Br J Dermatol 2023; **188**: 22–31
https://doi.org/10.1093/bjd/ljac021
Advance access publication date: 26 October 2022

BJD
British Journal of Dermatology
Clinical Trial

Safety and efficacy of bimekizumab through 2 years in patients with moderate-to-severe plaque psoriasis: longer-term results from the BE SURE randomized controlled trial and the open-label extension from the BE BRIGHT trial

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Linked Article: Mirali *et al. Br J Dermatol* 2023; **188**:5–6.

Abstract

Background BE SURE 1-year results demonstrated the superior efficacy of bimekizumab compared with adalimumab with no unexpected safety findings.

Objectives To provide efficacy and safety data over 2 years of bimekizumab treatment compared with adalimumab from BE SURE and the BE BRIGHT open-label extension (OLE) in patients with moderate-to-severe plaque psoriasis.

Methods The 56-week double-blinded BE SURE phase III randomized controlled trial randomized patients 1 : 1 : 1 to bimekizumab 320 mg every 4 weeks (Q4W), bimekizumab 320 mg Q4W to week 16 then every 8 weeks (Q8W), or adalimumab 40 mg every 2 weeks to week 24 then bimekizumab 320 mg Q4W. After completing BE SURE, patients could enter the ongoing BE BRIGHT OLE, with possible dosing adjustments based on Psoriasis Area and Severity Index (PASI). The primary outcome in BE BRIGHT was incidence of treatment-emergent adverse events (TEAEs); safety data are reported by study period through week 104. Efficacy data are reported for the intention-to-treat population through week 104 by initial randomization group, with ≥90% improvement from baseline PASI (PASI 90) and 100% improvement (PASI 100) as key outcomes.

Results Of the patients randomized to bimekizumab, 158 were assigned to Q4W, and 161 to Q4W/Q8W. At week 104, PASI 90 was achieved by 91.2% and 89.7%, and PASI 100 was achieved by 72.3% and 68.1%, for Q4W and Q4W/Q8W, respectively; comparable to week 16 results. Among the 159 patients randomized to adalimumab, responses rapidly and substantially increased after the week 24 bimekizumab switch; at week 104, 96.9% and 70.2% of patients achieved PASI 90 and PASI 100 respectively. Through weeks 24–104, the three most common TEAEs in any bimekizumab-treated group were nasopharyngitis, oral candidiasis and upper respiratory tract infection. Rates of serious TEAEs were low.

Conclusions Clinical responses observed through week 16 of BE SURE in patients randomized to bimekizumab were sustained through 104 weeks of treatment, regardless of Q4W or Q8W maintenance dosing. Response rates were also sustained through week 104 in patients who switched from adalimumab to bimekizumab at week 24, and were similar to those observed in the bimekizumab groups. Bimekizumab was well tolerated with no new safety signals.

Accepted: 16 September 2022
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What is already known about this topic?

- In the BE SURE phase III clinical trial, bimekizumab demonstrated superiority to adalimumab in the treatment of patients with moderate-to-severe plaque psoriasis, with no unexpected safety findings over 1 year of treatment.
- Clinical responses and health-related quality of life rapidly improved in patients who switched from adalimumab treatment to bimekizumab, achieving similar response levels to patients treated with bimekizumab for the full year.

What does this study add?

- This study reports safety and efficacy results from the BE SURE trial and the open-label extension from the BE BRIGHT trial in order to evaluate bimekizumab over the longer term.
- The findings of this study help us to understand whether clinical responses observed over 1 year with bimekizumab are sustained over 2 years of treatment, and whether improvements in responses are sustained after switching from adalimumab to bimekizumab.
- Furthermore, this study assesses long-term safety of bimekizumab.

Over the past 2 decades, there have been major advances in the treatment of plaque psoriasis with the introduction of biologic therapies.[1] These therapies have been designed to target key immune mediators involved in the pathogenesis of psoriasis, such as the proinflammatory cytokines interleukin (IL)-23, IL-17 and tumour necrosis factor.[2] However, despite major therapeutic advancements, some patients with psoriasis are undertreated and do not achieve high levels of skin clearance, as recommended in disease guidelines, and even fewer achieve complete skin clearance.[3–5] These patients experience lower quality of life, and higher levels of burdensome symptoms, such as itching.[6] Additionally, in a real-world setting many therapies lose effectiveness over time, often resulting in patients switching or stopping treatment,[7] which, given the chronic nature of psoriasis, adds to the cumulative lifetime disease burden.

Adalimumab is used in many healthcare settings as the guideline-recommended first-line biologic psoriasis treatment, owing to the clinical experience supporting its safety, efficacy and improvements in health-related quality of life (HRQoL), and to its availability as a lower-cost biosimilar in some countries.[8–16] As previously reported, in the BE SURE phase III trial, bimekizumab demonstrated superiority vs. adalimumab in both coprimary endpoints at week 16 [90% improvement from baseline in Psoriasis Area and Severity Index (PASI 90) and Investigator's Global Assessment (IGA) score of 0 or 1, indicating clear or almost clear skin], with no unexpected safety findings over 1 year of treatment.[17] Additionally, BE SURE demonstrated that clinical responses and HRQoL rapidly improved in patients who switched to bimekizumab after 24 weeks of adalimumab treatment, achieving similar response levels to patients treated with bimekizumab for 1 year.[17]

Here, we report the safety and efficacy of bimekizumab during BE SURE (NCT03412747) and the BE BRIGHT open-label extension (OLE) trial (NCT03598790) through 2 years of treatment, by initial patient randomization group, to understand whether clinical and HRQoL responses observed over 1 year of treatment with bimekizumab were sustained over 2 years. Additional considerations included how well bimekizumab was tolerated, and whether improvements in responses observed after switching from adalimumab to bimekizumab were sustained.

Materials and methods

Patients

Patients who completed week 56 of BE SURE were eligible for enrollment into the BE BRIGHT OLE, provided no withdrawal criteria were met (outlined previously).[17] All patients entering BE SURE and the BE BRIGHT OLE provided written informed consent documented in accordance with local regulations, the International Conference on Harmonization Good Clinical Practice requirements, and the ethical principles originating from the Declaration of Helsinki. At week 56 of BE SURE, patients enrolling into the BE BRIGHT OLE completed their final study visit assessments, which served as the BE BRIGHT OLE baseline assessments, and then received their first dose of open-label bimekizumab.

