-6.9)	5.9 (5.1-6.9)
TEAEs leading to death	1.9 (0.0-10.8)	0.5 (0.0-2.7)	0.3 (0.1-0.7)	0.3 (0.1-1.0)	0.3 (0.2-0.6)	0.4 (0.2-0.6)

Abbreviations: EAIR, exposure-adjusted incidence rate; Q4W, every 4 weeks; Q8W, every 8 weeks; TEAE, treatment-emergent adverse event.

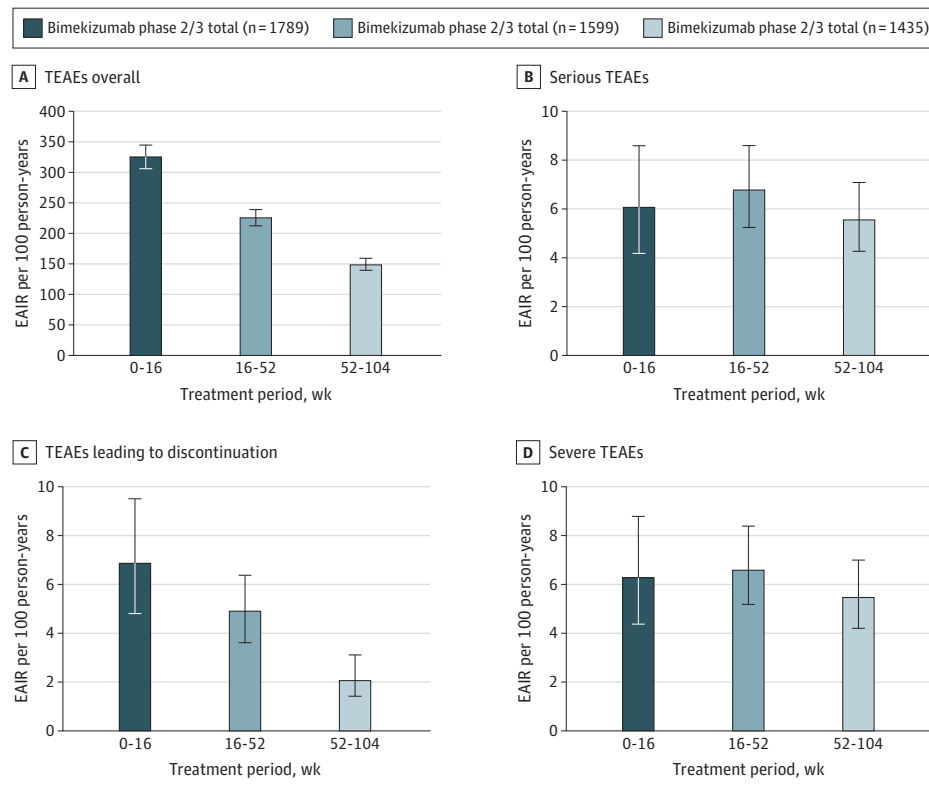
^a For patients who received both Q4W and Q8W bimekizumab doses during the trials, TEAEs were assigned to the dose most recently received before the date of onset of the TEAE. Patients who received both bimekizumab, 320 mg, Q4W and Q8W at different times in the trials are included in the total population count of each treatment group, but only once in each bimekizumab total group. Therefore, the total number of patients in both the Q4W and Q8W

groups exceeds the total number of patients in the bimekizumab total groups. The data cutoff for the ongoing BE BRIGHT trial was November 9, 2020.

^b Data are reported for events that occurred during the initial 16-week treatment period of the BE VIVID and BE READY placebo-controlled phase 3 randomized clinical trials, using a different pool of patients to the longer-term analyses.

^c Assessed by the investigators as related to treatment.

Figure 1. Incidence Rates of Treatment-Emergent Adverse Events (TEAEs) by Treatment Period



Data are reported as the exposure-adjusted incidence rate (EAIR) per 100 person-years for TEAEs that occurred during the initial 16-week treatment period of the phase 2/3 trials (weeks 0-16), during the maintenance period (weeks 16-52) and during the second year (weeks 52-104). Error bars represent 95% CIs.

