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ORIGINAL RESEARCH

Bimekizumab Efficacy and Safety in Japanese Patients with Plaque Psoriasis in BE VIVID: A Phase 3, Ustekinumab and Placebo-Controlled Study

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ABSTRACT

Introduction: Bimekizumab treatment resulted in improved clinical outcomes in patients with moderate-to-severe plaque psoriasis in BE VIVID, a 52-week, phase 3, randomized, ustekinumab and placebo-controlled study. We present data from the BE VIVID Japan patient subpopulation.

Methods: Globally, patients were randomized to receive bimekizumab 320 mg every 4 weeks (Q4W), ustekinumab (45/90 mg weight-based at baseline and week 4, then every 12 weeks), or placebo (Q4W through week 16, then bimek-

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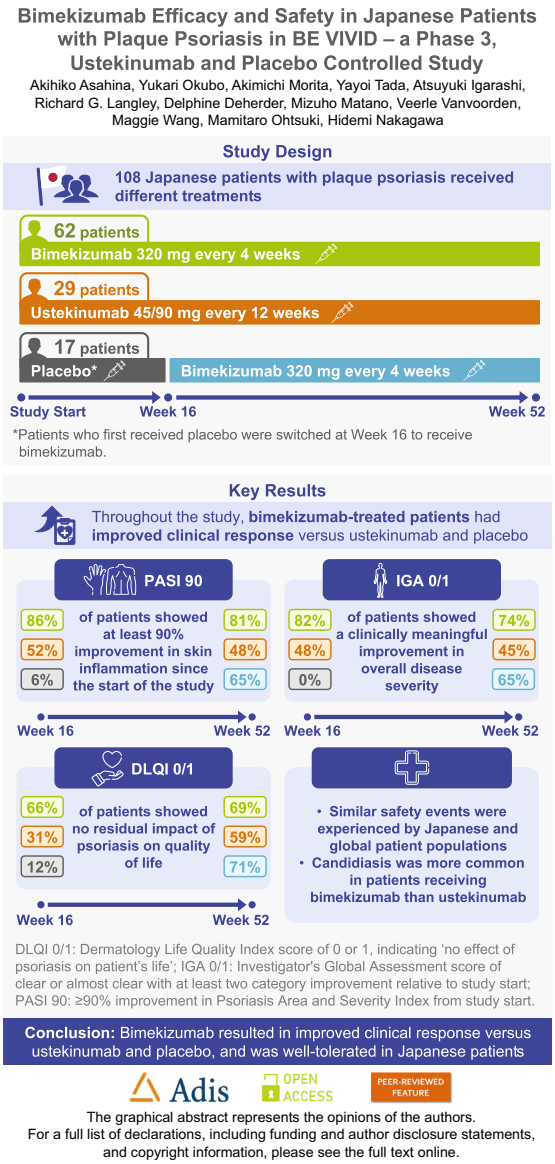
izumab 320 mg Q4W). Efficacy endpoints included week 16 Psoriasis Area and Severity Index (PASI) 90 and Investigator's Global Assessment (IGA) 0/1, and other outcomes [PASI 100, PASI 75, IGA 0, Dermatology Life Quality Index (DLQI) 0/1, absolute PASI, scalp IGA, Psoriasis Symptoms and Impacts Measure (P-SIM) responses]. Safety analyses were conducted.

Results: There were 108 Japanese randomized patients (bimekizumab: 62; ustekinumab: 29; placebo: 17). At week 16, bimekizumab-treated patients had a higher clinical response versus ustekinumab and placebo (PASI 90: 85.5% versus 51.7% and 5.9%; IGA 0/1: 82.3% versus 48.3% and 0.0%). Over 52 weeks, improved clinical response was maintained with bimekizumab, including patients switching from placebo at week 16. Overall, the safety profile in Japanese patients was consistent with that observed in the global population.

Conclusion: Bimekizumab resulted in improved clinical response versus ustekinumab and placebo, and was well-tolerated in Japanese patients.

Trial registration: NCT03370133.

Graphical Abstract:



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Keywords: Absolute PASI; Active control; Bimekizumab; Japan subpopulation; Plaque psoriasis; Randomized controlled trial; Ustekinumab

Key Summary Points

Why carry out this study?

Biologic treatments targeting the IL-17 pathway have been recommended for treating patients with psoriasis, specifically in those who have not adequately responded to standard systematic therapies

Bimekizumab (BKZ) treatment, which inhibits IL-17A and IL-17F, has showed clinically meaningful improvements in patients with moderate-to-severe plaque psoriasis in BE VIVID, a global, 52-week, phase 3, randomized, ustekinumab and placebo-controlled study

This study aimed to evaluate the efficacy and safety of BKZ in the BE VIVID Japan patient subpopulation

What was learned from the study?

BKZ treatment resulted in improved clinical response compared with ustekinumab and placebo, and was well-tolerated in Japanese patients

These findings support the use of BKZ as a viable treatment option for Japanese patients with moderate-to-severe plaque psoriasis

DIGITAL FEATURES

This article is published with digital features, including a graphical abstract, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.21762908.

INTRODUCTION

Plaque psoriasis is a chronic, immune-mediated, inflammatory disease characterized by prominent skin lesions, which can be scaly, thick, and occasionally pruritic [1], and a substantial disease burden impacting on patient quality of life (QoL) [2, 3]. Psoriasis is additionally associated with increased risk of several comorbidities [4].

Interleukin (IL)-17A and IL-17F play a central role in the pathogenesis of psoriasis and psoriatic arthritis [5–7], and both are overexpressed in psoriatic lesional skin [5, 7, 8]. IL-17A and IL-17F share ~50% structural similarity and form homo- and heterodimers, with overlapping proinflammatory functions [9–11]. Biologic therapy, including treatments targeting the IL-17 pathway, are recommended by the Japanese Dermatological Association for patients with plaque-type psoriasis who have not adequately responded to standard systemic therapies and have ≥ 10% body surface area (BSA) affected, or who have refractory skin or joint symptoms intractable to systemic therapies and significantly impaired QoL [12].

