Bimekizumab for the treatment of moderate-to-severe plaque psoriasis: efficacy, safety, pharmacokinetics, pharmacodynamics and transcriptomics from a phase IIa, randomized, double-blind multicentre study*

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Summary

Background Bimekizumab is a monoclonal antibody that selectively inhibits both interleukin (IL)-17A and IL-17F, which is currently under investigation for treatment of moderate-to-severe plaque psoriasis. Maintenance dosing every 4 weeks is well established with IL-17 inhibitors for psoriasis.

Objectives To investigate the possible dosing interval during bimekizumab maintenance therapy to maintain clear skin, to inform phase III studies.

Methods Forty-nine patients with moderate-to-severe plaque psoriasis received bimekizumab 320 mg at weeks 0/4, followed at week 16 by bimekizumab 320 mg (n = 17) or placebo (n = 32). Efficacy, safety, pharmacokinetics, immunogenicity and biopsy transcriptomic analyses were assessed to week 28.

Results At week 8, 47% of patients achieved a 100% improvement from baseline in Psoriasis Area and Severity Index (PASI 100), increasing to 57% at week 12 (8 weeks after the second dose) before decreasing. In those who received bimekizumab at week 16, PASI 100 rate increased to comparable peak levels at week 20, but reduced by week 28 to 41% (12 weeks after the third dose). The week 8 transcriptional signature observed in lesional psoriatic skin rapidly normalized to levels consistent with nonlesional skin, resulting in molecular remission. Keratinocyte-related gene products such as CXCL1 (C-X-C motif chemokine ligand 1), IL-8 (encoded by the CXCL8 gene), CCL20 (C-C motif chemokine), IL-36c and IL-17C were profoundly normalized to levels associated with non-lesional skin.

Conclusions Here, inhibition of IL-17F in addition to IL-17A resulted in rapid, deep clinical responses. Additionally, profound normalization of keratinocyte biology and the psoriatic transcriptome was observed, including normalization of both IL17 and IL23 gene expression by week 8. These data provide evidence to support evaluation of bimekizumab maintenance dosing both every 8 and every 4 weeks in phase III clinical trials.
The introduction of biologics that target tumour necrosis factor (TNF) or interleukin (IL)-12/23 has enabled the majority of patients with plaque psoriasis to achieve a 75% improvement from baseline in Psoriasis Area and Severity Index (PASI 75). More recently, biologics targeting IL-23 and IL-17A have further raised treatment expectations, with PASI 90 becoming a realistic goal, and many patients also achieving PASI 100 (complete skin clearance). Increasing evidence highlights the central role of IL-17A and IL-17F in the underlying disease pathobiology of psoriasis, by driving aberrant keratinocyte biology. Both keratinocyte proliferation and release of factors such as CXCL1 (C-X-C motif chemokine ligand 1), IL-8 (encoded by CXCL8 gene) and IL-6, it is much more abundant in psoriatic skin. Increasing evidence highlights the central role of both IL-17A and IL-17F in the underlying disease pathobiology of psoriasis, by driving aberrant keratinocyte biology. Both keratinocyte proliferation and release of factors such as CXCL1, IL-8 and IL-6, it is much more abundant in psoriatic skin. IL-17A and IL-17F are principally produced by activated Th17 cells and exist in dimeric isoforms (homodimers IL-17A/A and IL-17F/F, and heterodimer IL-17A/F). Each dimer binds an IL receptor complex, IL-17RA/IL-RC, and therefore can transduce similar signalling and activation of target genes. It has been found that all IL-17 isoforms are produced in active plaques of psoriasis vulgaris, and thus each has potential to stimulate ‘downstream’ activation of keratinocytes and other cell types that ultimately create visible psoriasis lesions.