Study design

At BE SURE baseline, patients were randomized 1 : 1 : 1 to bimekizumab 320 mg every 4 weeks (Q4W) for 56 weeks; bimekizumab 320 mg Q4W for 16 weeks then every 8 weeks (Q8W) through weeks 16–56; adalimumab 80 mg at baseline followed by 40 mg 1 week later and every 2 weeks (Q2W) thereafter until week 24, at which point patients switched to bimekizumab 320 mg Q4W regardless of response to adalimumab and continued to receive bimekizumab until the end of BE SURE.[17] After completing the 56-week trial, patients could enroll into the BE BRIGHT OLE (Figure 1). Patients who did not enroll, or discontinued prior to week 56, underwent a safety follow-up visit 20 weeks after their last dose of study treatment.

In the ongoing BE BRIGHT OLE, patients have the opportunity to receive bimekizumab treatment for at least 144 weeks, with a safety follow-up visit 20 weeks after patients' last dose of study treatment. Therefore, all patients who enrolled in BE SURE and entered the BE BRIGHT OLE can receive at least 4 years of treatment. Here, we report results of an interim analysis up to week 104 from BE SURE baseline (week 48 of the BE BRIGHT OLE), based on patients' initial randomization groups (dose groups during the OLE were combined in this efficacy and safety analysis).

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On entering the BE BRIGHT OLE, eligible patients were assigned to their open-label bimekizumab treatment regimen using interactive-response technology, such that patients and study sites remained blinded to treatment given during BE SURE. BE BRIGHT open-label treatment assignment was determined by double-blinded treatment and PASI response at week 56 of BE SURE (Figure 1). All patients who did not achieve PASI 90 at BE SURE week 56 received bimekizumab 320 mg Q4W on entering BE BRIGHT. Week 56 PASI 90 responders entering BE BRIGHT from the bimekizumab 320 mg Q8W group continued to receive Q8W dosing, while responders entering BE BRIGHT from the bimekizumab 320 mg Q4W group were randomized at a ratio of 4 : 1 to Q4W or Q8W dosing. At BE BRIGHT week 24, for patients receiving bimekizumab 320 mg Q4W, if PASI 90 was achieved, the investigator was permitted to reduce the patient's dosing interval from Q4W to Q8W.

Safety outcomes

Treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal, were prespecified outcomes. TEAEs were defined as any adverse event (AE) with an onset on or after the first dose of study treatment and up to 20 weeks after the final dose. TEAEs were coded according to the Medical Dictionary for Regulatory Activities version 19.0. SAEs were defined as any AE meeting one or more of the following criteria: death, life-threatening, significant or persistent disability/incapacity, congenital anomaly/birth defect (including that occurring in a fetus), important medical event, and initial inpatient hospitalization or prolongation of hospitalization. Prespecified safety topics of interest included infections [serious, opportunistic, fungal, and tuberculosis (TB)], neutropenia, hypersensitivity, suicidal ideation and behaviour (SIB), depression, major cardiovascular events (MACE), liver function test changes/enzyme elevations, malignancies and inflammatory bowel disease (IBD). Data were reviewed periodically by cardiovascular and neuropsychiatric adjudication committees. Safety data are reported as exposure-adjusted incidence rates (EAIRs) of new cases per 100 patient-years (PYs) and are reported through weeks 0–24, 24–56 and 56–104 based on patients' initial randomization groups. A breakdown of *Candida* infections is reported by initial randomization group.

Efficacy outcomes

Efficacy outcomes are reported based on randomized dosing regimen during the BE SURE double-blinded treatment period, regardless of bimekizumab dose assigned upon entry to the BE BRIGHT OLE. Here, we report the PASI 90, IGA 0/1, PASI 100 (complete skin clearance) and Dermatology Life Quality Index (DLQI) 0/1 (no effect of skin disease on a patient's life) response rates through week 104 (BE BRIGHT OLE week 48).

Statistical analysis

For all efficacy and safety results, descriptive statistics were used to provide an overview of the results. In the BE BRIGHT OLE, no statistical hypothesis testing was performed. For all efficacy endpoints, analyses were performed on the intention-to-treat (ITT) population, including all patients randomized at BE SURE baseline. Missing data were primarily accounted for using modified nonresponder imputation (mNRI), with nonresponder imputation (NRI) and observed case (OC) data also reported. For mNRI, patients with missing data following treatment discontinuation owing to lack of efficacy were considered nonresponders at subsequent timepoints; multiple imputation methodology was used for all other missing data.