Common biologic therapies targeting the IL-17 pathway inhibit IL-17 or target the IL-17 receptor complex [13–16]. Anti-IL-17A agents have demonstrated efficacy in treating patients with moderate-to-severe psoriasis; however, nearly one-third of patients have discontinued treatment within 5 years due to ineffectiveness, primary or secondary failure, infection, or other causes, and require additional treatment options [17]. Additionally, other factors may affect patient preferences when choosing biologic therapy and patients may prioritize different factors. A survey of 395 Japanese patients with psoriasis reported patients preferred drugs with long-term and early-onset efficacy, sustained efficacy after drug withdrawal, and low risk of serious infection, among other factors [18].

Bimekizumab is a humanized monoclonal immunoglobulin G1 antibody that selectively binds with high affinity to IL-17A and IL-17F, inhibiting downstream signaling [19, 20]. In four phase 3/3b clinical trials, bimekizumab demonstrated clinical superiority over placebo, adalimumab, secukinumab, and ustekinumab in patients with moderate-to-severe plaque psoriasis [21–24]. Recently, bimekizumab was approved in Japan for the treatment of plaque

psoriasis, generalized pustular psoriasis, and psoriatic erythroderma in patients who are not sufficiently responding to existing treatments [25].

Prevalence and severity of psoriasis can significantly vary between populations and countries due to genetic and environmental factors [26–28]. A lower prevalence of psoriasis in all ages was reported in Japan (0.4%), compared with Europe (0.7–2.9%) and the USA (5.1%) [26]. Additionally, psoriasis occurs predominantly in males in Japan [29, 30], unlike the approximately equal distribution of males and females in Western countries [28]. Higher expression of IL-17A and IL-17-regulated proinflammatory cytokines has been shown in Asian versus Western patients with plaque psoriasis [27]. Asian patients also tend to have milder forms of psoriasis, characterized by lesions of less epidermal thickness and radial expansion, compared with Western patients [27].

Absolute Psoriasis Area and Severity Index (PASI) thresholds represent relevant treatment targets in psoriasis and can supplement percentage PASI improvement when assessing treatment efficacy [31]. Among Japanese patients with plaque psoriasis, absolute PASI values of ≤ 2 or ≤ 3 have been used to demonstrate the efficacy of biologics [32, 33]. Absolute PASI values have also been shown to correlate with better QoL [or low Dermatology Life Quality Index (DLQI) values] [34].

Given the differences in disease epidemiology and severity between Japanese versus Western patient populations, this analysis of the BE VIVID Japan patient subpopulation aimed to evaluate the efficacy of bimekizumab in these patients. Absolute PASI values are reported alongside percentage PASI improvement, and other efficacy and safety outcomes.

METHODS

Study Design

BE VIVID (NCT03370133) was a phase 3, randomized, double-blinded, ustekinumab and placebo-controlled, multicenter study of bimekizumab in patients with moderate-to-severe plaque psoriasis. The study design was published previously [24]. The reported analysis was prespecified in the protocol and includes patients enrolled in BE VIVID, recruited from 30 sites in Japan between February 2018 and December 2019. Eligible patients were randomized to receive bimekizumab 320 mg every 4 weeks (Q4W), ustekinumab (45 mg for patients ≤ 100 kg or 90 mg for patients > 100 kg) at weeks 0, 4, and every 12 weeks (Q12W), or placebo Q4W to week 16 followed by bimekizumab 320 mg Q4W to week 52 (Supplementary Fig. S2).

After completion of BE VIVID, eligible patients could enroll in BE BRIGHT (NCT03598790), a 144-week, open-label extension study assessing the long-term safety, tolerability, and efficacy of bimekizumab. Those not enrolled in BE BRIGHT had a safety follow-up visit 20 weeks after the last dose of study treatment.

All participants provided written informed consent. All results presented in this article are in aggregate form, and no personally identifiable information was used in this study. The study protocol, amendments, and patient-informed consent were reviewed by a national, regional, or independent ethics committee or institutional review board. This study was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonization–Good Clinical Practice requirements, ethical principles that have their origin in the principles of the Declaration of Helsinki, and local laws of countries involved.

Patients

Adults aged ≥ 18 years with moderate-to-severe plaque psoriasis [PASI ≥ 12, $\geq 10\%$ BSA affected by psoriasis and Investigator's Global Assessment (IGA) score ≥ 3 on a 5-point scale] for ≥ 6 months before screening were enrolled. Patients were included if they were eligible for systemic psoriasis therapy and/or phototherapy. Patients were excluded if they previously received bimekizumab and/or ustekinumab;

had not responded within the first 12 weeks to any anti-IL-17 biologic or to > 1 non-anti-IL-17 biologic treatment; had a current or history of opportunistic, recurrent, or chronic infection. Full details of inclusion and exclusion criteria have been published previously [24].

Study Procedures

Efficacy and safety assessments were made at baseline, weeks 1, 2, 4, and Q4W thereafter through week 52. Data from the Psoriasis Symptoms and Impacts Measure (P-SIM), a 14-item patient-reported outcome (PRO) measure assessing severity of key signs, symptoms, and effects of psoriasis, where items, including pain, itch, and scaling, were scored daily (0–10; no–very severe) using a handheld electronic device [35], and averaged weekly through week 16. DLQI was measured at baseline, weeks 1, 2, 4, Q4W to week 16, and then Q12W thereafter through week 52.

Efficacy Outcomes

Efficacy endpoints in this analysis include the proportion of patients with an improvement of ≥ 90% from baseline in PASI (PASI 90) and IGA response score of 0 (clear skin) or 1 (almost clear skin) with ≥ 2 category improvement relative to baseline), both at week 16. Other endpoints in this analysis include the proportion of patients with PASI 100 (complete skin clearance) at week 16; IGA 0 response at week 16; PASI 75 at week 4; scalp IGA 0/1 response at week 16 in patients with scalp psoriasis at baseline; PASI 90 and IGA responses at weeks 12 and 52; P-SIM responses for itch (> 2.39), scaling (> 2.86), and pain (> 1.98) at week 16. P-SIM response thresholds were previously determined to represent a meaningful improvement in phase 3 study protocols of bimekizumab in psoriasis [36]. The proportion of patients with DLQI 0/1 (i.e., no effect of psoriasis on patient's life), PASI 100, PASI 75, IGA 0, and absolute PASI ≤ 1, PASI ≤ 2, and PASI ≤ 3 responses through week 52 were also included.

