Bimekizumab efficacy and safety in patients with moderate to severe hidradenitis suppurativa: two 48-week, randomised, double-blind, placebo-controlled, multicentre phase 3 trials (BE HEARD I and II)

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SUMMARY

Background

Patients with hidradenitis suppurativa (HS) face significant unmet clinical needs and limited therapeutic options. We assessed the efficacy and safety of bimekizumab, a monoclonal IgG1 antibody that selectively inhibits interleukin (IL)-17F in addition to IL-17A, in patients with moderate to severe HS.

Methods

BE HEARD I and II were two identically designed, 48-week randomised, double-blind, placebo-controlled, multicentre phase 3 trials. Patients aged 18 years or older with moderate to severe HS were randomised 2:2:2:1 using interactive response technology (stratified by worst Hurley Stage at baseline and baseline systemic antibiotic use) to receive subcutaneous bimekizumab 320 mg every 2 weeks, bimekizumab 320 mg every 2 weeks to week 16 then every 4 weeks, bimekizumab 320 mg every 4 weeks, or placebo to week 16 then bimekizumab 320 mg every 2 weeks via a 1 mL prefilled syringe. The primary endpoint was the HS Clinical Response (HiSCR50) at week 16. Efficacy analyses included all randomised study patients (intention-to-treat population); safety analyses included all patients who received at least one full or partial dose of study treatment in the safety set, and of bimekizumab in the active medication set. These trials are registered at ClinicalTrials.gov: NCT04242446, NCT04242498 (both completed).

Findings

BE HEARD I occurred from Feb 19, 2020 to Feb 19, 2023, and 505 patients were enrolled and randomised; BE HEARD II occurred from March 2, 2020 to September 28, 2022, and 509 patients were enrolled and randomised. The primary endpoint at week 16 was met in the bimekizumab every 2 weeks group using modified non-responder imputation; higher responder rates were observed with bimekizumab versus placebo in both trials: BE HEARD I: 48% (138/289) versus 29% (21/72), (odds ratio: 2·23 [97·5% CI 1·16–4·31]; p=0·0060); BE HEARD II: 52% (151/291) versus 32% (24/74) (2·29 [1·22–4·29]; p=0·0032). In BE HEARD II HiSCR50 was also met in the bimekizumab every 4 weeks group (54% [77/144] versus 32% [24/74] with placebo; 2·42 [1·22–4·80]; p=0·0038). Responses were maintained or increased to week 48. Serious treatment-emergent adverse events were reported in 40 (8%, BE HEARD I) and 24 (5%, BE HEARD II) bimekizumab-treated patients

over 48 weeks. The most frequently reported TEAEs through week 48 were hidradenitis in both trials, in addition to coronavirus infection and diarrhoea in BE HEARD I, and oral candidiasis and headache in BE HEARD II. One death, due to congestive heart failure in a patient with significant cardiovascular history treated with bimekizumab every 2 weeks in BE HEARD I, was reported across the two trials (considered unrelated to bimekizumab treatment by the investigator). No new safety signals were observed.

Interpretation

Bimekizumab demonstrated rapid and deep clinically meaningful responses that were maintained up to 48 weeks, and was well-tolerated in patients with HS.

Funding

UCB Pharma.

RESEARCH IN CONTEXT

Evidence before this study

We searched PubMed with the term "hidradenitis suppurativa" and screened by title to identify research and clinical trials of biologic agents in patients with hidradenitis suppurativa (HS). Manuscripts published between January 1, 2006 and December 31, 2022 were extracted. HS is a chronic, systemic, relapsing inflammatory skin disease associated with disability and co-morbidities, a detrimental impact on patients' quality of life, and increased risk of depression and suicidality. Patients with HS face significant unmet clinical need, however the only biologic therapies currently approved are the TNFα inhibitor adalimumab and, since this literature review was performed, the interleukin (IL)-17A inhibitor secukinumab in Europe. As important pathogenic drivers, both IL-17A and IL-17F are potential therapeutic targets in HS. Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits IL-17F in addition to IL-17A. In a phase 2 trial, bimekizumab has demonstrated clinically meaningful and consistent improvements versus placebo, including in stringent outcome measures, and was well-tolerated. Based on these results, phase 3 studies were initiated.