Table 2. Incidence Rates of TEAEs of Interest^a

Variable	EAIR per 100 person-years (95% CI)			
	Phase 3			Phase 2/3, bimekizumab, total (n = 1789)
	Bimekizumab, 320 mg Q4W (n = 1456)	Bimekizumab, 320 mg Q8W (n = 930)	Bimekizumab, total (n = 1495)	
Serious infections	1.4 (0.9-2.1)	0.3 (0.1-1.0)	1.1 (0.7-1.5)	1.0 (0.7-1.4)
Active tuberculosis	0	0	0	0
Fungal infections	25.7 (23.2-28.4)	16.5 (13.8-19.7)	20.7 (18.9-22.8)	20.1 (18.4-22.0)
<i>Candida</i> infections	18.9 (16.8-21.1)	10.6 (8.5-13.1)	14.6 (13.1-16.3)	14.2 (12.8-15.7)
Oral candidiasis	16.4 (14.5-18.5)	9.6 (7.6-12.0)	12.9 (11.5-14.4)	12.6 (11.3-14.0)
Oropharyngeal candidiasis	1.1 (0.7-1.7)	0.3 (0.1-1.0)	0.9 (0.6-1.3)	0.8 (0.6-1.2)
Skin candidiasis	0.7 (0.4-1.2)	0.8 (0.3-1.6)	0.7 (0.4-1.1)	0.7 (0.4-1.0)
Vulvovaginal candidiasis	0.8 (0.5-1.3)	0	0.6 (0.3-0.9)	0.6 (0.3-0.9)
Esophageal candidiasis	0.2 (0.1-0.6)	0.1 (0.0-0.6)	0.2 (0.1-0.4)	0.2 (0.1-0.4)
Tinea infections	3.0 (2.3-4.0)	2.9 (1.9-4.3)	2.8 (2.2-3.5)	2.7 (2.1-3.3)
Fungal infections NEC ^b	3.8 (2.9-4.8)	2.3 (1.4-3.6)	3.1 (2.5-3.9)	3.1 (2.5-3.7)
Inflammatory bowel disease	0.2 (0.0-0.5)	0.1 (0.0-0.6)	0.1 (0.0-0.4)	0.1 (0.0-0.3)
Adjudicated MACE	0.5 (0.3-1.0)	0.3 (0.1-1.0)	0.5 (0.3-0.8)	0.5 (0.3-0.8)
Malignant neoplasms	0.6 (0.3-1.1)	0.9 (0.4-1.8)	0.7 (0.4-1.1)	0.8 (0.5-1.2)
Excluding NMSC	0.3 (0.1-0.7)	0.7 (0.3-1.5)	0.4 (0.2-0.8)	0.5 (0.2-0.8)
NMSC	0.3 (0.1-0.7)	0.2 (0.0-0.8)	0.3 (0.1-0.6)	0.3 (0.2-0.6)
Adjudicated SIB	0.1 (0.0-0.3)	0	0.0 (0.0-0.2)	0.0 (0.0-0.2)
Neutropenia	0.8 (0.5-1.3)	0.2 (0.0-0.8)	0.6 (0.3-1.0)	0.8 (0.6-1.2)
Hepatic events	3.7 (2.9-4.7)	2.9 (1.9-4.3)	3.2 (2.6-4.0)	4.3 (3.6-5.2)
Elevated liver enzyme levels ^c	3.1 (2.4-4.1)	2.2 (1.3-3.4)	2.6 (2.0-3.3)	3.6 (3.0-4.4)
Serious hypersensitivity reactions ^d	0.2 (0.0-0.5)	0.1 (0.0-0.6)	0.1 (0.0-0.4)	0.2 (0.1-0.4)
Injection site reactions	2.7 (2.0-3.6)	1.7 (1.0-2.9)	2.3 (1.8-2.9)	2.3 (1.8-2.9)

Abbreviations: EAIR, exposure-adjusted incidence rate; MACE, major adverse cardiac event; NEC, not elsewhere classified; NMSC, nonmelanoma skin cancer; Q4W, every 4 weeks; Q8W, every 8 weeks; SIB, suicidal ideation and behavior; TEAE, treatment-emergent adverse event.