Safety Outcomes

The occurrence of treatment emergent adverse events (TEAEs) and serious TEAEs was evaluated over 52 weeks of treatment, including common TEAEs, and safety topics of interest, including infections (serious, opportunistic, fungal, and tuberculosis), liver function test changes or enzyme elevations, inflammatory bowel disease, major cardiovascular adverse events, malignancies, anaphylactic reactions, neutropenia, and suicidal ideation and behavior. Suicidal ideation and behavior events, and major cardiovascular adverse events were adjudicated by an independent committee.

Statistical Analysis

Full details of statistical analyses performed have been previously reported [24]. Efficacy analyses included all randomized patients in the intention-to-treat (ITT) population. Clinical responses of treatment groups at specific timepoints were compared using the stratified Cochran-Mantel–Haenszel test. For binary variables, nonresponder imputation (NRI) was used to account for missing data. Observed case (OC) data were also reported. Given the small sample size of the Japan subpopulation, *p*-values were not reported.

Safety analyses of the initial treatment period included patients who had ≥ 1 dose of study treatment (safety set), while that of initial and maintenance treatment periods included patients who had ≥ 1 dose of active bimekizumab or ustekinumab (active medication set).

RESULTS

Patients

Of the 735 patients screened in the overall population, 122 were from Japan. Of these, 108 were included in the ITT population: 62 patients received bimekizumab, 29 received ustekinumab, and 17 received placebo. For the initial and maintenance periods, the number of patients who discontinued the study was similar

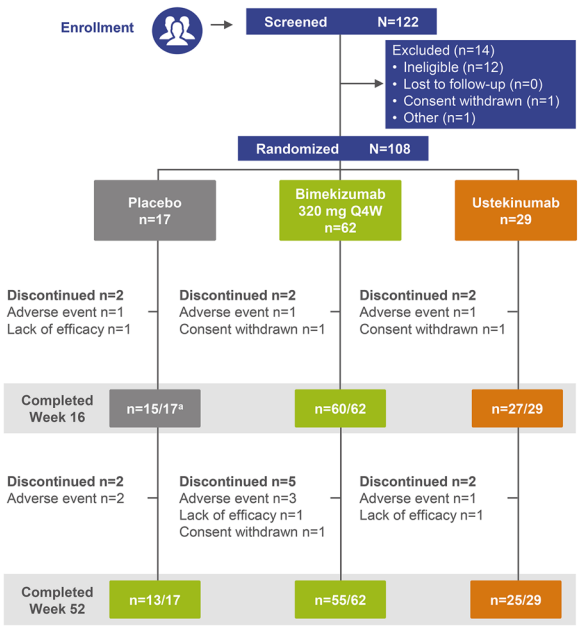


Fig. 1 Japanese patient subpopulation trial profile. The *n* numbers at weeks 16 and 52 represent the number of patients in each treatment arm who completed the study up to that time, and whose data were considered for inclusion in the analysis. [a]Patients were switched from placebo to bimekizumab 320 mg Q4W at week 16. Q4W: every 4 weeks

between treatment arms, considering the imbalance in size due to the randomization ratio (Fig. 1).

Demographics and baseline disease characteristics were balanced across treatment groups and were generally consistent with the BE VIVID global patient population, although some parameters were lower in the Japanese subpopulation, including mean weight, disease duration, DLQI, and prior biologic exposure (Table 1) [24]. Enrolled Japan subpopulation patients had a mean PASI of 22.3, mean BSA of 32.3, and 43/108 (39.8%) of patients had an IGA score of 4, indicating their psoriasis was severe. Most patients were male (89/108; 82.4%), and the mean age and weight across all patients were 51.6 years and 72.6 kg, respectively. Twenty-one (19.4%) patients had prior biologic exposure.

Clinical Efficacy Endpoints (NRI)

More patients receiving bimekizumab than those receiving ustekinumab and placebo achieved PASI 90 and an IGA score of 0/1 at week 16. PASI 90 was achieved by 85.5% bimekizumab- versus 51.7% ustekinumab- and 5.9% placebo-treated patients (Fig. 2a). IGA 0/1 was achieved by 82.3% bimekizumab- versus 48.3% ustekinumab- and 0% placebo-treated patients (Fig. 2b).

Complete skin clearance (PASI 100) was achieved by more patients receiving bimekizumab at week 16 versus ustekinumab and placebo (51.6% versus 13.8% and 0%, respectively; Fig. 2c). More patients receiving bimekizumab achieved IGA 0 at week 16 versus ustekinumab and placebo (51.6% versus 17.2% and 0%, respectively; Fig. 2d).

Higher responses were observed with bimekizumab treatment versus ustekinumab and placebo as early as week 4, after one bimekizumab dose. At week 4, PASI 75 was achieved by 85.5% bimekizumab- versus 3.4% ustekinumab- and 0% placebo-treated patients (Supplementary Fig. S1a). Higher response rates at week 4 were also observed for PASI 90 and IGA 0/1 (Supplementary Fig. S1b and S1c).

The higher proportion of bimekizumab-treated patients achieving PASI 90 and IGA 0/1 versus ustekinumab were maintained through week 52. At week 52, PASI 90 was achieved by 80.6% bimekizumab- versus 48.3% ustekinumab-treated patients (Fig. 3a). IGA 0/1 was achieved by 74.2% bimekizumab- versus 44.8% ustekinumab-treated patients (Fig. 3b). PASI 100, IGA 0, and PASI 75 response rates were also maintained through week 52 in bimekizumab-treated patients (Fig. 3c–e). By week 52, patients who switched from placebo to bimekizumab at week 16 showed similar responses in all efficacy outcomes to patients initially randomized to receive bimekizumab (Fig. 3).