A significant challenge in chronic diseases such as psoriasis is the need for patients to receive medication over long periods of time. Less frequent treatment administration may increase treatment adherence and quality of life. The commonly used IL-17A inhibitors, secukinumab and ixekizumab, both require dosing every 4 weeks (Q4W) during maintenance treatment, and loss of response with these agents has driven efforts to optimize response with more frequent intervals as already used with the IL-17 receptor inhibitor, brodalumab. There remains an unmet need for a treatment that provides both high rates of complete skin clearance and less frequent dosing. Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits both IL-17A and IL-17F. Preclinical studies in human in vitro assays have shown that dual inhibition of IL-17A and IL-17F with bimekizumab leads to a greater inhibitory effect than blockade of either cytokine alone. Phase II
studies in patients with moderate-to-severe plaque psoriasis demonstrated high rates of skin clearance with bimekizumab, which were well-maintained with Q4W maintenance dosing.24,25

Here, we present results from a phase II exploratory trial designed to investigate whether high rates of skin clearance can be achieved with a prolonged bimekizumab maintenance dosing interval, and whether bimekizumab treatment is associated with the molecular resolution of psoriasis and other inflammatory markers.

**Patients and methods**

**Study design**

This prospective, randomized, patient-blinded, investigator-blinded, parallel-group phase IIa study (NCT03025542) was conducted in eight study sites in Australia, Canada, USA and Moldova. Patients were randomized 2 : 1 to two treatment groups, both of which received bimekizumab dosed at 320 mg via subcutaneous administration at weeks 0 and 4; at week 16 the first group received placebo [the bimekizumab plus placebo (BKZ+PBO) group] and the second group received a third dose of bimekizumab 320 mg (the BKZ group) (Figure 1). Further details of randomization and study blinding are described in Appendix S1 (see Supporting Information).

The institutional review board or independent ethics committee at all the investigational sites approved the protocol, and the study was performed in accordance with the Declaration of Helsinki and Good Clinical Practice.

**Endpoints and assessments**

The primary efficacy endpoint was change from baseline in PASI at week 28 in each treatment group. The primary pharmacokinetic variable was plasma bimekizumab concentration over the course of the trial. The primary immunological variable was anti-bimekizumab antibody detection prior to and following study treatment. The primary safety variable was incidence of adverse events (AEs). Secondary efficacy endpoints were the proportion of patients achieving PASI 75, PASI 90 and PASI 100, and IGA 0/1 [IGA score of 0 or 1 (clear or almost clear) with ≥ 2-point improvement from baseline] at week 16.

**Bioanalytical and transcriptome analyses**

Blood samples for the purpose of measuring pharmacokinetics were collected at baseline (predose) and at all subsequent
study visits. Samples for anti-drug antibody (ADA) analysis were also taken at each visit, except week 2. Skin biopsies for transcriptome analysis were taken from lesional psoriatic plaques and paired nonlesional skin at baseline and week 8, and from lesional psoriatic plaques only at weeks 16 and 28 (Figure 1). Detailed methods for bioanalytical and transcriptome analyses can be found in Appendix S1.

Statistical analyses and sample size

The safety set consisted of all patients who received ≥ 1 dose of study drug, with the full analysis set (FAS) consisting of the subset of the safety set who had a valid PASI measurement at baseline.

Efficacy variables were based on the FAS. Results were combined across all patients for the first 16 weeks and separated by treatment group thereafter. Changes from baseline and responder variables were defined relative to the last available measurement prior to the first bimekizumab injection. Missing data were imputed as last observation carried forward for continuous variables and using nonresponder imputation for binary variables. Descriptive statistics were used.

All safety variables were performed using the safety set. Treatment-emergent AEs (TEAEs) were defined as any AE occurring from the first dose of study drug up to 140 days after the final dose (i.e. up to the week-36 safety follow-up visit). AEs occurring after this date were not classified as TEAEs and were excluded. AEs were coded using MedDRA version 19.0 (https://www.meddra.org).

For pharmacokinetic data, actual blood sampling times for bimekizumab concentrations were obtained relative to the start time of the first injection. Individual concentrations were summarized by treatment group at each scheduled visit based on the pharmacokinetic per-protocol set. ADA status (positive/negative) was summarized as a categorical endpoint (number and percentage of patients) by treatment group for all time-points and overall, based on the safety set.