^a For patients who received both Q4W and Q8W bimekizumab doses during the trials, TEAEs were assigned to the dose most recently received before the date of onset of the TEAE. Patients who received both bimekizumab, 320 mg, Q4W and Q8W at different times in the trials are included in the total population count of each treatment group, but only once in each bimekizumab total group. Therefore, the total number of patients in both the Q4W and Q8W groups exceeds the total number of patients in the bimekizumab total groups. The data cutoff for the ongoing BE BRIGHT trial was November 9, 2020.

^b Includes oral fungal infection, skin fungal infection, vulvovaginal mycotic infection, onychomycosis, tongue fungal infection, fungal infection, fungal pharyngitis, genital fungal infection, fungal oropharyngitis, anal fungal infection, ear fungal infection, and fungal esophagitis.

^c Liver function tests included the following preferred terms reported as adverse events: increased hepatic enzyme, aspartate aminotransferase, γ -glutamyl transferase, alanine aminotransferase, liver function test, transaminases, blood bilirubin, and abnormal liver function test.

^d There were no incidences of acute anaphylactic reactions associated with bimekizumab.

years; weeks 52-104: 5.5 per 100 person-years; 95% CI, 4.2-7.0 per 100 person-years) (Figure 1D). The most frequently reported TEAEs by MedDRA-preferred term were nasopharyngitis (19.1 per 100 person-years; 95% CI, 17.4-20.9), oral candidiasis (12.6 per 100 person-years; 95% CI, 11.3-14.0), and upper respiratory tract infection (8.9 per 100 person-years; 95% CI, 7.8-10.1) (eTable 4 in the Supplement).

Deaths

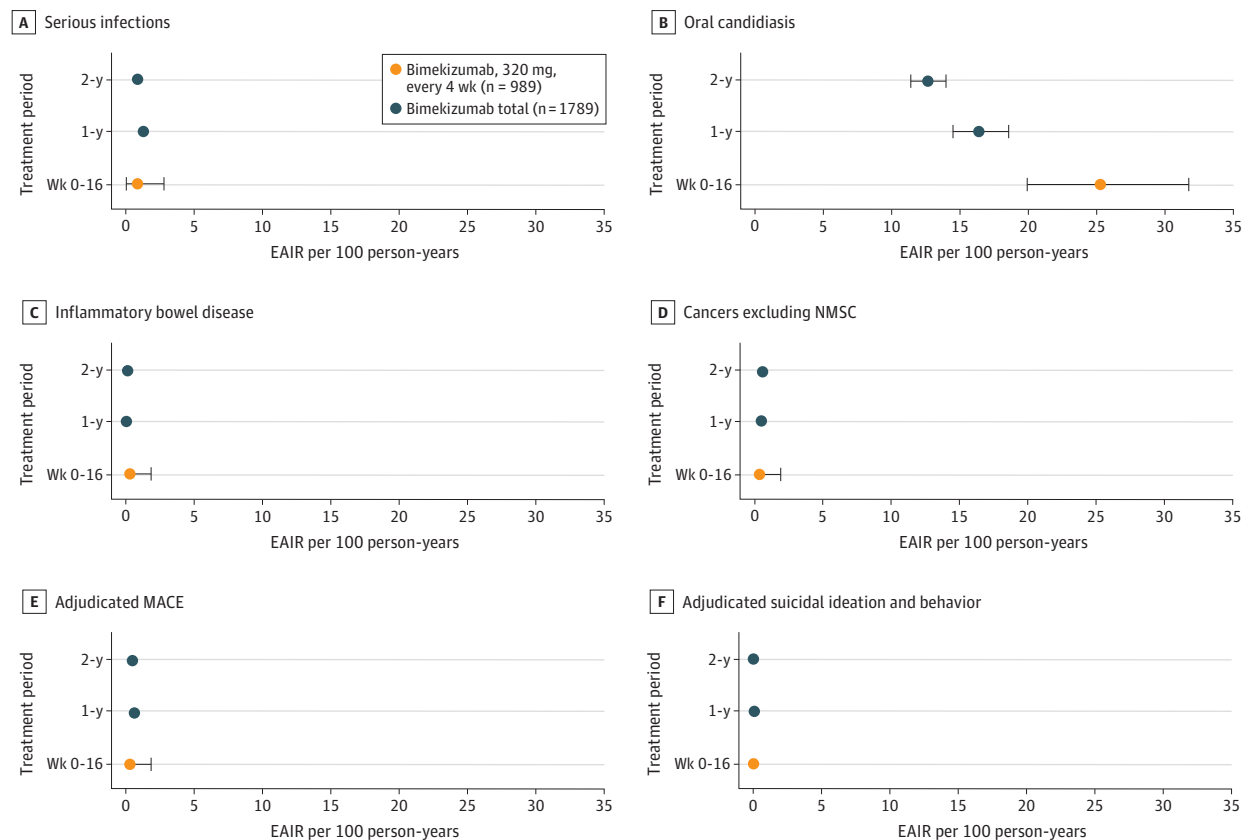
In total, 11 deaths (0.4 per 100 person-years) were reported for patients receiving bimekizumab in the phase 2/3 trials (Table 1). Causes of death were reported under the following MedDRA-preferred terms, each for 1 patient, unless otherwise specified: cardiopulmonary failure, myocardial infarction, cardiac arrest (3 patients), death (unknown cause, 3 months after last bimekizumab dose), brain neoplasm, completed suicide, dyspnea, chronic obstructive pulmonary disease, circulatory