At week 16, more bimekizumab-treated patients achieved absolute PASI thresholds than ustekinumab- and placebo-treated patients. PASI $\leq$ 1 was achieved by 72.6% bimekizumab- versus 31.0% ustekinumab- and 0% placebo-treated patients (Fig. 3g). PASI $\leq$ 2 was achieved by 87.1% bimekizumab- versus 55.2%

Table 1 Patient demographics and disease characteristics

Characteristic[a]	Placebo		Bimekizumab 320 mg Q4W		Ustekinumab[b]		Overall	
	Japan (*n* = 17)	Global (*N* = 83)	Japan (*n* = 62)	Global (*N* = 321)	Japan (*n* = 29)	Global (*N* = 163)	Japan (*n* = 108)	Global (*N* = 567)
Age (years), mean ± SD	53.2 ± 13.3	49.7 ± 13.6	49.7 ± 12.4	45.2 ± 14.0	54.9 ± 13.8	46.0 ± 13.6	51.6 ± 13.0	46.1 ± 13.9
Weight (kg), mean ± SD	71.9 ± 13.4	89.1 ± 26.4	74.1 ± 18.3	88.7 ± 23.1	69.8 ± 15.8	87.2 ± 21.1	72.6 ± 16.9	88.4 ± 23.0
Male, *n* (%)	16 (94.1)	60 (72.3)	53 (85.5)	229 (71.3)	20 (69.0)	117 (71.8)	89 (82.4)	406 (71.6)
Duration of psoriasis (years), mean ± SD	10.4 ± 7.1	19.7 ± 13.8	12.0 ± 8.0	16.0 ± 11.6	15.6 ± 10.2	17.8 ± 11.6	12.7 ± 8.7	17.1 ± 12.0
PASI, mean ± SD	20.5 ± 6.6	20.1 ± 6.8	23.1 ± 9.9	22.0 ± 8.6	21.5 ± 8.9	21.3 ± 8.3	22.3 ± 9.2	21.5 ± 8.3
BSA (%), mean ± SD	30.3 ± 17.0	27.0 ± 16.3	33.5 ± 20.0	29.0 ± 17.1	30.9 ± 20.7	27.3 ± 16.7	32.3 ± 19.6	28.2 ± 16.9
IGA, *n* (%)[c]	8 (47.1)	54 (65.1)	39 (62.9)	201 (62.6)	18 (62.1)	96 (58.9)	65 (60.2)	351 (61.9)
3: moderate	9 (52.9)	28 (33.7)	23 (37.1)	119 (37.1)	11 (37.9)	66 (40.5)	43 (39.8)	213 (37.6)
4: severe								
DLQI total, mean ± SD	7.6 ± 6.0	10.0 ± 6.8	7.2 ± 4.7	9.9 ± 6.3	7.8 ± 5.4	11.0 ± 6.9	7.4 ± 5.1	10.2 ± 6.6
P-SIM score (mean ± SD), *n*	14	67	58	260	27	124	99	451
Pain	3.9 ± 3.2	5.1 ± 2.9	5.2 ± 2.8	5.7 ± 2.9	5.2 ± 3.5	5.7 ± 2.9	5.0 ± 3.0	5.6 ± 2.9
Itch	5.6 ± 2.5	6.1 ± 2.5	6.1 ± 2.3	6.6 ± 2.4	6.4 ± 2.6	6.6 ± 2.4	6.1 ± 2.4	6.5 ± 2.4
Scaling	6.0 ± 2.5	6.6 ± 2.3	6.1 ± 2.4	6.7 ± 2.3	6.9 ± 2.5	6.8 ± 2.4	6.3 ± 2.4	6.7 ± 2.3
Prior systemic therapy, *n* (%)	14 (82.4)	64 (77.1)	55 (88.7)	267 (83.2)	24 (82.8)	132 (81.0)	93 (86.1)	463 (81.7)

Table 1 continued

Characteristic[a]	Placebo		Bimekizumab 320 mg Q4W		Ustekinumab[b]		Overall	
	Japan (*n* = 17)	Global (*N* = 83)	Japan (*n* = 62)	Global (*N* = 321)	Japan (*n* = 29)	Global (*N* = 163)	Japan (*n* = 108)	Global (*N* = 567)
Prior biologic therapy, *n* (%)[d]	3 (17.6)	33 (39.8)	14 (22.6)	125 (38.9)	4 (13.8)	63 (38.7)	21 (19.4)	221 (39.0)
Anti-TNF	2 (11.8)	16 (19.3)	2 (3.2)	51 (15.9)	2 (6.9)	24 (14.7)	6 (5.6)	91 (16.0)
Anti-IL-17	1 (5.9)	18 (21.7)	9 (14.5)	76 (23.7)	1 (3.4)	38 (23.3)	11 (10.2)	132 (23.3)
Anti-IL-23	0	5 (6.0)	4 (6.5)	16 (5.0)	1 (3.4)	6 (3.7)	5 (4.6)	27 (4.8)

BSA body surface area, *DLQI* Dermatology Life Quality Index, *IGA* Investigator's Global Assessment, *IL* interleukin, *PASI* Psoriasis Area Severity Index, *PRO* patient-reported outcome, *P-SIM* Psoriasis Symptoms and Impacts Measure, a 14-item PRO measure assessing severity of key signs, symptoms, and effects of psoriasis, where items were scored daily (0–10, no–very severe) using a handheld electronic device and averaged weekly through week 16, Q4W every 4 weeks, *SD* standard deviation, *TNF* tumor necrosis factor

[a]Randomized set

[b]Patients received ustekinumab at baseline and week 4, then every 12 weeks thereafter; ustekinumab dosing was based on weight: patients ≤100 kg at baseline received one ustekinumab 45 mg injection and one placebo injection, patients >100 kg at baseline received two ustekinumab 45 mg injections

[c]In each treatment group of the global study population, one patient with mild IGA score was mistakenly enrolled