No formal statistical sample size estimation was performed owing to the exploratory nature of this study, which was not powered for any conclusive statistical analysis of efficacy, pharmacokinetics, safety or immunological variables. The sample size and 2:1 randomization were determined based on the number of patients required in the current study to provide reliable pharmacokinetic/pharmacodynamic model parameter estimates when combined with data from the phase IIb trial, BE ABLE 1.25

Results

Patients and baseline demographics

Beginning 27 December 2016, 73 patients were screened and 49 patients were randomized: 32 to the BKZ+PBO group and 17 to the BKZ group (Figure 2). The last study visit occurred on 11 December 2017. Patient demographics and baseline characteristics were generally balanced (Table 1), with the exception of the higher mean BSA involvement in the BKZ group, attributed to two patients with BSA involvement > 60% (82-5% and 72-1%, respectively). Mean baseline PASI was 18-3 in the BKZ+PBO group and 23-4 in the BKZ group. The overall study population was comparable to that in other studies of bimekizumab in psoriasis.25–29

Clinical response

The primary efficacy endpoint in this trial was change in PASI from baseline at week 28. Absolute change from baseline at week 28 was −10-8 [95% confidence interval (CI) −13-5 to...
–8.0] in the BKZ+PBO group and –19.7 (95% CI –24.2 to –15.2) in the BKZ group. Substantial improvements in PASI response rate were observed after two bimekizumab doses, at weeks 0 and 4, reaching a maximum mean decrease across all patients of 94% at week 16 (12 weeks after the second dose).

Rapid responses were demonstrated by the proportion of patients achieving PASI 75, PASI 90 and PASI 100 responses during the first 8 weeks, with 16% achieving PASI 100 at week 4 (Figure 3). This response rate increased to 47% by week 8 (4 weeks after the second dose). PASI 75 and PASI 90 responder rates reached a maximum at week 16 (92% and 80%, respectively), whereas the maximal PASI 100 response rate of 57% was observed at week 12 (8 weeks after the second dose), before decreasing to 49% at week 16 (12 weeks after the second dose).

Patients who received an additional bimekizumab dose at week 16 generally maintained their PASI 90 response at week 28 (12 weeks later), with a similar trend observed for IGA 0/1 response, while responses were diminished at week 28 in patients who received placebo at week 16 (Figure 4). In patients who received an additional dose at week 16, the PASI 100 response rate was increased at week 20, but a moderate reduction was observed at week 28, whereas a large reduction was observed at week 28 in patients who received no additional dose (week 28 response rates 41% vs. 13%, respectively).

**Safety**

Overall, TEAEs were reported in 88% of patients at a similar incidence between treatment groups (Table 2). Among the TEAEs occurring in ≥ 5% of all patients, the two most common were upper respiratory tract infection (18%) and nasopharyngitis (12%).

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**Table 1** Demographics and baseline characteristics

| Demographics                          | BKZ+PBO group* (n = 32) | BKZ group* (n = 17) | All patients (N = 49) |
|---------------------------------------|-------------------------|---------------------|-----------------------|
| Age (years), mean (SD)                | 41.8 (14.1)             | 45.9 (10.4)         | 43.2 (13.0)           |
| Male, n (%)                           | 15 (47)                 | 11 (65)             | 26 (53)               |
| White, n (%)                          | 30 (94)                 | 12 (71)             | 42 (86)               |
| Body mass index, kg/m², mean (SD)     | 30.1 (5.6)              | 31.0 (5.9)          | 30.4 (5.7)            |
| Baseline disease characteristics      |                         |                     |                       |
| Disease duration (years), mean (SD)   | 13.5 (12.3)             | 14.9 (10.5)         | 14.0 (11.6)           |
| PASI, mean ± SD                       | 18.3 (6.7)              | 23.4 (10.1)         | 20.1 (8.3)            |
| Body surface area (%) (mean, SD)      | 22.0 (12.4)             | 34.8 (21.5)         | 26.4 (17.1)           |
| Investigator’s Global Assessment, n (%) |                       |                     |                       |
| 3: moderate                            | 28 (88)                 | 14 (82)             | 42 (86)               |
| 4: severe                              | 4 (13)                  | 3 (18)              | 7 (14)                |
| Prior biologic therapy, n (%)          | 4 (13)                  | 0 (0)               | 4 (8)                 |