collapse (2 patients), respiratory failure, and hypovolemic shock. No deaths were assessed by the investigators as related to treatment.

Infections

The EAIR of infections was 96.7 per 100 person-years. The EAIR of serious infections was low (phase 2/3 trials: 1.0 per 100 person-years; 95% CI, 0.7-1.4 per 100 person-years), and in the phase 3 trials was lower with bimekizumab, 320 mg, Q8W (0.3 per 100 person-years; 95% CI, 0.1-1.0 per 100 person-years) compared with Q4W (1.4 per 100 person-years; 95% CI, 0.9-2.1 per 100 person-years) (Table 2). The incidence of serious infections did not increase with a longer duration of bimekizumab exposure (weeks 0-16: 1.0 per 100 person-years; 95% CI, 0.2-2.9 per 100 person-years; 1 year: 1.4 per 100 person-years; 95% CI, 0.9-2.0 per 100 person-years; 2 years: 1.0 per 100 person-years; 95% CI, 0.7-1.4 per 100 person-years)

Figure 2. Cumulative Incidence Rates for Selected Treatment-Emergent Adverse Events (TEAEs) of Interest



Serious infections (A), oral candidiasis (B), inflammatory bowel disease (C), malignant neoplasms other than nonmelanoma skin cancer (NMSC) (D), adjudicated major adverse cardiac event (MACE) (E), and adjudicated suicidal ideation and behavior (F) are reported as the exposure-adjusted incidence rate (EAIR) per 100 person-years. Data reported for weeks 0-16 were pooled from 3 pivotal phase 3 studies (BE VIVID, BE READY, and BE SURE). All patients

assigned to bimekizumab received bimekizumab, 320 mg, every 4 weeks (Q4W). Longer-term data through to 1 year (clinical cutoff date November 1, 2019) and 2 years (clinical cutoff date November 9, 2020) of bimekizumab treatment were pooled from 4 phase 2 and 4 phase 3 randomized clinical trials. Error bars represent 95% CIs.

(Figure 2A). The most common serious infection was cellulitis (4 events). No cases of active TB were reported (Table 2).