[d]Includes patients with multiple prior biologic use

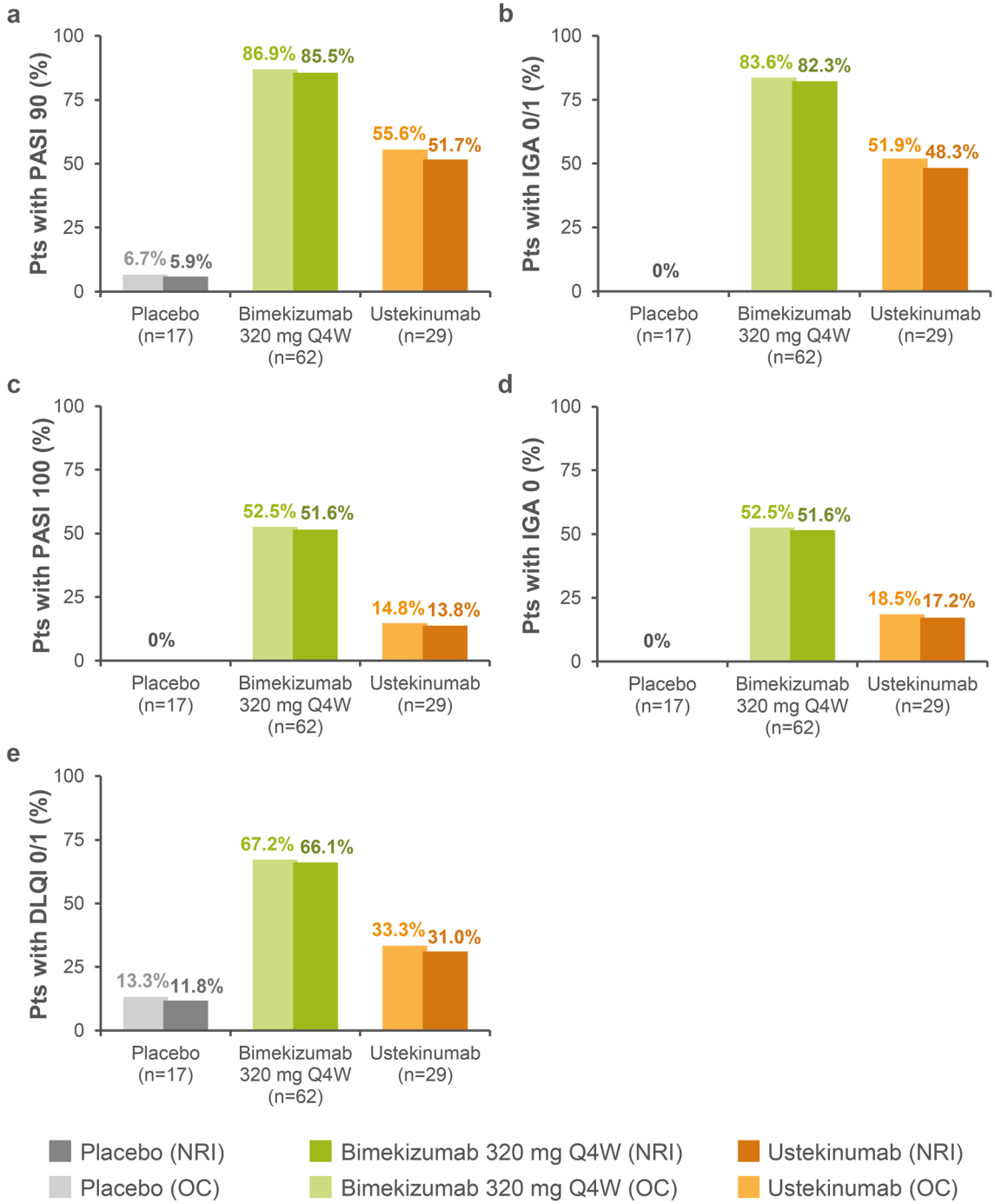
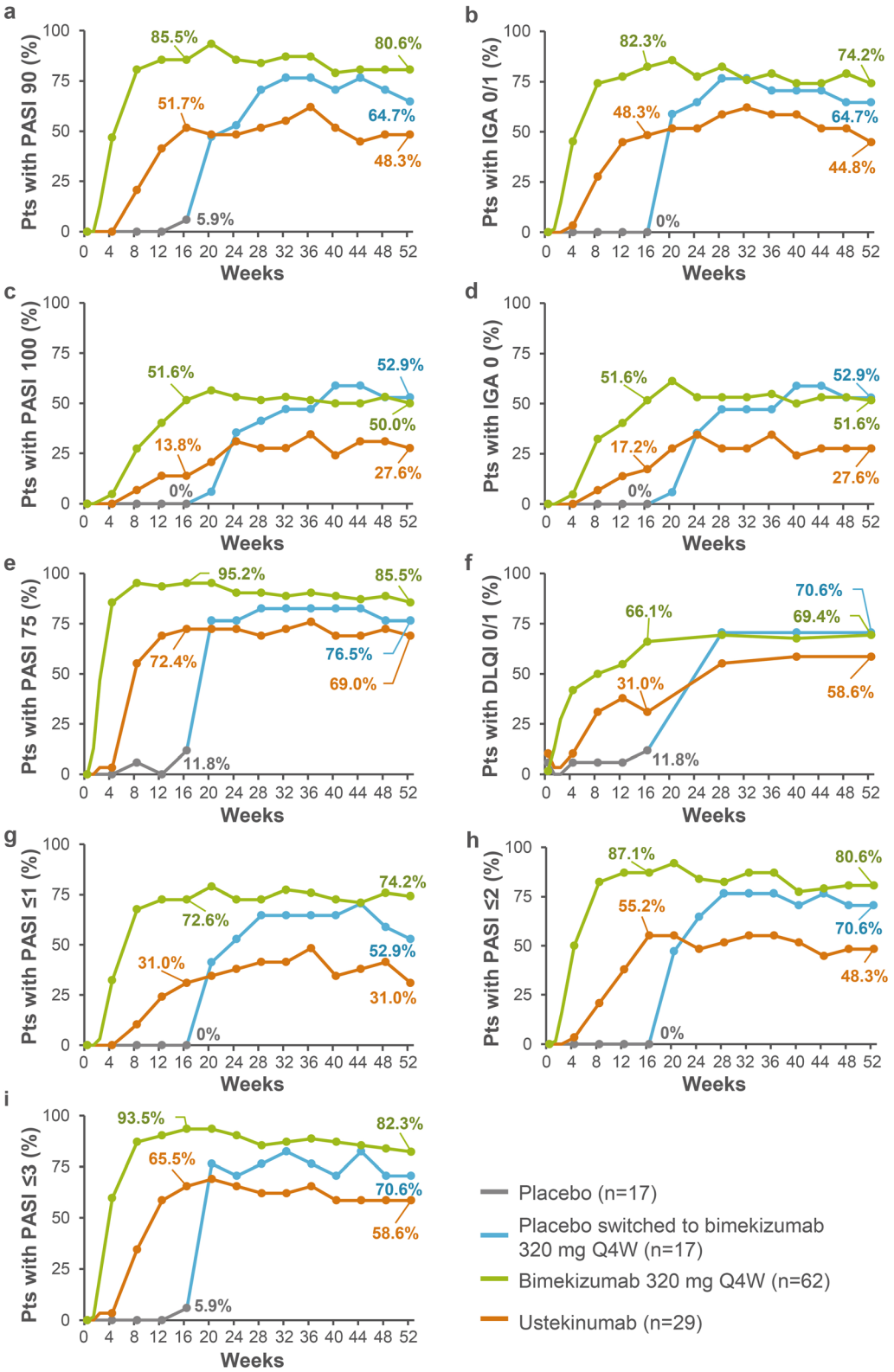