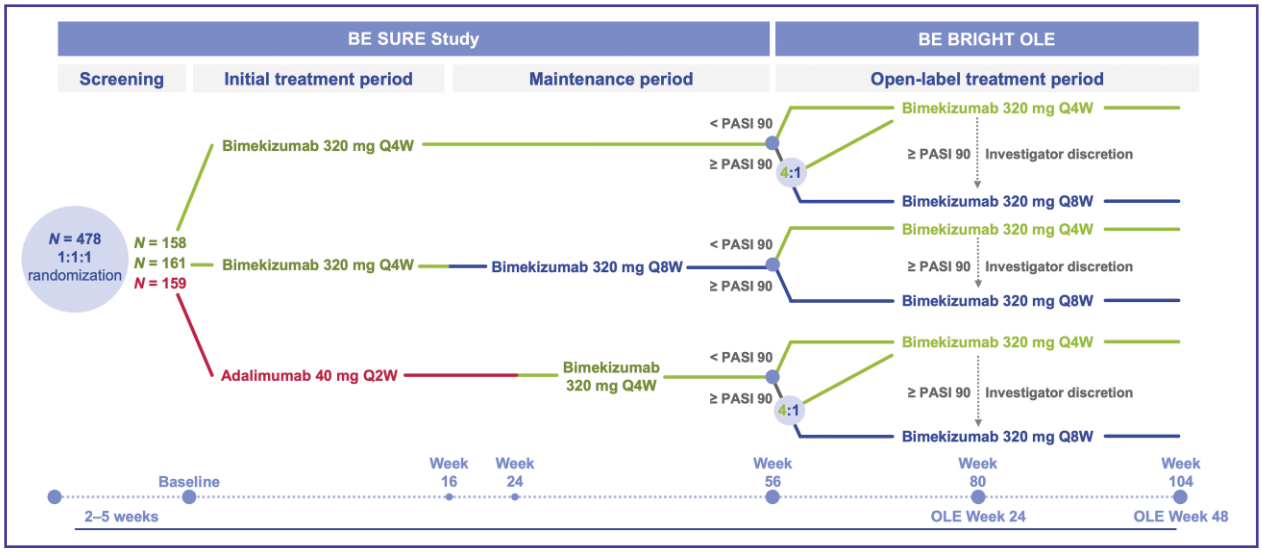

Figure 1 BE SURE and BE BRIGHT OLE study design. At week 56, dose adjustments [bimekizumab 320 mg Q4W or Q8W] occurred based on ≥90% improvement from BE SURE baseline in Psoriasis Area and Severity Index response (PASI 90); patients receiving bimekizumab Q4W who achieved PASI 90 were randomized 4 : 1 to receive bimekizumab 320 mg Q4W or Q8W; patients receiving bimekizumab Q8W who achieved PASI 90 were allocated to bimekizumab Q8W; and all patients who did not achieve PASI 90 were allocated to bimekizumab Q4W. At OLE week 24, dose adjustments occurred based on PASI 90 response; patients who received bimekizumab Q4W who achieved PASI 90 were switched to bimekizumab Q8W at the discretion of the investigator. OLE, open-label extension; Q2W, every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks.

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Results

Patient disposition and baseline characteristics

In BE SURE, 478 patients were randomly assigned to receive bimekizumab 320 mg Q4W ($N=158$), bimekizumab 320 mg Q4W/Q8W ($N=161$), or adalimumab followed by bimekizumab 320 mg Q4W ($N=159$) (Figure 1). Patient demographic and clinical characteristics at baseline, which have been previously reported, were similar across treatment groups and were as expected for a moderate-to-severe psoriasis population targeted for biologic therapy.[17]

Of patients randomized to bimekizumab Q4W, bimekizumab Q4W/Q8W, and adalimumab/bimekizumab, 137 of 158, 139 of 161, and 131 of 159 entered the BE BRIGHT OLE, respectively (Figure 2). Discontinuations during the BE BRIGHT OLE are shown in Figure 2 and Figure S1 (see Supporting Information).

Efficacy

At week 104 (BE BRIGHT OLE week 48), 91.2% and 89.7% of patients randomized to bimekizumab Q4W and bimekizumab Q4W/Q8W achieved PASI 90, respectively (mNRI) (Table 1 and Figure 3a). These results were similar to those observed at week 16 of BE SURE, indicating that initial high responses were maintained through 2 years of bimekizumab. In patients randomized to adalimumab followed by bimekizumab, the rapid increase in response observed following the switch to bimekizumab at BE SURE week 24 was durable through week 104; at week 104 (80 weeks after switching to bimekizumab), 96.9% of patients sustained achievement of PASI 90, following the rapid increase from 53.9% at week 24 (mNRI). This week 104 response rate was similar to that in patients who were initially randomized to bimekizumab at BE SURE baseline (Table 1 and Figure 3a).

Similar results were observed for IGA 0/1; at week 104, 90.5% of patients randomized to bimekizumab Q4W and 92.6% of patients randomized to bimekizumab Q4W/Q8W achieved IGA 0/1 (mNRI), which was maintained from week 16 (Table 1 and Figure 3c). For patients initially randomized to adalimumab who switched to bimekizumab at week 24 of BE SURE, IGA 0/1 responses were durable to week 104 at 96.2%, after increasing rapidly from 60.3% at week 24 (Table 1 and Figure 3b).

High rates of complete skin clearance (PASI 100) were durable from week 16 to week 104 for patients randomized at BE SURE baseline to receive bimekizumab, regardless of maintenance dose; at week 104, 72.3% of patients randomized to Q4W and 68.1% of patients randomized to Q4W/Q8W achieved PASI 100. For patients randomized to adalimumab/bimekizumab, 70.2% achieved PASI 100 at week 104; this was sustained after the rapid increase from 31.8% following the week 24 bimekizumab switch (mNRI) (Table 1 and Figure 3c).

Improvements in clinical outcomes in the bimekizumab treatment arms were accompanied by improvements in HRQoL. The proportion of patients achieving DLQI 0/1 at week 16 of BE SURE was sustained through to week 104, with 79.8% and 81.3% of patients randomized to bimekizumab Q4W and Q4W/Q8W achieving DLQI 0/1 at week