The overall EAIR of opportunistic infections was 1.2 per 100 person-years (95% CI, 0.9-1.7). Almost all opportunistic infections reported with bimekizumab were localized mucocutaneous fungal infections predefined as opportunistic by company convention, except for 1 serious case of ophthalmic herpes zoster that resolved with treatment and did not lead to discontinuation.

Fungal infections occurred at a rate of 20.1 per 100 person-years (95% CI, 18.4-22.0) (phase 2/3). Most were *Candida* infections (14.2 per 100 person-years; 95% CI, 12.8-15.7 per 100 person-years); EAIRs for other fungal infections, including *Tinea* infections, were low (Table 2).

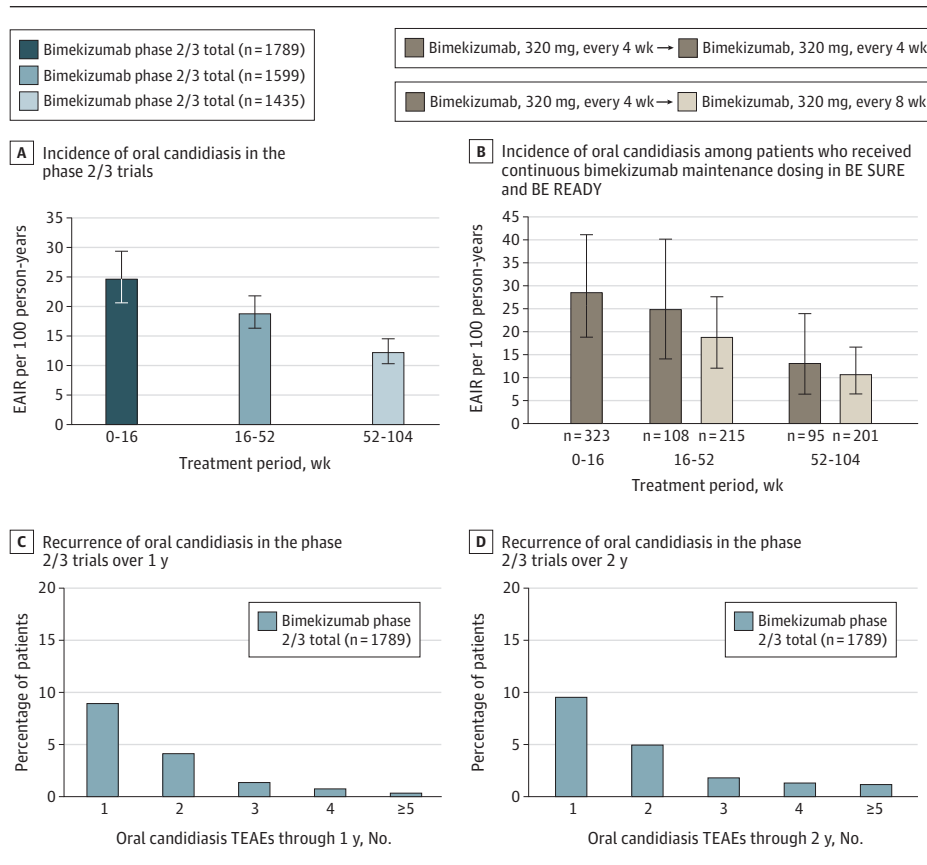
Candidiasis

Candida infections were predominantly reported as oral candidiasis (12.6 per 100 person-years; 95% CI, 11.3-14.0 per 100 person-years) (Table 2). Of the patients in the phase 2/3 trials, 275 of 1789 (15.4%) reported an oral candidiasis event in the first year and 131 of 1435 (9.1%) during the second year. The