PASI, Psoriasis Area and Severity Index. *Both the BKZ+PBO and BKZ groups received bimekizumab 320 mg at weeks 0 and 4; at week 16 the BKZ+PBO group received placebo and the BKZ group received a third dose of bimekizumab 320 mg.

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**Figure 3** Psoriasis Area and Severity Index (PASI) response to week 16 for the combined treatment groups (nonresponder imputation). PASI 75/90/100, ≥ 75%/90%/100% improvement from baseline PASI.
Three patients reported serious TEAEs: one case of nonrelated, severe peripheral sensorimotor neuropathy and one case of nonrelated, severe syncope (114 days after the final dose of study medication), in two patients in the BKZ + PBO group, and one case of nonrelated, acute cholecystitis and pancreatitis in a patient in the BKZ group. No serious TEAEs were considered related to the study drug, and all resolved with no sequelae. Two patients, both in the BKZ group, discontinued treatment due to TEAEs: one reported a nonserious TEAE of decreased lymphocyte count (29 days after study commencement) and the other reported one TEAE of increased alanine aminotransferase and two TEAEs of increased gamma-glutamyltransferase (the first being 15 days after the last dose of study medication). There were no deaths.

**Pharmacokinetics and anti-drug antibodies**

The plasma bimekizumab concentrations following subcutaneous administration were consistent with expectations and other bimekizumab studies, maintaining trough concentrations of around 8–12 µg mL⁻¹ over the first 10–12 weeks from the start of treatment (Figure 4d) (Figure S1 shows plasma concentration target range rationale; see Supporting Information). In patients who received a third dose at week 16 (the BKZ group), an increase in plasma bimekizumab concentrations was observed, whereas an exponential decrease in levels was observed in patients who did not receive an additional dose, with the expected elimination rate associated with a T½ of ~23 days.

The total incidence of anti-bimekizumab antibodies over the 36-week trial period, defined as a single postdose titre that was confirmed positive, was 34% (11 of 32) in the BKZ+PBO group and 47% (eight of 17) in the BKZ group (noting that a neutralizing antibody assay was not available at time of study). One patient in the BKZ+PBO group was confirmed positive at baseline and again at weeks 20, 24 and 28, and at the safety follow-up visit, but with no increase in titre. Review of the individual pharmacokinetic and PASI time-course data suggests there was no impact of anti-bimekizumab antibodies on any of drug exposure, clinical response or safety across the 28-week treatment period.

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**Figure 4** Psoriasis Area and Severity Index (PASI) score and Investigator’s Global Assessment (IGA) 0/1 responses at weeks 16, 20 and 28 (non-responder imputation), and bimekizumab (BKZ) plasma concentration from baseline to week 36. The bimekizumab plus placebo (BKZ+PBO) group received two doses of BKZ 320 mg at weeks 0 and 4, with placebo at week 16; the BKZ group received three doses of bimekizumab 320 mg, at weeks 0, 4 and 16. (a) 90% improvement in PASI (PASI 90) responses. (b) PASI 100 responses (total clearance). (c) IGA 0/1 responses: score of 0 (clear) or 1 (almost clear) with ≥ 2-category improvement relative to baseline IGA, scored on a 5-point scale. (d) Bimekizumab plasma concentration. See Figure S1 (Supporting Information) for the bimekizumab plasma concentration target range rationale.
Transcriptome analyses: molecular resolution of the psoriasis transcriptome by bimekizumab

The molecular effect of bimekizumab was examined using changes in transcript abundance at week 8 vs. baseline. These changes were analysed relative to the psoriasis transcriptome, defined as the set of differentially expressed probesets (and unique mapped genes) in baseline lesional skin compared with paired nonlesional skin biopsies.