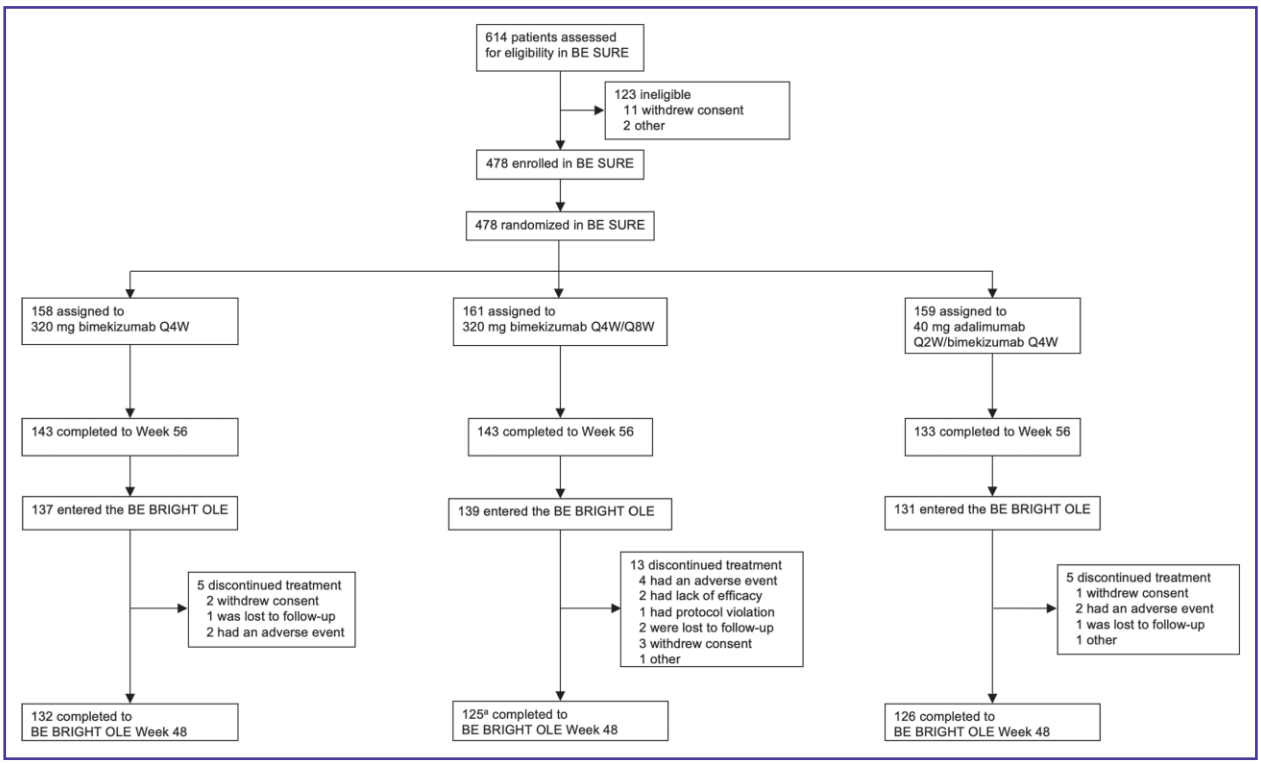

Figure 2 Flowchart showing distribution of patients included in the study. Further details of dose switching during the BE BRIGHT OLE are provided in Figure S1 (see Supporting Information). A more detailed disposition through week 56 has been reported previously.[17] [a]The status of one patient at BE BRIGHT OLE week 48 was pending at the time of the data cutoff. OLE, open-label extension; Q4W, every 4 weeks; Q8W, every 8 weeks.

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Table 1 Overview of efficacy outcomes in BE SURE (weeks 0–56) and the BE BRIGHT open-label extension (OLE) (weeks 56–104) by initial randomization group

	Bimekizumab 320 mg Q4W ($N=158$)			Bimekizumab 320 mg Q4W/Q8W ($N=161$)			Adalimumab/bimekizumab ($N=159$)[a]		
	OC, *n*/*N* (%)	NRI, *n* (%)[b]	mNRI, %	OC, *n*/*N* (%)	NRI, *n* (%)[b]	mNRI, %	OC, *n*/*N* (%)	NRI, *n* (%)[b]	mNRI, %
PASI 90									
Week 16	138/151 (91.4)	138 (87.3)	91.2	137/152 (90.1)	137 (85.1)	89.4	75/148 (50.7)	75 (47.2)	50.2
Week 56	134/140 (95.7)	134 (84.8)	92.1	133/143 (93.0)	133 (82.6)	89.6	130/133 (97.7)	130 (81.8)	94.3
Week 104	121/129 (93.8)	121 (76.6)	91.2	118/125 (94.4)	118 (73.3)	89.7	121/123 (98.4)	121 (76.1)	96.9
PASI 100									
Week 16	95/151 (62.9)	95 (60.1)	61.6	99/152 (65.1)	99 (61.5)	62.8	38/148 (25.7)	38 (23.9)	26.0
Week 56	114/140 (81.4)	114 (72.2)	78.4	113/143 (79.0)	113 (70.2)	75.8	106/133 (79.7)	106 (66.7)	74.2
Week 104	102/129 (79.1)	102 (64.6)	72.3	100/125 (80.0)	100 (62.1)	68.1	98/123 (79.7)	98 (61.6)	70.2
IGA 0/1									
Week 16	138/151 (91.4)	138 (87.3)	91.8	134/152 (88.2)	134 (83.2)	87.6	91/148 (61.5)	91 (57.2)	60.3
Week 56	130/140 (92.9)	130 (82.3)	91.2	134/43 (93.7)	134 (83.2)	92.5	128/133 (96.2)	128 (80.5)	93.6
Week 104	118/129 (91.5)	118 (74.7)	90.5	120/125 (96.0)	120 (74.5)	92.6	119/123 (96.7)	119 (74.8)	96.2
DLQI 0/1									
Week 16	98/151 (64.9)	98 (62.0)	63.8	103/152 (67.8)	103 (64.0)	66.6	74/148 (50.0)	74 (46.5)	48.1
Week 56	117/140 (83.6)	117 (74.1)	78.4	127/142 (89.4)	127 (78.9)	81.7	116/132 (87.9)	116 (73.0)	80.9
Week 104	112/130 (86.2)	112 (70.9)	79.8	109/125 (87.2)	109 (67.7)	81.3	111/124 (89.5)	111 (69.8)	81.3

DLQI, Dermatology Life Quality Index; IGA, Investigator's Global Assessment; mNRI, modified nonresponder imputation; NRI, nonresponder imputation; OC, observed case; PASI, Psoriasis Area and Severity Index; Q2W: every 2 weeks; Q4W, every 4 weeks; Q8W, every 8 weeks. Data are presented for patients according to initial randomization group, regardless of bimekizumab BE BRIGHT OLE dosing regimen. For mNRI, patients with missing data following treatment discontinuation owing to lack of efficacy were considered nonresponders at subsequent timepoints; multiple imputation methodology was used for all other missing data. The double-blinded treatment period ended at week 56. Week 104 corresponds to OLE week 48. [a]Patients received adalimumab 80 mg at baseline followed by 40 mg 1 week later and Q2W thereafter until week 24, when patients switched to bimekizumab 320 mg Q4W. [b]NRI data for weeks 16 and 56 have been previously reported.[17] DLQI 0/1 represents a DLQI score of 0 or 1, indicating no effect of psoriasis on quality of life. IGA 0/1 represents an IGA score of 0 (clear) or 1 (almost clear) with at least a two-category improvement in IGA relative to BE SURE baseline, scored on a 5-point scale. PASI 90/100 represents ≥90%/100% improvement in PASI from BE SURE baseline.

104, respectively. In patients switching from adalimumab to bimekizumab, DLQI 0/1 responder rates rapidly increased within 16 weeks and were sustained to week 104; 49.3% achieved DLQI 0/1 at week 24, and 81.3% achieved DLQI 0/1 at week 104 (mNRI) (Table 1 and Figure 3d).

For patients initially randomized to bimekizumab Q4W/Q8W (those who received bimekizumab Q4W until BE SURE week 16, then switched to bimekizumab Q8W) who continued receiving bimekizumab Q8W in the BE BRIGHT OLE ($n=106$), 93.4% (mNRI) achieved PASI 90 at week 104 (NRI 86.8%). Note that only patients who were receiving Q4W/Q8W in BE SURE and achieved PASI 90 at week 56 continued Q8W dosing in the OLE, as per the study design (Figure 1).