cumulative EAIR of oral candidiasis decreased with a longer duration of bimekizumab exposure as shown in Figure 2B (weeks 0-16: 25.3 per 100 person-years; 95% CI, 19.9-31.8 per 100 person-years; 1 year: 16.4 per 100 person-years; 95% CI, 14.5-18.5 per 100 person-years; 2 year: 12.6 per 100 person-years; 95% CI, 11.3-14.0 per 100 person-years). In the phase 2/3 trials, the incidence of oral candidiasis decreased by treatment period as shown in Figure 3A (weeks 0-16: 24.7 per 100 person-years; 95% CI, 20.6-29.3 per 100 person-years; weeks 16-52: 18.9 per 100 person-years; 95% CI, 16.3-21.8 per 100 person-years; weeks 52-104: 12.3 per 100 person-years; 95% CI, 10.3-14.6 per 100 person-years). Most oral candidiasis events were mild or moderate in severity, 5 were reported as severe (0.2 per 100 person-years; 95% CI, 0.1-0.4), and none were reported as serious.

In the phase 3 trials, the EAIR of oral candidiasis was lower for patients who received bimekizumab, 320 mg, Q8W (9.6 per 100 person-years; 95% CI, 7.6-12.0 per 100 person-years) vs bimekizumab, 320 mg, Q4W (16.4 per 100 person-years; 95% CI, 14.5-18.5 per 100 person-years) (Table 2). In BE SURE and BE READY, in which both bimekizumab Q4W and Q8W mainte-

Figure 3. Incidence and Recurrence of Oral Candidiasis Treatment-Emergent Adverse Events (TEAEs) Over 1 and 2 Years



A, Data are reported as the exposure-adjusted incidence rate (EAIR) per 100 person-years for events that occurred during the initial 16-week treatment period of the phase 2/3 trials (weeks 0-16), during the maintenance period (weeks 16-52), and during the second year (weeks 52-104). B, Data are reported as the EAIR per 100 person-years for all patients who received 1 or more doses of bimekizumab at week 16 or later and received continuous bimekizumab maintenance dosing (every 4 weeks [Q4W] or every 8 weeks [Q8W]) during the maintenance periods of the BE READY and BE SURE phase 3 studies and the BE BRIGHT open-label extension. All patients received bimekizumab, 320 mg, Q4W during the initial 16-week period of BE READY and BE SURE. C, Data are reported to 1 year and 2 years of treatment for all patients in the phase 2/3 trials who received 1 or more doses of bimekizumab. Error bars represent 95% CIs.

nance dosing regimens were possible, the EAIR of oral candidiasis was lower in the second year compared with the first for patients who received either bimekizumab Q4W or Q8W continuous maintenance dosing. In addition, the EAIR of oral candidiasis was lower in each period for patients who received continuous Q8W bimekizumab maintenance dosing compared with continuous Q4W maintenance dosing (weeks 16-52, Q8W: 18.6 per 100 person-years; 95% CI, 12.0-27.5 per 100 person-years; Q4W: 24.6 per 100 person-years; 95% CI, 14.1-40.0 per 100 person-years; weeks 52-104, Q8W: 10.6 per 100 person-years; 95% CI, 6.4-16.5 per 100 person-years; Q4W: 13.0 per 100 person-years; 95% CI, 6.2-23.8 per 100 person-years) (Figure 3B).

Over 2 years of treatment, 170 patients (9.5%) reported 1 incidence of oral candidiasis, 88 (4.9%) reported 2 incidences, 33 (1.8%) reported 3 incidences, 22 (1.2%) reported 4 incidences, and 20 (1.1%) reported 5 or more incidences (Figure 3D). The method of oral candidiasis treatment was at the discretion of the investigators and most patients with oral candidiasis were treated with nystatin and/or fluconazole. The median treatment duration with antifungal therapies was 12.0 days (IQR, 7.0-22.0 days). Most events were resolved with treatment; 3 patients (0.2%) with oral candidiasis discontinued bimekizumab.

In the phase 2/3 trials, 2 patients (0.1%) with esophageal candidiasis, 1 (<0.1%) with oropharyngeal candidiasis, and

1 (<0.1%) with skin *Candida* discontinued bimekizumab treatment. Of these, 1 patient receiving bimekizumab, 320 mg, Q4W reported a serious, severe case of esophageal candidiasis; this patient was hospitalized, received antifungal therapy, and the infection resolved after 14 days. No other serious *Candida* infections were reported.