Fig. 2 Week 16 efficacy in the Japan patient subpopulation. **a** PASI 90 response; **b** IGA 0/1 response; **c** PASI 100 response; **d** IGA score of 0; **e** DLQI 0/1 response. *DLQI 0/1* Dermatology Life Quality Index score of 0 or 1, indicating "no effect of psoriasis on patient's life," *IGA 0/1* Investigator's Global Assessment score of 0 (clear) or 1 (almost clear) with ≥ 2 category improvement relative to baseline in Investigator's Global Assessment, scored on a 5-point scale, *NRI* nonresponder imputation, *OC* observed case, *PASI XX* ≥ XX% improvement from baseline in Psoriasis Area and Severity Index score, *Pts* patients, *Q4W* every 4 weeks


a
Pts with PASI 90 (%)
85.5%
80.6%
51.7%
64.7%
48.3%
5.9%
b
Pts with IGA 0/1 (%)
82.3%
74.2%
48.3%
64.7%
44.8%
0%
c
Pts with PASI 100 (%)
51.6%
52.9%
50.0%
13.8%
27.6%
0%
d
Pts with IGA 0 (%)
51.6%
52.9%
51.6%
17.2%
27.6%
0%
e
Pts with PASI 75 (%)
95.2%
85.5%
76.5%
72.4%
69.0%
11.8%
f
Pts with DLQI 0/1 (%)
70.6%
66.1%
69.4%
31.0%
58.6%
11.8%
g
Pts with PASI ≤1 (%)
74.2%
72.6%
52.9%
31.0%
31.0%
0%
h
Pts with PASI ≤2 (%)
87.1%
80.6%
55.2%
70.6%
48.3%
0%
i
Pts with PASI ≤3 (%)
93.5%
82.3%
65.5%
70.6%
58.6%
5.9%
0 4 8 12 16 20 24 28 32 36 40 44 48 52
Weeks
Placebo (n=17)
Placebo switched to bimekizumab 320 mg Q4W (n=17)
Bimekizumab 320 mg Q4W (n=62)
Ustekinumab (n=29)

◀**Fig. 3** Efficacy over time (week 0–52) in the Japan patient subpopulation (NRI). **a** PASI 90 response; **b** IGA 0/1 response; **c** PASI 100 response; **d** IGA 0 response; **e** PASI 75 response; **f** DLQI 0/1 response; **g** PASI ≤ 1 response; **h** PASI ≤ 2 response; **i** PASI ≤ 3 response. At week 16, patients receiving placebo were switched to bimekizumab 320 mg Q4W. Missing data imputed by nonresponse. *DLQI 0/1* Dermatology Life Quality Index score of 0 or 1, indicating "no effect of psoriasis on patient's life," *IGA 0/1* Investigator's Global Assessment score of 0 (clear) or 1 (almost clear), with ≥ 2 category improvement relative to baseline in Investigator's Global Assessment, scored on a 5-point scale, *NRI* nonresponder imputation, *PASI ≤ X* absolute Psoriasis Area and Severity Index of ≤ X, *PASI XX* ≥ XX% improvement in Psoriasis Area and Severity Index score, *Pts* patients, *Q4W* every 4 weeks

ustekinumab- and 0% placebo-treated patients (Fig. 3h). PASI ≤ 3 was achieved by 93.5% bimekizumab- versus 65.5% ustekinumab- and 5.9% placebo-treated patients (Fig. 3i).

A fast onset of clinical (absolute PASI) response was also observed with bimekizumab. After one bimekizumab dose at week 4, more bimekizumab patients achieved PASI ≤ 2 (50.0%) versus ustekinumab (3.4%) and placebo (0%) (Fig. 3h).

At week 52, absolute PASI responses were maintained or improved, with more bimekizumab- versus ustekinumab-treated patients achieving absolute PASI thresholds. PASI ≤ 1 was achieved by 74.2% versus 31.0% (Fig. 3g), PASI ≤ 2 by 80.6% versus 48.3% (Fig. 3h), and PASI ≤ 3 by 82.3% versus 58.6% (Fig. 3i) of bimekizumab- versus ustekinumab-treated patients, respectively.