Safety

Safety data by treatment period (weeks 0–24, weeks 24–56 and weeks 56–104) are presented in Table 2. During weeks 56–104, total exposure time at risk was comparable across the three treatment groups, at 124.7 PYs, 123.7 PYs and 119.2 PYs for patients initially randomized to bimekizumab Q4W, bimekizumab Q4W/Q8W and adalimumab, respectively. EAIRs of TEAEs through weeks 56–104 were 157.3, 147.4 and 202.5 per 100 PYs for patients randomized to bimekizumab Q4W, bimekizumab Q4W/Q8W, and adalimumab/bimekizumab at BE SURE baseline, respectively; EAIRs of serious TEAEs during this period were 3.2, 6.6 and 5.1 per 100 PYs, respectively (Table 2). Apart from oral candidiasis and other fungal events classified as opportunistic, after patients switched from adalimumab to bimekizumab EAIRs of TEAEs generally decreased.

Discontinuations owing to TEAEs were low over 2 years and decreased in the second year; 2.4 per 100 PYs in the bimekizumab Q4W group, 3.2 per 100 PYs in the bimekizumab Q4W/Q8W group and 1.7 per 100 PYs in the adalimumab/bimekizumab group (Table 2). One death occurred in the bimekizumab Q4W group. This patient was a 65-year-old man with a history of hypertension, brain aneurysm, type 2 diabetes, hyperlipidaemia and smoking, who died owing to cardiac arrest 2 years after starting bimekizumab treatment. The event was considered to be due to atherosclerosis, and was not deemed to be related to treatment.

The three most common overall TEAEs during weeks 56–104 for patients initially randomized to bimekizumab Q4W, Q4W/Q8W and adalimumab/bimekizumab were nasopharyngitis, oral candidiasis and upper respiratory tract infection (Table 2). Overall, cases of oral candidiasis were predominantly mild or moderate, and EAIRs decreased between weeks 24–56 and weeks 56–104 for patients randomized to bimekizumab Q4W and Q4W/Q8W. In the second year of treatment (weeks 56–104; all patients receiving bimekizumab), there were 38 patients who experienced oral candidiasis; the maximum event severity was rated as mild for 19 patients and moderate for 19 patients, with none experiencing a severe case. No instances of oral candidiasis led to treatment discontinuation. *Candida* infections, chiefly oral candidiasis, accounted for the majority of fungal infections reported with bimekizumab treatment (Table S1; see Supporting Information).

Among the TEAEs of interest during weeks 56–104, there were no incidences of adjudicated SIB or active TB, which was consistent with other treatment periods (Table 2). There was one instance each of IBD, neutropenia and serious hypersensitivity reaction, and two instances each of depression and adjudicated MACE. The rates of serious infections and malignancies were low throughout the entire 2 years of treatment and were similar between

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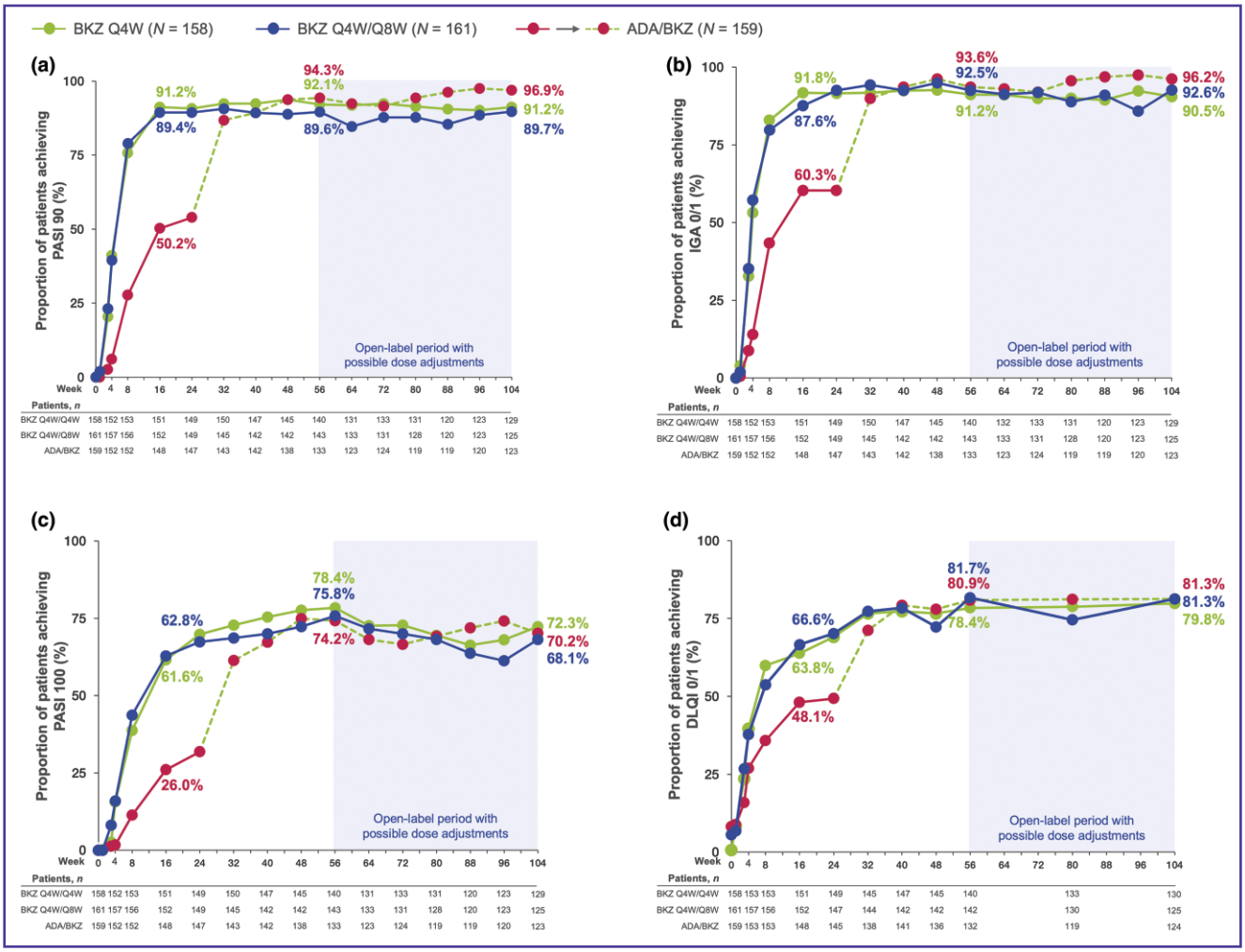