Added value of this study

Bimekizumab is a first in class biologic for inhibition of IL-17F in addition to IL-17A, and has demonstrated clinically meaningful improvements in physician-reported and patient-reported outcome measures through 48 weeks of treatment. The BE HEARD I and II trials showed that HS patients treated with bimekizumab achieved rapid and maintained improvements in the signs and symptoms of disease, including the HiSCR50 primary outcome, versus those who received placebo at week 16, with responses maintained or increased over time to week 48. Rapid improvements were observed in patients who switched from placebo to bimekizumab treatment at week 16. The trials were the first phase 3 studies in HS to report the more stringent HiSCR75 and HiSCR90 endpoints longer-term, to week 48, and demonstrated deep and maintained levels of clinical response with bimekizumab. The safety profile of bimekizumab in BE HEARD I and II was consistent with other bimekizumab indications and with other IL-17A inhibitors in development for HS; no new safety signals were identified.

Implications of all the available evidence

The BE HEARD I and II trials are the first phase 3 trials to assess the effects of inhibition of IL-17F and IL-17A in patients with HS. The outcomes of these trials support the hypothesised roles of both IL-17F and IL-17A in the pathogenesis of the disease, and support bimekizumab as a promising new therapeutic option for patients with moderate to severe HS. Given the heterogeneity and complexity of HS, future research should include studies targeting optimal pharmacologic, surgical, and adjuvant therapies to optimise treatment goals meaningful to patients. Real-world evidence studies and Network Meta-Analyses may also help to inform future clinician decision making in the management of moderate to severe HS.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic, relapsing inflammatory skin disease associated with significant co-morbidities, and a detrimental impact on patients' quality of life.[1-3] Painful inflammatory nodules, abscesses, and draining tunnels (DTs) in folding areas of the skin are the defining manifestations of HS, which affects ~0·4–1·0% of the population globally and disables as many as 14·5% of patients.[1, 4, 5] A lack of disease recognition results in substantially delayed diagnosis and intervention. HS impacts not only skin-related quality of life, but physical and mental health. Depression and anxiety affect up to 42·9% of patients, with incidence of completed suicide higher than in the background population.[2, 6] Unemployment rates are high, and absenteeism is reported by around half of patients with jobs.[5, 7]

The only biologic therapies currently approved for treatment of moderate to severe HS are the tumour necrosis factor α (TNF-α) inhibitor adalimumab and the interleukin (IL)-17A inhibitor secukinumab in Europe.[8-10] A recent multinational study reported that nearly half of clinicians and patients expressed dissatisfaction with existing medical interventions, exposing the unmet need for novel effective therapies that provide rapid and maintained responses.[5]

HS pathophysiology is complex and involves immune activation with progression to chronic inflammation.[3, 11] IL-17A and IL-17F are closely related pro-inflammatory cytokines that synergise with other pro-inflammatory cytokines to drive inflammation, including neutrophil influx into the lesions; a key hallmark of HS.[12] Distinct IL-17-secreting cells can be found in lesional HS tissues, including IL-17A- and IL-17F-only producing cells.[13] While IL-17A and IL-17F have overlapping biology in humans, with both isoforms upregulated in HS, they are regulated differently via duration of stimulation. STAT5-inducing cytokines (e.g., IL-2, IL-7 and IL-15) and IL-1β (which is upregulated in HS) preferentially drive IL-17-secreting cells to produce IL-17F, which may explain why IL-17F is more highly upregulated than IL-17A in HS lesional tissue.[13, 14]

Bimekizumab is a monoclonal IgG1 antibody that selectively inhibits IL-17F in addition to IL-17A which, compared with inhibitors of interleukin-17A alone, results in the additional inhibition of the IL-17F/F isomer.[15, 16] Dual inhibition of IL-17F and IL-17A in human *in vitro* models of HS with bimekizumab has been shown to more

effectively suppress the production of pro-inflammatory cytokines, compared with inhibition of either isoform alone, and at phase 3, bimekizumab demonstrated superior efficacy over the selective IL-17A inhibitor secukinumab in patients with moderate to severe plaque psoriasis.[16, 17] Bimekizumab has also demonstrated efficacy in patients with HS; in a phase 2 study, clinically meaningful and consistent improvement in HS Clinical Response (HiSCR) versus placebo was shown.[18] Based on these findings, the efficacy and safety of bimekizumab were assessed in two phase 3 clinical trials in patients with moderate to severe HS. As per other phase 3 programs,[9, 10] we conducted two independent, confirmatory trials across separate centres. Side-by-side results from each trial are presented here through 48 weeks of treatment. The primary objective of these trials was to evaluate the efficacy of bimekizumab in patients with moderate to severe HS.