Patient-Reported Outcomes (PROs)

Bimekizumab-treated patients experienced greater benefits in terms of QoL than ustekinumab- and placebo-treated patients. At week 16, a greater proportion of bimekizumab-treated patients reported DLQI 0/1 (i.e., no effect of psoriasis on patient's life) versus ustekinumab- and placebo-treated patients (66.1% versus 31.0% and 11.8%, respectively; Fig. 2e). A higher DLQI 0/1 response among bimekizumab-treated patients was observed as early as week 4 (Supplementary Fig. S1d), and maintained through week 52 (Fig. 3f).

At week 16, a higher proportion of bimekizumab-treated patients achieved P-SIM responses versus placebo-treated patients. A higher proportion of bimekizumab-treated patients achieved P-SIM responses based on pain item score improvement thresholds versus ustekinumab-treated patients (Supplementary Table S1).

Safety

The frequency of TEAEs was overall similar across all treatment groups during the initial 16-week treatment period (Table 2). Through weeks 0–16, TEAEs occurred in 40/62 (64.5%) bimekizumab-, 17/29 (58.6%) ustekinumab-, and 7/17 (41.2%) placebo-treated patients. Serious TEAEs were reported in 1/62 (1.6%) bimekizumab-, 1/29 (3.4%) ustekinumab-, and 0/17 placebo-treated patients.

Throughout the study (weeks 0–52), 65/77 (84.4%) patients receiving ≥ 1 bimekizumab dose (including patients who switched from placebo at week 16) and 23/29 (79.3%) patients receiving ≥ 1 ustekinumab dose reported TEAEs. Serious TEAEs occurred in 5/77 (6.5%) bimekizumab- and 2/29 (6.9%) ustekinumab-treated patients. Treatment-related TEAEs occurred in 33/77 (42.9%) patients receiving ≥ 1 bimekizumab dose and 8/29 (27.6%) patients receiving ≥ 1 ustekinumab dose. Discontinuations due to TEAEs were reported in 6/77 (7.8%) bimekizumab- and 2/29 (6.9%) ustekinumab-treated patients. No deaths were reported.

Common TEAEs in bimekizumab-treated patients throughout the study were nasopharyngitis, oral candidiasis, and eczema. Up to and including week 52, *Candida* and *Tinea* infections were reported in 16/77 (20.8%) and 8/77 (10.4%) bimekizumab-treated, and 0/29 and 1/29 (3.4%) ustekinumab-treated patients. The most common *Candida* and *Tinea* infections included oral candidiasis and Tinea pedis. Of the 13 bimekizumab-treated patients who reported oral candidiasis in weeks 0–52, none were serious or severe (ten were mild and three

Table 2 Overview of adverse events

Safety event[a]	Initial period (weeks 0–16)			Initial and maintenance periods (weeks 0–52)	
	Placebo ($n = 17$) *n* (%)	Bimekizumab 320 mg Q4W ($n = 62$) *n* (%)	Ustekinumab ($n = 29$) *n* (%)	Bimekizumab 320 mg Q4W[b] ($n = 77$) *n* (%)	Ustekinumab ($n = 29$) *n* (%)
Summary of TEAEs					
Any TEAE	7 (41.2)	40 (64.5)	17 (58.6)	65 (84.4)	23 (79.3)
Serious TEAEs	0	1 (1.6)	1 (3.4)	5 (6.5)	2 (6.9)
Discontinuation due to TEAEs	1 (5.9)	1 (1.6)	1 (3.4)	6 (7.8)	2 (6.9)
Treatment-related TEAEs	1 (5.9)	19 (30.6)	5 (17.2)	33 (42.9)	8 (27.6)
Severe TEAEs	0	0	1 (3.4)	2 (2.6)	1 (3.4)
Deaths	0	0	0	0	0
Common TEAEs					
Nasopharyngitis	1 (5.9)	8 (12.9)	2 (6.9)	20 (26.0)	7 (24.1)
Oral candidiasis	0	6 (9.7)	0	13 (16.9)	0
Eczema	0	2 (3.2)	1 (3.4)	9 (11.7)	1 (3.4)
Folliculitis	0	2 (3.2)	0	7 (9.1)	0
Contact dermatitis	0	2 (3.2)	0	6 (7.8)	1 (3.4)
Pharyngitis	0	3 (4.8)	0	6 (7.8)	2 (6.9)
Tinea pedis	0	3 (4.8)	0	6 (7.8)	1 (3.4)
TEAEs of interest[c]					
Fungal infections	0	11 (17.7)	0	23 (29.9)	1 (3.4)
Candida	0	7 (11.3)	0	16 (20.8)[d]	0
Tinea	0	4 (6.5)	0	8 (10.4)	1 (3.4)
Hepatic events	0	2 (3.2)	0	4 (5.2)	0
Elevated liver enzymes[e]	0	2 (3.2)	0	2 (2.6)	0
Adjudicated suicidal ideation and behavior	0	0	0	1 (1.3)	0

Q4W every 4 weeks, *TEAE* treatment emergent adverse event

[a]Data for the initial period are from patients in the safety set, and data for initial and maintenance periods are from patients in the active medication set

[b]Includes patients switching from placebo to bimekizumab 320 mg Q4W at week 16, where only events occurring after switching are included in this column

[c]There were zero cases of other safety topics of interest (not presented in table), including systematic opportunistic infections, interstitial lung disease, active tuberculosis, inflammatory bowel disease, adjudicated major cardiovascular adverse events, malignancies, anaphylactic reactions, or neutropenia events

[d]In bimekizumab-treated patients, there were 13 cases of oral candidiasis, three cases of esophageal candidiasis, and one case of oropharyngeal candidiasis (numbers are not additive)

[e]Elevated liver enzymes/liver function tests included the following preferred terms reported as adverse events: hepatic enzyme increased and gamma-glutamyltransferase increased

were moderate) and two led to discontinuation (these cases were recurrent). All bimekizumab-treated patients who reported Tinea pedis were mild cases and none led to discontinuation. There were 3/77 (3.9%) esophageal *Candida* infections among bimekizumab-treated and none among ustekinumab-treated patients. Of the three cases, two were mild, while one (1.3%) was serious, severe, and led to discontinuation (patient was hospitalized, received antifungal therapy, and the infection resolved in 14 days). There was a higher number of reported cases of candidiasis in weeks 0–16 (7/62; 11.3%) than weeks 16–52 (4/60; 6.7%); the number of cases with candidiasis were not additive. There were no other serious infections in bimekizumab-treated patients. All opportunistic infections were localized mucocutaneous fungal infections and were defined as opportunistic by convention.