Inflammatory Bowel Disease

The EAIR of IBD was low (0.1 per 100 person-years; 95% CI, 0.0-0.3 per 100 person-years) and did not increase with longer duration of bimekizumab exposure (weeks 0-16: 0.3 per 100 person-years; 95% CI, 0.0-1.8 per 100 person-years; 1 year: 0.1; 95% CI, 0.0-0.3 per 100 person-years; 2 years: 0.1 per 100 person-years; 95% CI, 0.0-0.3 per 100 person-years) (Figure 2C). In total, 4 cases were reported (2 Crohn disease, 1 colitis, and 1 ulcerative colitis); all occurred in the phase 3 trials (Table 2). Three cases of IBD led to discontinuation of treatment, 2 of which were considered by the investigators to be related to treatment.

Malignant Neoplasms

In the phase 2/3 trials, excluding nonmelanoma skin cancer, there were 14 incidences of cancer (0.5 per 100 person-years; 95% CI, 0.2-0.8 per 100 person-years) (Table 2); the EAIR remained low with a longer duration of bimekizumab exposure (Figure 2D). Overall, including nonmelanoma skin cancer, 26

cancers were reported in 24 patients (0.8 per 100 per 100 person-years; 95% CI, 0.5-1.2 per 100 person-years) (Table 2). No incidences of cancer were assessed by the investigators as related to treatment.

Other TEAEs of Interest

The EAIR of adjudicated major adverse cardiac events in the phase 2/3 trials was 0.5 per 100 person-years (95% CI, 0.3-0.8 per 100 person-years) (Table 2) and did not increase with a longer duration of bimekizumab exposure (Figure 2E). The EAIR of neutropenia was 0.8 per 100 person-years (95% CI, 0.6-1.2 per 100 person-years) (Table 2); most cases were mild or moderate and 2 led to discontinuation of treatment. The EAIR of serious hypersensitivity reactions was low (0.2 per 100 person-years; 95% CI, 0.1-0.4 per 100 person-years) (Table 2). Injection site reactions occurred at an EAIR of 2.3 per 100 person-years (95% CI, 1.8-2.9 per 100 person-years); all cases were mild or moderate and none led to discontinuation. Hepatic events occurred at an EAIR of 4.3 per 100 person-years (95% CI, 3.6-5.2 per 100 person-years) and were predominantly reports of increased liver enzyme levels (Table 2). The increased liver enzyme levels observed mostly had alternative causes and were reversed with either continued treatment or shortly after discontinuation, such that bimekizumab was still at therapeutic levels.

Overall, the incidence of adjudicated SIB was low (0.0 per 100 person-years; 95% CI, 0.0-0.2 per 100 person-years) (Table 2; Figure 2F); 1 patient receiving bimekizumab, 320 mg, Q4W recorded a positive electronic Columbia Suicide Severity Rating Scale response to question 4 (active suicidal ideation with some intent to act), which was adjudicated as SIB and led to discontinuation of treatment. One event of completed suicide in a patient receiving bimekizumab was adjudicated as SIB after the data cutoff for these analyses and therefore is not included in the EAIR of SIB reported herein. The patient had no known psychiatric medical history, but financial issues were reported as risk factors; the event was assessed by the investigators as not related to treatment.

Discussion

In these analyses, data were pooled to include 2 years of study treatment for patients with moderate to severe plaque psoriasis who received bimekizumab across 4 phase 2 randomized clinical trials and 4 phase 3 randomized clinical trials. Overall, the incidence of TEAEs decreased with a longer duration of bimekizumab exposure. In the phase 3 trials, the incidence of TEAEs was lower in patients treated with bimekizumab, 320 mg, Q8W compared with Q4W. The rate of discontinuation due to TEAEs was low.