METHODS

Study design and patients

BE HEARD I and II were randomised, double-blind, placebo-controlled, multicentre phase 3 trials conducted in 86 (BE HEARD I) and 90 (BE HEARD II) sites across Western Europe, Central/Eastern Europe, North America, and Asia/Japan/Australia.

Adult patients (18 years or older) with moderate to severe HS were enrolled. Moderate to severe disease was defined as ≥5 inflammatory lesions (abscesses and/or inflammatory nodules) affecting ≥2 distinct anatomic areas, one of which was at least Hurley Stage II or III (at both screening and baseline visits), evidenced by clinical history and physical examination, and diagnosed at least six months prior to baseline visit. Eligible patients also had a documented history of inadequate response to systemic antibiotics for HS (majority tetracyclines, clindamycin, and rifampicin) at screening. Patients using a stable-dose (pro re nata use not accepted) of doxycycline, minocycline, or an equivalent systemic tetracycline for 28 days prior to baseline were allowed to continue antibiotics and enrol in the studies, alongside those not on antibiotics. Patients were excluded if they had >20 DTs at baseline, had another active skin disease or condition that could interfere with HS assessment, had received TNF within 12 weeks, or IL-17 biologic response modifier therapy within six months, of baseline, topical therapy within 14 days of baseline, or were on systemic therapy for HS. Full eligibility and exclusion criteria are detailed in appendix 1 (pp 10–13).

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 of Harmonisation Good Clinical Practice requirements, the ethical principles that have their origin in the Declaration of Helsinki, and local laws of involved countries. Ethics approval was obtained from relevant institutional review boards at participating sites. All patients provided written informed consent in accordance with local requirements.

Randomisation and masking

Patients were randomly assigned (2:2:2:1) using interactive response technology to receive bimekizumab 320 mg every 2 weeks to week 48, bimekizumab 320 mg every 2 weeks to week 16 followed by every 4 weeks to week 48, bimekizumab 320 mg every 4 weeks to week 48, or placebo to week 16 followed by bimekizumab 320 mg every 2 weeks to week 48, based on a predetermined production randomisation and packaging schedule provided by the funder. Randomisation was stratified by worst Hurley Stage at baseline (II or III) and baseline systemic antibiotic use (yes/no). To maintain double-blinding, all patients received two injections every 2 weeks through week 46. Throughout the study, patients, investigators, and sponsor remained blinded to treatment assignment except for unblinded staff needed for study drug administration and reconciliation (further details in supplementary appendix 2).

Procedures

At week 16 (start of the 32-week maintenance treatment period), patients randomised to bimekizumab 320 mg every 2 weeks or every 4 weeks for 48 weeks continued their respective dose. Patients randomised to bimekizumab 320 mg every 2 weeks, followed by 320 mg every 4 weeks, began 4-week dosing. Patients who originally received placebo received bimekizumab 320 mg every 2 weeks for the remaining duration of the 48 weeks. All procedures apply to both BE HEARD I and BE HEARD II, unless otherwise specified.

Bimekizumab was supplied in a 1 mL prefilled syringe at a concentration of 160 mg/mL, and placebo was supplied as a 1 mL prefilled syringe of 0.9% sodium chloride aqueous solution for injection. Study treatments were administered in the clinic as two subcutaneous injections by unblinded study personnel.