Among other safety topics of interest, 2/77 (2.6%) bimekizumab-treated patients reported an elevated liver enzymes event. Both patients had confounding factors and alternative explanations (alcohol consumption) for these abnormalities. There was 1/77 (1.3%) case of adjudicated suicidal ideation and behavior (referring to active suicidal ideation with some intent to act in a patient with pre-existing psychiatric conditions) in the bimekizumab arm, and none with ustekinumab. Across all treatment groups, there were no cases of inflammatory bowel disease, adjudicated major cardiovascular adverse events, malignancies, anaphylactic reactions, or neutropenia events.

DISCUSSION

In this phase 3 active comparator and placebo-controlled trial, bimekizumab demonstrated improved efficacy compared with ustekinumab and placebo for the treatment of adult patients with moderate-to-severe plaque psoriasis. Overall, the Japan patient subpopulation results were generally consistent with the global study population [24]. These findings suggest bimekizumab may be a viable treatment option in Japan, and effectiveness of bimekizumab treatment and dosing regimens in Japanese patients may be approximated from observations in Western populations.

Bimekizumab showed a faster onset of clinical response among Japanese patients compared with ustekinumab. The rapid onset was comparable between patients who received bimekizumab from week 0 and those who switched from placebo to bimekizumab at week 16. A fast onset of effectiveness is relevant as the Japanese Dermatological Association views this as an important consideration when selecting biologic therapy for psoriatic patients in Japan [12]. Japanese patients with psoriasis have also shown a preference for drugs with early-onset efficacy [18].

Patients with chronic plaque psoriasis can lose treatment response over time [12, 37], and may need to switch treatments to maintain high skin clearance levels [12]. In this analysis, high proportions of bimekizumab-treated patients maintained good skin clearance through 52 weeks of treatment.

Additionally, more bimekizumab-treated patients reached absolute PASI thresholds versus ustekinumab or placebo. Absolute PASI has been used as an efficacy measure in Japanese clinics, as evidenced in a number of studies assessing absolute PASI responses in Japanese patients with moderate-to-severe psoriasis [32–34].

As psoriasis often has a detrimental impact on patient QoL [2], it is important that clinical improvements in skin clearance can be linked to QoL improvements. A correlation between absolute PASI and DLQI has been shown in a study of Japanese patients with moderate-to-severe plaque psoriasis: in those who experienced a relapse, a change in absolute PASI response correlated with a steeper increase in DLQI scores compared with baseline [34]. As this analysis measured relative and absolute PASI responses, DLQI, PROs, and other clinical outcomes, it provides holistic insight—across clinical and QoL outcomes—of the clinical benefits of bimekizumab in Japanese patients with psoriasis.

Overall, safety results for Japanese patients were consistent with the BE VIVID global study population [24], with a slightly higher incidence of TEAEs related to skin and

subcutaneous disorders, in particular eczema and contact dermatitis. Over 52 weeks, the occurrence of common TEAEs was comparable between bimekizumab and ustekinumab, except for oral candidiasis. As the IL-17 pathway controls fungal infections of the oral mucosa, and is subject to heightened inhibition through bimekizumab's inhibition of IL-17F and IL-17A [38–42], oral candidiasis would be expected to be more common in bimekizumab- versus ustekinumab-treated patients. Moreover, the frequency of oral candiasis infections was similar to observations in previous bimekizumab trials [19, 24, 43, 44], and was higher than observations with other IL-17 inhibitors [13, 14]. This might result from bimekizumab's inhibition of IL-17F and IL-17A; further investigations can confirm this. Finally, while there was a higher number of reported candidiasis cases among Japanese patients in weeks 0–16 than in weeks 16–52, the results should be interpreted with caution given the small number of patients.

Limitations

Inferential comparisons of the outcomes and calculation of *p*-values were not prespecified given the small patient numbers in this analysis. Therefore, *p*-values have not been reported as the interpretation of those results may be limited. Absolute numbers and percentages have instead been reported for the various outcomes. Nonetheless, the current analysis provides evidence of bimekizumab efficacy and safety in Japanese patients, whereby clinical response is consistent with the overall population.

Head-to-head comparator trials are important for comparing between treatments; studies comparing bimekizumab with IL-17A or TNFα inhibitors have been published previously [22, 23]. These studies, together with the present analysis, contribute toward the wider program evaluating bimekizumab efficacy and safety in adults with moderate-to-severe plaque psoriasis.

Finally, long-term data on bimekizumab efficacy and safety will be available through the ongoing open-label extension study (BE BRIGHT), which has recruited patients from this analysis and others in the "bimekizumab for psoriasis" program. These data would allow patients and clinicians in Japan to make informed treatment decisions.

CONCLUSIONS

Consistent with results of the global study population, bimekizumab treatment led to improved clinical responses compared with ustekinumab and placebo in the Japan subpopulation. Clinically meaningful responses and benefits in PROs and QoL were rapid in onset and durable through 52 weeks, providing evidence that bimekizumab could offer an additional treatment option for Japanese patients with moderate-to-severe plaque psoriasis. Bimekizumab was well-tolerated and the safety profile in this analysis was consistent with the known mechanism of action and previous studies.

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Compliance With Ethics Guidelines. All participants provided written informed consent. All results presented in this article are in aggregate form, and no personally identifiable information was used in this study. The study protocol, amendments, and patient-informed consent were reviewed by a national, regional, or independent ethics committee or institutional review board. This study was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonisation–Good Clinical Practice requirements, ethical principles that have their origin in the principles of the Declaration of Helsinki, and local laws of countries involved.

Data Availability. Underlying data from this manuscript may be requested by qualified researchers 6 months after product approval in the USA 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 datasets, study protocol, 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 pre-specified time, typically 12 months, on a password protected portal.

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