Figure 3 Efficacy responses according to randomized treatment group through 104 weeks by initial randomization group [modified nonresponder imputation (mNRI)]. (a) Proportion of patients achieving ≥90% improvement from BE SURE baseline in PASI 90. (b) Proportion of patients achieving a score of 0 (clear) or 1 (almost clear) with at least a two-category improvement relative to BE SURE baseline in IGA, scored on a 5-point scale (IGA 0/1). (c) Proportion of patients achieving 100% improvement from BE SURE baseline in PASI (PASI 100). (d) Proportion of patients achieving a DLQI score of 0 or 1 indicating no effect of psoriasis on quality of life (DLQI 0/1). Data are presented for the intention-to-treat (ITT) population by initial randomization group, regardless of BKZ OLE dosing regimen. Dose adjustments upon entering the OLE were based on PASI 90 status at week 56 and prior dosing regimen in BE SURE. For mNRI, patients with missing data following treatment discontinuation owing to lack of efficacy were considered nonresponders at subsequent timepoints; multiple imputation methodology was used for all other missing data. ADA, adalimumab; BKZ, bimekizumab; DLQI, Dermatology Life Quality Index; IGA, Investigator's Global Assessment; OLE, open-label extension; PASI, Psoriasis Area and Severity Index; Q4W, every 4 weeks; Q8W, every 8 weeks.

treatment groups (Table 2). Elevated liver enzymes were high, at 15.8 per 100 PYs, in patients who received adalimumab during the first 24 weeks, then decreased after the bimekizumab switch.

Discussion

Results observed in this study confirm that the clinical response rates achieved after the first 16 weeks were sustained after 2 years of treatment for patients randomized to bimekizumab in the ITT population, regardless of bimekizumab Q4W or Q8W maintenance dose regimen, with no new safety findings. In addition, results suggest that switching from adalimumab to bimekizumab without washout, as may be desirable in real-world clinical practice, does not impose new safety concerns and rapidly improves responses; patients can achieve and sustain similar responses to those who received 2 years of bimekizumab from baseline.

Despite major advances in the treatment of plaque psoriasis, some patients never achieve clear skin, lose clearance early in treatment, or lose clearance over time with current conventional systemics and biologics.[3–5,18,19] This is a concern given the chronic nature of psoriasis and, consequently, patients face lower HRQoL and high cumulative lifetime burden from psoriasis. Therefore, patients have to consider switching treatments to obtain better responses.[7] In the phase III extension trial of the IL-17A inhibitor ixekizumab (UNCOVER-3) PASI 90 and PASI 100 were achieved by 79.7% and 56.3% of patients after 2 years of treatment, respectively (OC).[20] While not directly comparable, the higher response rates observed after 2 years with bimekizumab 320 mg Q4W/Q8W in the trial reported here [94.4%

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Table 2 Overview of adverse event incidence rates in BE SURE (weeks 0–56) and the BE BRIGHT open-label extension (OLE) (weeks 56–104) by initial randomization group