Lesion counts and Dermatology Life Quality Index (DLQI, which assesses general skin-related quality of life) assessments were made to week 48 (appendix 2). Skin pain was assessed in two pre-specified secondary endpoints using the newly developed, validated HS Symptom Daily Diary (HSSDD); absolute change from baseline in skin pain as assessed by the 'worst pain' item of the HSSDD, and pain response defined as a decrease from baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change. The HSSDD is a five-item, HS-specific patient reported outcome that assesses patients' perception of the core symptoms of HS experienced in the last 24 hours (items include worst skin pain, average skin pain, smell/odour, itch at its worst, and drainage/oozing from HS lesions).[19] Developed in line with FDA guidance, each item is rated by a patient on an 11-point numerical rating scale, from 0 'no symptom' to 10 'symptom as bad as you can imagine'. For each item, the HSSDD score is derived from the weekly averages of the daily scores from a given week. Higher scores indicate a higher level of symptomology. A weekly HSSDD score for each item was only calculated if ≥4 non-missing daily values were available, otherwise the HSSDD score for the given item was reported as missing. Safety was assessed at baseline and each study visit. The safety follow-up visit was conducted 20 weeks after final dose of study treatment in patients who did not enter the subsequent open-label extension study (NCT04901195), or who prematurely withdrew.

Outcomes

Efficacy endpoints included HS Clinical Response (HiSCR50/75), abscess and inflammatory nodule (AN) count, DT count, DLQI, and skin pain. The primary outcome of each trial was assessed independently using HiSCR50 at week 16. HiSCR50 was defined as a ≥50% reduction from baseline in total AN count, with no increase from baseline in AN or DT count.[20] Key secondary endpoints in ranked testing order were: achievement of HiSCR75 (defined as a ≥75% reduction from baseline in total AN count, with no increase from baseline in AN or DT count) at week 16; at least one occurrence of flare in BE HEARD II only (defined as ≥25% increase in AN count with an increase of ≥2 AN relative to baseline) by week 16; absolute change from baseline in DLQI score at week 16 (minimum clinically important difference defined as a four-point reduction in DLQI total score);[21] absolute change from baseline in skin pain score at week 16, assessed by the "worst skin pain" item (11-point numeric rating scale; HSSDD) and HS skin pain response at

week 16 based on a threshold for clinically meaningful change (defined as a within-patient ≥3-point reduction from baseline in HSSDD weekly worst skin pain score among patients with a baseline score ≥3). Secondary endpoints were assessed at the individual trial level.

Additional prespecified exploratory endpoints evaluated the long-term efficacy of bimekizumab measured by HiSCR50, HiSCR75, HiSCR90 and HiSCR100, change from baseline in AN count and change from baseline in DT count. Other prespecified exploratory endpoints are listed in appendix 1 (pp 15–16).

Treatment-emergent adverse events (TEAEs) were reported for all study groups from weeks 0–16 and for all patients who received bimekizumab treatment from baseline to week 48. Occurrence of TEAEs, including serious and those leading to treatment discontinuation was evaluated. Incidence of adverse events and serious adverse events throughout the trials were coded using medical dictionary for regulatory activities version 19.0.

Prespecified safety topics of interest included: infections (serious, opportunistic, fungal, and tuberculosis); neutropenia; hypersensitivity (including anaphylaxis); suicidal ideation and behaviour; major adverse cardiovascular events; hepatic events; malignancies, and inflammatory bowel disease. Inflammatory bowel disease, liver function test elevations, suicidal ideation and behaviour, and major adverse cardiovascular events were adjudicated by independent external committees. An independent Data Monitoring Committee assessed safety data and provided recommendations on study conduct and safety data analyses during studies.

Statistical analyses

The primary objective was to evaluate the efficacy of bimekizumab compared with placebo in patients with moderate to severe HS, by assessing HiSCR50 response at week 16. Study power was calculated for the primary endpoint on the assumption that in each trial, responder rates for HiSCR50 at week 16 were 60% for bimekizumab every 2 weeks, 50% for bimekizumab every 4 weeks, and 25% for placebo. The assumed responder rates for these calculations accounted for a dropout rate of approximately 10%. Using these assumptions, the power provided by a sample size of 490 patients per trial (280 bimekizumab every 2 weeks; 140 bimekizumab every 4 weeks; 70 placebo) to demonstrate statistical superiority of

bimekizumab relative to placebo at a two-sided significance level of 0·025 was 99% (bimekizumab every 2 weeks) and 90% (bimekizumab every 4 weeks). Both trials were independently powered to test primary and ranked secondary endpoints.

Efficacy analyses included all randomised study patients (intention-to-treat population). Safety analyses included all patients who received at least one full or partial dose of study treatment in the safety set, and of bimekizumab in the active medication set. Multiplicity and type I error were controlled for primary and secondary efficacy endpoints using a fixed-sequence closed testing procedure under a parallel gatekeeping framework. Evaluation of statistical significance for each endpoint in the sequence was dependent on the previous comparison reaching statistical significance with a two-sided α level of 0·025, where the two bimekizumab dose regimens were tested independently vs placebo. See appendix 1 for the testing hierarchies for both studies (pp 26–27).