Bimekizumab treatment led to a rapid, deep normalization of the psoriasis transcriptome at week 8, following two doses. Probesets that were more highly expressed in psoriatic skin had a median percentage improvement of 97%, representing normalization to near nonlesional levels (Figure 5). Bimekizumab also normalized probesets that were downregulated in lesional skin by 84%. Overall, there was a strong negative correlation between gene expression changes at baseline and gene expression changes elicited by bimekizumab treatment (Pearson correlation coefficient $r = -0.97$, $P < 0.001$). Principal component analysis indicated a homogeneous and deep molecular response across patients, with lesional samples at week 8 closely resembling baseline nonlesional samples in latent space. A heatmap of the expression of probesets in the psoriasis transcriptome further illustrates the comprehensive scope of the molecular response to bimekizumab, both in terms of the breadth of disease genes whose expression was reversed towards nonlesional levels and the homogeneity of the molecular response among patients (Figure 5c).

Of the 1082 probesets differentially upregulated in lesional skin at baseline [842 differentially expressed genes (DEGs)], 880 (81%) were also significantly reversed following bimekizumab treatment at week 8. Conversely, 716 (60%) of the 1201 downregulated probesets (835 DEGs) in the psoriasis transcriptome were significantly upregulated at week 8. By relaxing the treatment effect size threshold from $\geq 2$ to $\geq 1.5$, the number of reversed probesets rose to 1069 (99%) and 1182 (98%), respectively. Tables S1 and S2 (see Supporting Information) detail the top 50 probesets downregulated and upregulated by bimekizumab in lesional skin at week 8.

IL-17-responsive genes, induced by stimulation of cultured keratinocytes with supernatant from Th17 cells [Figure 6; and Figure S2 (see Supporting Information)], were among the more strongly normalized genes in the psoriasis transcriptome, with a median percentage improvement of 105% 4 weeks after the second dose. Selected marker genes that drive plaque formation were also deeply normalized by week 8 (Figures 7 and 8). These genes capture key upstream cytokines (IL17A, IL17F, and IL23A and IL12B); downstream effectors such as antimicrobial peptides (S100A7) and proinflammatory

Table 2: Treatment-emergent adverse events (TEAEs)

| Event                                      | BKZ+PBO group a (n = 32) | BKZ group a (n = 17) | All patients (N = 49) |
|--------------------------------------------|--------------------------|---------------------|-----------------------|
| Any TEAEs                                  | 28 (88)                  | 15 (88)             | 43 (88)               |
| Serious TEAEs                              | 2 (6)                    | 1 (6)               | 3 (6)                 |
| Discontinuation due to TEAEs               | 0 (0)                    | 2 (12)              | 2 (4)                 |
| Treatment-related TEAEs                    | 11 (34)                  | 9 (53)              | 20 (41)               |
| Severe TEAEs                               | 1 (3)                    | 3 (18)              | 4 (8)                 |
| Deaths                                     | 0 (0)                    | 0 (0)               | 0 (0)                 |
| Most common TEAEs (≥ 5% of all patients)   |                          |                     |                       |
| Infections and infestations b              |                          |                     |                       |
| Upper respiratory tract infection          | 6 (19)                   | 3 (18)              | 9 (18)                |
| Nasopharyngitis                            | 2 (6)                    | 4 (24)              | 6 (12)                |
| Urinary tract infection                    | 4 (13)                   | 0 (0)               | 4 (8)                 |
| Viral upper respiratory tract infection    | 2 (6)                    | 2 (12)              | 4 (8)                 |
| Gastrointestinal viral                     | 2 (6)                    | 1 (6)               | 3 (6)                 |
| Investigations                             |                          |                     |                       |
| Alanine aminotransferase increased         | 2 (6)                    | 3 (18)              | 5 (10)                |
| Gamma-glutamyltransferase increased        | 2 (6)                    | 3 (18)              | 5 (10)                |
| White blood cell count decreased           | 2 (6)                    | 3 (18)              | 5 (10)                |
| Aspartate aminotransferase increased       | 2 (6)                    | 2 (12)              | 4 (8)                 |
| Neutrophil count decreased                 | 1 (3)                    | 3 (18)              | 4 (8)                 |
| Blood cholesterol increased                | 1 (3)                    | 2 (12)              | 3 (6)                 |
| Metabolism and nutrition disorders         |                          |                     |                       |
| Hyperkalaemia                              | 4 (13)                   | 1 (6)               | 5 (10)                |
| Nervous system disorders                   |                          |                     |                       |
| Headache                                   | 3 (9)                    | 1 (6)               | 4 (8)                 |