	Weeks 0–24			Weeks 24–56			Weeks 56–104		
	BKZ 320 mg Q4W, *N* = 158 (72.2 PYs)	BKZ 320 mg Q4W/Q8W, *N* = 161 (73.2 PYs)	ADA/BKZ, *N* = 159 (72.4 PYs)	BKZ 320 mg Q4W, *N* = 152 (94.3 PYs)	BKZ 320 mg Q4W/Q8W, *N* = 149 (91.4 PYs)	ADA/BKZ, *N* = 149 (89.8 PYs)	BKZ 320 mg Q4W, *N* = 137 (124.7 PYs)	BKZ 320 mg Q4W/Q8W, *N* = 139 (123.7 PYs)	ADA/BKZ, *N* = 131 (119.2 PYs)
Summary of TEAEs									
Any TEAE	300.7 (247.6–361.8)	310.4 (256.5–372.3)	297.5 (244.8–358.3)	198.5 (161.7–241.2)	198.3 (162.0–240.2)	256.7 (211.1–309.1)	157.3 (127.6–191.9)	147.4 (119.1–180.3)	202.5 (165.0–246.1)
Serious TEAEs	5.6 (1.5–14.4)	1.4 (0.0–7.7)	7.0 (2.3–16.3)	2.1 (0.3–7.7)	9.0 (3.9–17.7)	10.4 (4.7–19.6)	3.2 (0.9–8.3)	6.6 (2.8–13.0)	5.1 (1.9–11.2)
Severe TEAEs	4.2 (0.9–12.3)	2.8 (0.3–9.9)	7.0 (2.3–16.3)	5.4 (1.8–12.6)	9.1 (3.9–17.8)	8.0 (3.2–16.5)	3.2 (0.9, 8.3)	5.8 (2.3–11.9)	5.1 (1.9–11.2)
TEAEs leading to discontinuation	4.2 (0.9–12.2)	8.3 (3.0–18.1)	7.0 (2.3–16.3)	3.2 (0.7–9.4)	2.2 (0.3–7.9)	5.6 (1.8–13.1)	2.4 (0.5–7.1)	3.2 (0.9–8.3)	1.7 (0.2–6.1)
Drug-related TEAEs	66.6 (47.8–90.3)	75.6 (55.4–100.9)	62.0 (43.9–85.1)	50.8 (36.3–69.2)	44.1 (30.7–61.4)	63.0 (45.9–84.2)	25.9 (17.2–37.4)	32.2 (22.1–45.2)	37.7 (26.4–52.3)
Deaths	0	0	1.4 (0.0–7.7)	0	0	0	0.8 (0.0–4.5)	0	0
Three most common TEAEs[a]									
Nasopharyngitis	49.4 (33.8–69.8)	40.2 (26.5–58.5)	60.2 (42.6–82.6)	20.6 (12.2–32.6)	17.6 (9.9–29.1)	24.8 (15.1–38.3)	28.6 (19.3–40.8)	14.1 (8.0–22.9)	21.0 (13.1–31.8)
Oral candidiasis	21.9 (12.2–36.0)	27.7 (16.7–43.3)	0	23.2 (14.2–35.8)	15.0 (8.0–25.7)	32.4 (21.2–47.5)	10.2 (5.3–17.8)	9.5 (4.7–17.0)	13.6 (7.6–22.4)
Upper respiratory tract infection	9.9 (4.0–20.4)	17.0 (8.8–29.7)	22.0 (12.3–36.2)	8.8 (3.8–17.3)	12.5 (6.2–22.3)	10.4 (4.8–19.8)	6.7 (2.9–13.2)	9.4 (4.7–16.8)	8.9 (4.3–16.3)
TEAEs of interest									
Serious infections	0	1.4 (0.0–7.7)	1.4 (0.0–7.7)	1.1 (0.0–5.9)	2.2 (0.3–8.0)	4.5 (1.2–11.5)	0.8 (0.0–4.5)	0	0
Active tuberculosis	0	0	0	0	0	0	0	0	0
Opportunistic infections	1.4 (0.0–7.7)	4.1 (0.9–12.1)	0	1.1 (0.0–5.9)	0	2.2 (0.3–8.1)	0	0	2.6 (0.5–7.5)
Fungal infections	36.1 (23.2–53.8)	39.0 (25.5–57.2)	1.4 (0.0–7.7)	36.3 (24.5–51.9)	26.1 (16.4–39.6)	45.2 (31.5–62.9)	16.6 (10.0–25.9)	15.0 (8.8–24.1)	23.9 (15.5–35.3)
Candida infections[b]	26.4 (15.6–41.7)	29.3 (17.9–45.3)	0	25.7 (16.1–38.9)	16.2 (8.9–27.2)	33.7 (22.2–49.0)	11.1 (5.9–18.9)	10.4 (5.4–18.1)	17.7 (10.6–27.6)
Oral candidiasis	21.9 (12.2–36.0)	27.7 (16.7–43.3)	0	23.2 (14.2–35.8)	15.0 (8.0–25.7)	32.4 (21.2–47.5)	10.2 (5.3–17.8)	9.5 (4.7–17.0)	13.6 (7.6–22.4)
Neutropenia	2.8 (0.3–10.1)	0	5.6 (1.5–14.4)	0	0	0	0	0	0.8 (0.0–4.7)
Inflammatory bowel disease	0	0	0	0	0	0	0	0.8 (0.0–4.5)[c]	0
Malignancies	0	5.5 (1.5–14.2)	1.4 (0.0–7.7)	0	2.2 (0.3–8.0)	1.1 (0.0–6.2)	0.8 (0.0–4.5)	2.5 (0.5–7.2)	0
NMSC	0	4.1 (0.9–12.1)	0	0	0	1.1 (0.0–6.2)	0	1.6 (0.2–5.9)	0
Adjudicated SIB	0	0	0	0	0	0	0	0	0
Depression	0	0	0	0	0	1.1 (0.0–6.2)	0.8 (0.0–4.5)	0.8 (0.0–4.5)	0
Serious hypersensitivity reactions	0	0	0	0	0	0	0	0	0.8 (0.0–4.7)[d]
Elevated liver enzymes	4.2 (0.9–12.2)	5.5 (1.5–14.1)	15.8 (7.9–28.3)	1.1 (0.0–5.9)	2.2 (0.3–8.0)	6.9 (2.5–15.0)	2.4 (0.5–7.1)	1.6 (0.2–5.9)	6.1 (2.4–12.5)
Adjudicated MACE	0	0	0	0	0	0	0	0.8 (0.0–4.5)	0.8 (0.0–4.7)

ADA, adalimumab; BKZ, bimekizumab; MACE, major adverse cardiovascular event; NMSC, nonmelanoma skin cancer; OLE, open-label extension; PYs, patient years; Q4W, every 4 weeks; Q8W, every 8 weeks; SIB, suicidal ideation and behaviour; TEAE, treatment-emergent adverse event. Data are presented for weeks 0–24, 24–56 and 56–104 by initial randomization group, regardless of BKZ OLE dosing regimen. Both BKZ treatment groups were receiving BKZ 320 mg Q4W until week 16. [a]Note that the three most common TEAEs were the same for patients treated with BKZ with for every time period shown. [b]Further details on *Candida* infections during BE SURE and the BE BRIGHT OLE are provided in Table S1 (see Supporting Information). [c]One event of Crohn disease. [d]One event of dermatitis. Data are presented as exposure-adjusted incidence rate (95% confidence interval).

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PASI 90 and 80.0% PASI 100 (OC)] may suggest an additional benefit from inhibiting IL-17F in addition to IL-17A.

Both bimekizumab randomization groups sustained high levels of clinical improvement through 104 weeks of treatment, and both had similar safety profiles. While dose adjustments in these groups occurred during the BE BRIGHT OLE, which may limit the conclusions that can be drawn regarding individual dose regimens from this ITT analysis, most patients continued to receive their initial Q4W or Q8W maintenance dose through week 104, and both groups demonstrated similar efficacy responses over time (Figure S1; see Supporting Information). While there were a higher number of patients remaining on the bimekizumab Q4W regimen, these results contribute to the evidence that Q8W is an effective maintenance dosing regimen for patients treated with bimekizumab, which reduces patients' disease and treatment burden.[17,21] This suggests that bimekizumab can be dosed less frequently during the maintenance period than current IL-17 inhibitors, such as ixekizumab and secukinumab, for which the recommended maintenance dosage is Q4W, and brodalumab, for which Q2W is recommended.[22]

Bimekizumab was well tolerated and the occurrence of TEAEs was similar between treatment groups, and generally decreased over time. The three most common TEAEs through weeks 0–24, 24–56 and 56–104 were nasopharyngitis, oral candidiasis and upper respiratory tract infection, similar to those reported in the BE SURE 1-year study.[17] For patients randomized to adalimumab, an increased rate of oral candidiasis was observed during weeks 24–56 following the switch to bimekizumab, although cases were mainly mild or moderate in severity. Oral candidiasis rates are higher with bimekizumab than with other IL-17 inhibitors.[23–26] However, all patient groups in the second year of treatment saw reduced oral candidiasis rates, compared with the previous period, and rates were lower with bimekizumab Q4W/Q8W compared with Q4W. No cases led to bimekizumab treatment discontinuation.

In addition to skin clearance, controlling inflammation through the use of biologic therapies may provide patients with other benefits, such as reducing progression of other comorbidities.[27–29] Furthermore, more highly controlled inflammation leads to greater benefits in HRQoL, with PASI 90/100 responders typically experiencing greater benefits in HRQoL than PASI 75 responders.[30] In this study, improvements in skin clearance observed with bimekizumab were consistent with improvements in HRQoL; DLQI 0/1 responder rates were improved at week 16 and were sustained through to week 104 for patients treated with bimekizumab.