For the primary and secondary endpoint analyses of HiSCR50/75, HSSDD worst skin pain response, and flare (secondary endpoint in BE HEARD II only, other endpoint in BE HEARD I) at week 16, odds ratios (OR, including 97·5% confidence intervals [CI]) versus placebo and p values (from Wald test) were obtained from a logistic regression model (appendix 1 p 14). For change from baseline in DLQI score and HSSDD worst skin pain response at week 16 secondary endpoints, least squares mean differences (including 97·5% CI) versus placebo and p values were based on an analysis of covariance model (appendix 1 p 14).

Rescue treatment for HS, including systemic antibiotics, intralesional injections of triamcinolone, and incision and drainage, were permitted if required as judged by the investigator (appendix 2).

For the primary analysis of binary endpoints specified in the statistical testing hierarchy, modified non-responder imputation (mNRI) was used, whereby patients who took any systemic antibiotic (new or increased dose for any indication) or who discontinued study treatment due to an adverse event or lack of efficacy were treated as non-responders at all subsequent visits, and other missing data were imputed using a multiple imputation (MI; appendix 1 p 14) model (mNRI [All-ABX], appendix 1 p 28). For the primary analysis of continuous endpoints specified in the statistical testing hierarchy, MI (MI [All-ABX]) was used, whereby patients who took

any systemic antibiotic (new or increased dose for any indication) or who discontinued study treatment due to an adverse event or lack of efficacy were treated as missing and subsequently imputed using MI, and other missing data were also imputed using MI. For HiSCR50, HiSCR75, HiSCR90 and HiSCR100 responses over time, in addition to other binary exploratory endpoints, an alternative post-hoc mNRI was used, where only patients who took systemic antibiotics identified as rescue medication for HS by the principal investigator or who discontinued due to an adverse event or lack of efficacy were treated as non-responders at all subsequent visits, and other missing data were imputed using MI (mNRI [HS-ABX]). For continuous exploratory endpoints, patients who took systemic antibiotics identified as rescue medication for HS by the principal investigator or who discontinued study treatment due to an adverse event or lack of efficacy were treated as missing and subsequently imputed using MI (MI [HS-ABX]). For all exploratory endpoints, other missing data were imputed via MI. For multiply imputed binary variables, the rounded average number of patients with response based on 100 imputations is reported. Observed case (OC) analyses are also presented whereby only data for patients on treatment were considered and missing data were not imputed.

All analyses were performed using SAS version 9·4. Both BE HEARD I (NCT04242446) and II (NCT04242498) trials are registered with ClinicalTrials.gov.

Role of the funding source

UCB Pharma contributed to study design, participated in data collection, completed the data analysis, and participated in data interpretation. UCB Pharma participated in writing, review, and approval of the manuscript. All authors had full access to the data, reviewed and approved the final version, and were responsible for the decision to submit for publication. A medical writing agency, employed by UCB Pharma, assisted with manuscript preparation under the authors' direction.

RESULTS

BE HEARD I was conducted between February 19, 2020 and February 19, 2023; BE HEARD II was conducted between March 2, 2020 and September 28, 2022. In both trials due to the coronavirus disease pandemic, all patients but one (enrolled in March 2020) were enrolled beginning in June 2020. Of the 778 patients screened in BE HEARD I, 505 were randomised to receive bimekizumab every 2 weeks (N=289),

bimekizumab every 4 weeks (N=144), or placebo (N=72) (Figure 1A); of the 726 patients screened in BE HEARD II, 509 were randomised to receive bimekizumab every 2 weeks (N=291), bimekizumab every 4 weeks (N=144) or placebo (N=74) (Figure 1B). Baseline demographics were generally representative of patients with moderate to severe HS (Table 1). Overall, 451 (89·3%) patients in BE HEARD I and 464 (91·2%) patients in BE HEARD II completed week 16; 333 (74·3%) of 448 and 387 (83·6%) of 463 patients completed week 48, respectively (Figure 1).