Nasopharyngitis, oral candidiasis, and upper respiratory tract infection were the most common TEAEs reported with bimekizumab. The risk of infections for patients with psoriasis is higher than in the general population, and anti-IL-17 biologics may increase this risk.^{4,29,30} In addition, the use of biologic and systemic treatments for psoriasis may increase the risk of serious infections.³¹ In these analyses, the EAIR of

serious infections was low (1.0 per 100 person-years), did not increase with longer exposure to bimekizumab, and was comparable with the estimated rate among patients with psoriasis in the Psoriasis Longitudinal Assessment and Registry (1.6 per 100 person-years),³² and EAIRs reported in clinical studies with other IL-17 inhibitors (secukinumab: 1.4 per 100 person-years^{10,33}; brodalumab: 1.0-1.3 per 100 person-years¹³; and ixekizumab: 1.3-2.3 per 100 person-years).^{8,12,34}

Interleukin-17 is involved in mucosal host defenses against fungal infections; therefore, anti-IL-17 biologics can be associated with an increased risk of oral mucocutaneous candidiasis.³⁵⁻³⁹ Consistent with individual study data,¹⁷⁻²² oral candidiasis was one of the most common TEAEs reported with bimekizumab (12.6 per 100 person-years), and the EAIR was higher than that reported in pooled studies up to 5 years with other IL-17 inhibitors (secukinumab: 1.9 per 100 person-years³³; ixekizumab: 0.8-1.2 per 100 person-years).^{12,34} In these pooled data, most oral candidiasis events with bimekizumab were mild to moderate in intensity, and the rate of discontinuation due to oral candidiasis was low (0.2%). The EAIR of oral candidiasis decreased with a longer duration of bimekizumab exposure and was lower with bimekizumab Q8W compared with Q4W. The EAIRs of other fungal infections were low.

Patients with psoriasis can be at increased risk of IBD.⁴⁰⁻⁴² In addition, rare exacerbations of IBD have been reported with inhibitors of IL-17A.^{43,44} In the phase 2/3 trials, the incidence of IBD with bimekizumab was low (0.1 per 100 person-years) and similar to rates reported in a psoriasis cohort study (Crohn disease: 0.03 per 100 person-years; ulcerative colitis: 0.07 per 100 person-years),⁴² and other long-term anti-IL-17 clinical studies (secukinumab: 0.01-0.3 per 100 person-years^{10,33}; ixekizumab: 0.2 per 100 person-years).¹² Cases of IBD in these pooled analyses were mild or moderate, 3 led to discontinuation, and 2 were assessed by the investigators as related to treatment. Inflammatory bowel disease events were not adjudicated for these analyses and, owing to the low incidence, it was not possible to identify specific characteristics that may have predisposed patients to develop IBD.

Psoriasis can place a substantial burden on patient quality of life, and patients may be at increased risk of depression and SIB.^{24,45} In these analyses, the incidence of adjudicated SIB was low and within the background rate for patients with psoriasis.⁴⁶

Limitations

This study has limitations. Although these analyses report safety data for a large population of patients who received bimekizumab, the data may not fully represent a real-world population owing to the specific patient inclusion and exclusion criteria of the trials analyzed. Furthermore, the population may be too small to draw definitive conclusions for more rare events.

Conclusions

In these analyses pooled to include 2 years of treatment in a cohort of patients from 8 randomized clinical trials, bimeki-

zumab demonstrated a favorable safety profile and no safety signals were observed. In the phase 3 trials, the incidence of AEs was lower with bimekizumab, 320 mg, Q8W compared with Q4W. Overall, bimekizumab was well tolerated in patients with moderate to severe plaque psoriasis, and there was no increased risk of AEs with longer duration of exposure.

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Additional Information: The trials examined in this article (BE ABLE 1, BE ABLE 2, PS0016, PS0018, BE VIVID, BE READY, BE SURE, and BE BRIGHT) were sponsored by UCB Pharma. Underlying data from this manuscript may be requested by qualified researchers 6 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 anonymized individual patient-level data and redacted trial documents, which may include analysis-ready data sets, study protocol, annotated case report form, statistical analysis plan, data set specifications, and clinical study report. Before use of the data, proposals need to be approved by an independent review panel at <http://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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