A key strength of this analysis was the length of observation (104 weeks), which allowed for a thorough examination of the maintenance of efficacy and safety of treatment over time. Another strength of this study was the use of multiple methods to analyse missing data; in this study, three different missing data imputation methods were used (mNRI, NRI and OC). High levels of efficacy for bimekizumab were observed regardless of imputation method. Although response rates were slightly lower with NRI, this was expected owing to the stringent nature of this analysis.

A potential limitation of this work is the clinical setting in which the study was conducted, as biologic treatment survival is often higher in clinical research than in real-world settings. This trend is observed in the real-world observational cohort study from the British Association of Dermatologists Biologic Interventions Register (BADBIR). The overall survival rate of the first course of biologics for 3523 biologic-naive patients in the first year of treatment was 77%, falling to 53% in the third year, with the majority of patient discontinuations resulting from ineffectiveness.[7] In future studies, it will be important to understand how bimekizumab is tolerated in both the longer term and in a real-world setting, and whether the high efficacy levels observed in this study are maintained over 2 years. Additionally, from week 56, the study was an open-label trial; lack of blinding may have increased the risk of bias.

In summary, clinical and HRQoL responses observed during the first 16 weeks of BE SURE in patients randomized to bimekizumab were sustained through 2 years of treatment regardless of bimekizumab maintenance dosing regimen, and switching from adalimumab to bimekizumab resulted in a rapid substantial and sustained increase in efficacy responses over the longer term. Bimekizumab was well tolerated, and no safety signals were identified with longer exposure to bimekizumab.

Acknowledgments

The authors thank the patients, the investigators and their teams who took part in this study. The authors also acknowledge Susanne Wiegratz (UCB Pharma, Monheim, Germany) for publication coordination, Natalie Nunez Gomez (UCB Pharma) for critical review and Poppy Wilson (Costello Medical, London, UK) for medical writing and editorial assistance based on the authors' input and direction. These studies were funded by UCB Pharma.

Funding sources

Funding for this study was provided by UCB Pharma. Support for thirdparty writing assistance for this article, provided by PoppyWilson, was funded by UCB Pharma in accordance with Good Publication Practice (GPP3) guidelines (http://www.ismpp.org/gpp3).

Conflicts of interest

See Appendix.

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 completed. All documents are available in English only, for a prespecified time, typically 12 months, on a password-protected portal.

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Ethics statement

All patients entering BE SURE and the BE BRIGHT open-label extension provided written informed consent documented in accordance with local regulations, the International Conference on Harmonization Good Clinical Practice requirements, and the ethical principles originating from the Declaration of Helsinki.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website.

Appendix

Conflicts of interest

D.T. has received honoraria for participation on advisory boards, and has acted as a speaker for and/or consultant

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for AbbVie, Almirall, Amgen, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celltrion, Eli Lilly, Galapagos, Galderma, Janssen, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi Genzyme and UCB Pharma. He has received research grants from LEO Pharma and Novartis. R.V. has received grants/research support from AbbVie, Amgen, Centocor, Dermira, Dermavant, Eli Lilly, Galderma, GSK, LEO Pharma, Novartis, Merck, Pfizer, Regeneron, Takeda and UCB Pharma and participated in a speakers bureau or received honoraria from AbbVie, Actelion, Amgen, Bausch-Health, Celgene, Cipher, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, Merck, Novartis, Pfizer and UCB Pharma. R.V. has received consulting fees from AbbVie, Actelion, Amgen, Bausch-Health, Celgene, Cipher, Eli Lilly, Galderma, GSK, Janssen, LEO Pharma, Merck, Novartis, Palladin, Pfizer and UCB Pharma. M.A.d.R. has received honoraria for participation on advisory boards, and acted as a speaker and/or a consultant for AbbVie, Almirall, Artax Biopharma, Biogen, Celgene, Eli Lilly, Janssen-Cilag, Janssen Pharmaceutica, LEO Pharma, Novartis and UCB Pharma. C.C. has acted as a consultant and/or principal investigator in clinical trials for AbbVie, Actelion, Amgen, Almirall, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly, Galderma, Incyte, Janssen-Cilag, LEO Pharma, MSD, Novartis, Pfizer, Samsung, Sanofi Genzyme and UCB Pharma. D.M.P. has received honoraria for participation on advisory boards, data safety monitoring boards, consultancy or as an investigator from Atacama Therapeutics, Bickel Biotechnology, Biofrontera AG, Bristol Myers Squibb, Celgene, Dermira, LEO Pharma, Novartis, Pfizer, Regeneron, Sanofi, TheraVida, Valeant. D.M.P. has received grants/research funding from Almirall, Amgen, AOBiome, Asana Biosciences, Bickel Biotechnology, Celgene, Dermavant, Dermira, Eli Lilly, LEO Pharma, Menlo Therapeutics, Merck, Novartis, Novo Nordisk, Ortho Dermatologics, Pfizer and Regeneron. B.S. has received consultancy honoraria from AbbVie, Almirall, Amgen, Arcutis, Arena, Aristea, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Dermavant, Dermira, Eli Lilly, Equillium, GSK, Janssen, LEO Pharma, Meiji Seika Pharma, Mindera, Novartis, Ortho Dermatologics, Pfizer, Regeneron, Sanofi Genzyme, Sun Pharma and UCB Pharma. B.S. has acted as a speaker for AbbVie, Amgen, Eli Lilly, Janssen, and Ortho Dermatologics and received a consulting fee as a Scientific Director for Corrona Psoriasis Registry. B.S. has been an investigator for AbbVie, Cara Therapeutics, Corrona Psoriasis Registry, Dermavant, Dermira and Novartis and received an honorarium as Editor-in-Chief for the *Journal of Psoriasis and Psoriatic Arthritis*. V.V., M.W., C.M. and D.d.C. are employees and shareholders of UCB Pharma. A.B.K. has acted as a consultant and investigator for AbbVie, Eli Lilly, Janssen, Bristol Myers Squibb, LEO Pharma, Meiji Pharma, Novartis, Pfizer, Regeneron and UCB Pharma and been an advisor to the Organization of Teratology Information Services (OTIS) and Ventxy Biosciences. A.B.K. has received fellowship funding from AbbVie and Janssen and is on the Board of Directors for Almirall.

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