In BE HEARD I, the median study medication duration (days [IQR]) was 334·0 days (252·0, 336·0) in patients who received bimekizumab every 2 weeks, 335·0 days (272·0, 336·0) in patients who received every 2 weeks followed by every 4 weeks, 333·0 days (194·0, 336·0) in patients who received bimekizumab every 4 weeks, and 336·0 days (280·0, 336·0) in patients who received placebo followed by bimekizumab every 2 weeks. In BE HEARD II, the median study medication duration (days [IQR]) was 334·0 days (314·0, 336·0) in patients who received bimekizumab every 2 weeks, 334·0 days (267·0, 336·0) in patients who received every 2 weeks followed by every 4 weeks, 335·0 days (306·0, 336·0) in patients who received bimekizumab every 4 weeks, and 336·0 days (334·0, 336·0) in patients who received placebo followed by bimekizumab every 2 weeks.

The primary endpoint HiSCR50 was met in the bimekizumab every 2 weeks group in both trials, with higher rates of HiSCR50 achievement observed in bimekizumab-treated groups compared to placebo. In BE HEARD I, 138 of 289 (48%) patients in the bimekizumab every 2 weeks group versus 21 of 72 (29%) patients in the placebo group achieved HiSCR50 (OR 2·23 [97·5% CI 1·16–4·31]; p=0·0060; Table 2). In BE HEARD II, 151 of 291 (52%) patients in the bimekizumab every 2 weeks group versus 24 of 74 (32%) patients in the placebo group achieved HiSCR50 (OR 2·29 [1·22–4·29]; p=0·0032). HiSCR50 achievement in patients who received bimekizumab every 2 weeks to week 16 was rapid across both trials (Figure 2A, B). Responses were observed as early as week 4, and were maintained or increased to week 48 (Figure 3A, B).

The primary endpoint was also met in the bimekizumab every 4 weeks group in BE HEARD II; 77 of 144 (54%) versus 24 of 74 (32%) patients in the placebo group achieved HiSCR50 (OR 2·42 [1·22–4·80]; p=0·0038; Table 2). In BE HEARD I, the primary endpoint was not met for patients treated with bimekizumab every 4 weeks;

65 of 144 (45%) versus 21 of 72 (29%) patients in the placebo group (OR 2·00 [CI 0·98–4·09]; p=0·030) achieved HiSCR50. Similar to the bimekizumab every 2 weeks group, the response in the bimekizumab every 4 weeks group was rapid in both trials (Figure 2A, B), with initial improvements observed by week 4 and maintained or increased over 48 weeks of treatment (Figure 3A, B).

For both trials, the key secondary endpoint of HiSCR75 at week 16 was met in the bimekizumab every 2 weeks group. In BE HEARD I, 97 of 289 (33%) patients achieved HiSCR75 versus 13 of 72 (18%) placebo-treated patients (OR 2·18 [1·02–4·64]; p=0·021; Table 2). In BE HEARD II, 104 of 291 (36%) bimekizumab every 2 weeks versus 12 of 74 (16%) placebo-treated patients achieved HiSCR75 (OR 3·01 [1·37–6·58]; p=0·0016). Achievement in the bimekizumab every 2 weeks group was rapid (by week 4) across both BE HEARD I and II (Figure 2C, D), and maintained or increased to week 48 (Figure 3C, D).

In BE HEARD II, HiSCR75 at week 16 was met in the bimekizumab every 4 weeks group: 49 of 144 (34%) versus 12 of 74 (16%) placebo-treated patients (OR 2·72 [1·18–6·27]; p=0·0071; Table 2). In the bimekizumab every 4 weeks group in BE HEARD I, 36 of 144 (25%) achieved HiSCR75 versus 13 of 72 (18%) placebo-treated patients; OR 1·42 (0·62–3·26) (did not achieve statistical significance).

Patients switching from placebo to bimekizumab every 2 weeks demonstrated rapid improvements in HiSCR50 and HiSCR75 in both trials after switching to bimekizumab, with responses increased to week 48 (Figure 3).