All values are n (%). aBoth the BKZ+PBO and BKZ groups received bimekizumab 320 mg at weeks 0 and 4; at week 16 the BKZ+PBO group received placebo and the BKZ group received a third dose of bimekizumab 320 mg. bIn addition, two cases of oral candidiasis, an adverse event of special interest, were reported, in patients in the BKZ+PBO group (4% of all patients).
chemotactic factors [CXCL1, CXCL8, CCL20 (C-C motif chemokine 20)]; markers of keratinocyte proliferation (KRT16); and feedforward cytokines (IL17C, IL36G, IL36A).

To evaluate response durability at a molecular level, median percentage improvement of the psoriasis transcriptome was assessed at weeks 8, 16 and 28 (Figure S3; see Supporting Information). Percentage improvement of upregulated genes reduced from a maximum of 97% at week 8 to 90% by week 16, 12 weeks after the second bimekizumab dose. At week 28, normalization was maintained in patients who received an additional dose at week 16 (94% improvement), but was substantially diminished if no extra dose was administered (60% improvement).

**Discussion**

Bimekizumab is a monoclonal antibody that selectively inhibits all IL-17A and IL-17F dimeric isoforms. Increasing evidence highlights the central role of both cytokines in psoriasis pathogenesis. Since the introduction of anti-IL-17 agents for
psoriasis treatment, patient expectations have shifted from achieving PASI 75 to maintenance of PASI 100, with infrequent dosing.

Analyses have shown that improvements in quality of life correlate with the achievement of complete skin clearance, which can also be attained through longer dosing intervals. Here, bimekizumab treatment resulted in a rapid response onset and achievement of high complete skin clearance rates in the first 16 weeks. While PASI 90 was maintained from week 8 to week 16, PASI 100 response was maximal at week 12 (8 weeks after the second bimekizumab dose) before decreasing. At week 16, patients received either placebo or a third bimekizumab dose. At week 28, 12 weeks later, substantial reductions in all efficacy endpoints were observed in patients who received placebo. In contrast, PASI 90 and IGA 0/1 were maintained in patients who received an additional bimekizumab dose, with a slight reduction in PASI 100. These observations suggest maintenance dosing every 12 weeks would be too infrequent for sustaining complete skin clearance, but this may be possible with dosing every 8 weeks (Q8W). These data helped provide an understanding of the basis for the dosing regimens selected for the phase III trials, which evaluated Q8W dosing, alongside Q4W dosing.

Figure 6 Relative expression of key genes in T helper (Th)17-stimulated keratinocytes. Human keratinocytes were stimulated with Th17 supernatant, with anti-interleukin (IL)-16 blocking antibodies, or without (control). Expression relative to unstimulated cells (shown as a horizontal line) is reported. BKZ, bimekizumab.
Figure 7 Expression of 12 key genes in treated lesional tissue at week 8 relative to baseline nonlesional (NL) and lesional tissue. Log2 normalized expression of probesets corresponding to specific marker genes that underpin psoriasis pathology, in baseline lesional and nonlesional samples and treated lesional samples at week 8. Hashed red horizontal lines correspond to the median baseline expression of a probeset in nonlesional tissue. Log fold change (FC) and false discovery rate (FDR)-adjusted P-values are calculated using the limma moderated t-test. IL, interleukin. BKZ, bimekizumab; CXCL, C-X-C motif chemokine ligand 1; CCL, C-C motif chemokine; KRT, keratin. **FDR < 0.001.

Figure 8 Drivers of plaque formation in psoriasis. Proinflammatory chemotactic factors: CXCL1 (C-X-C motif chemokine ligand 1), interleukin (IL)-8 (encoded by CXCL8) and CCL20 (C-C motif chemokine 20); upstream cytokines: IL-17A, IL-17F, IL-23A and IL-12B; markers of epithelial stress: IL-19, IL-36y and IL-36α; proliferation: KRT16; antimicrobial peptide: S100A7. TNF, tumour necrosis factor. The T17 cell represents IL-17-producing T cells (including cytotoxic T cells and T helper cells).
These data were combined with those from the phase IIb study BE ABLE 1 \textsuperscript{15} for pharmacokinetic/pharmacodynamic modelling and subsequent simulation (combined data not reported). It was concluded that an 8-week dosing interval during maintenance treatment (post week 16) was an option for the maintenance of high skin clearance (PASI 90/100) in the majority of patients with moderate-to-severe psoriasis. Furthermore, less frequent dosing (e.g. every 12 weeks or intermittently) is likely to lead to loss of response in some patients.

Transcriptomic analysis of nonlesional and lesional biopsies showed a clear and distinct molecular profile. Dual inhibition of IL-17A and IL-17F with bimekizumab normalized the psoriatic transcriptome associated with aberrant keratinocyte biology in psoriatic skin, leading to molecular resolution. Specifically, expression of genes encoding the antimicrobial peptides β-defensin 2 (DEFB2), S100 family, neutrophil chemotactic factors such as CXC1 and IL-8 (CCL8), and the chemotactic factor for TH17 cells, CCL20, was profoundly normalized. Other keratinocyte-derived factors such as IL-17C and IL-36γ, which are thought to amplify the IL-23/IL-17 axis in driving lesion chronicity, were also normalized to levels seen in nonlesional skin. Furthermore, expression of II23 transcripts, along with IL17A and IL17F transcripts themselves, was normalized to nonlesional levels. The affected pathways are consistent with data reported for other IL-17 therapies such as secukinumab and brodalumab,\textsuperscript{32,33} and in this study bimekizumab induced a 97% median normalization of the psoriasis transcriptome by week 8.

Therapies that directly target IL-23, such as risankizumab and guselkumab, demonstrate durable clinical responses and require maintenance dosing less frequent than Q4W.\textsuperscript{1,2} The near normalization of II23 transcript expression at 8 weeks after two bimekizumab doses, along with the almost complete normalization of the psoriatic transcriptome (including IL17A and IL17F expression), may in part explain the prolonged efficacy observed within the withdrawal arm of the study, and further supported an 8-week dosing interval with bimekizumab in phase III trials.\textsuperscript{26,28,29} Similar observations of prolonged efficacy were subsequently confirmed across the phase III studies.\textsuperscript{26,28,29}

In this study, we observed that bimekizumab, the only monoclonal antibody under investigation designed to selectively inhibit both IL-17A and IL-17F, demonstrates rapid and deep clinical responses along with a profound normalization of the psoriatic transcriptome, providing strong evidence that both IL-17A and IL-17F are key inflammatory entities underpinning psoriasis pathogenesis. In addition, unlike IL-17A therapeutics that require Q4W (or more frequent) maintenance dosing, these data supported the decision to evaluate Q8W maintenance dosing alongside Q4W dosing with bimekizumab in subsequent phase III psoriasis studies.\textsuperscript{26,28,29}

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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 S1 Supplementary methods.

Figure S1 Target plasma concentration range.

Figure S2 Molecular resolution of interleukin-17 pathway genes.

Figure S3 Time course of molecular resolution of the psoriasis transcriptome by bimekizumab.

Table S1 Top 50 genes downregulated by bimekizumab in lesional skin at week 8.

Table S2 Top 50 genes upregulated by bimekizumab in lesional skin at week 8.