Using mNRI (HS-ABX), HiSCR50 at week 48 in BE HEARD I was achieved by 87 of 143 (61%) of patients receiving bimekizumab every 2 weeks, 90 of 146 (61%) of patients receiving bimekizumab every 2 weeks followed by every 4 weeks, 76 of 144 (53%) of patients receiving bimekizumab every 4 weeks, and 33 of 72 (45%) of patients receiving placebo followed by bimekizumab every 2 weeks (appendix 1, p 28). In BE HEARD II, HiSCR50 at week 48 was achieved by 88 of 145 (61%) of patients receiving bimekizumab every 2 weeks, 93 of 146 (64%) of patients receiving bimekizumab every 2 weeks followed by every 4 weeks, 91 of 144 (63%) of patients receiving bimekizumab every 4 weeks, and 50 of 74 (68%) of patients receiving placebo followed by bimekizumab every 2 weeks. HiSCR75 results using HS-ABX are also reported in appendix 1, p 29. HiSCR90 and HiSCR100 responses achieved by

week 16 improved to week 48 with bimekizumab treatment across BE HEARD I and BE HEARD II (appendix 1, p 19, pp 30–31).

In BE HEARD II, significant differences in flare were not detected between the treatment and placebo arms (Table 2). Across both studies, reductions from baseline in AN and DT counts were observed by week 4 across bimekizumab treatment regimens, with counts numerically lower among patients treated with bimekizumab versus placebo (appendix 1, p 20, pp 32–33).

Patients treated with bimekizumab had greater improvements in patient-reported outcomes measuring effect of HS on health-related quality of life and core HS symptoms, including worst skin pain, compared to the placebo group at week 16. Across BE HEARD I and BE HEARD II, both bimekizumab treatment regimens experienced numerically greater improvements (i.e., decreased score) in DLQI and HSSDD worst skin pain (ranked key secondary endpoints) versus placebo at week 16, with clinically meaningful improvements observed (Table 2). Bimekizumab-treated patients achieved rapid improvements in HSSDD worst skin pain, as early as week 2, that were maintained over the 16 weeks HSSDD was assessed (appendix 1 p 34).

Bimekizumab was well-tolerated at both dosing regimens; the safety profile was consistent with the phase 2 study of bimekizumab in HS and phase 3 studies for other diseases.[17, 18, 22-24] During the initial placebo-controlled, 16-week treatment period, the frequency of TEAEs was generally similar across bimekizumab every 2 weeks, bimekizumab every 4 weeks, and placebo groups in both trials (Table 3). Though infrequent (<5%), there were numerically more serious or severe TEAEs in bimekizumab-treated patients compared with placebo-treated patients. There were no clinically meaningful differences in the incidence of serious or severe TEAEs, or of TEAEs leading to discontinuation, between bimekizumab treatment groups.

Similarly, through weeks 0–48, no clinically meaningful differences were noted in the incidence of discontinuations due to TEAEs between treatment groups, and serious TEAEs were infrequent and occurred at similar rates between bimekizumab treatment groups in both trials (appendix 1 pp 23–24). The most frequently reported TEAEs through week 48 were hidradenitis in both BE HEARD I and BE HEARD II

(related to HS worsening), in addition to coronavirus infection and diarrhoea in BE HEARD I, and oral candidiasis and headache in BE HEARD II.

Across 48 weeks, at least one TEAE occurred in 425 (86·0%) and 412 (82·2%) patients who received bimekizumab in BE HEARD I and BE HEARD II, respectively, with comparable rates across dosing groups (Table 3, appendix 1 pp 23–24). One death, due to congestive heart failure in a patient with significant cardiovascular history treated with bimekizumab every 2 weeks in BE HEARD I, was reported across the two trials; considered unrelated to bimekizumab treatment by the investigator. Study discontinuation due to TEAEs was similar across both trials and treatment groups, occurring in 40 (8·1%) and 27 (5·4%) bimekizumab-treated patients in BE HEARD I and BE HEARD II, respectively, through 48 weeks (Table 3, appendix 1 pp 23–24).

By week 48, fungal infection events occurred in 112 (22·7%) and 124 (24·8%) bimekizumab-treated patients in BE HEARD I and BE HEARD II, respectively, with incidence generally comparable across bimekizumab treatment groups (Table 3, appendix 1 pp 23–24), and lower with placebo to week 16 (Table 3). Of these fungal events, *Candida* infections were most common. Oral candidiasis occurred in 47 (9·5%) and 64 (12·8%) bimekizumab-treated patients in BE HEARD I and BE HEARD II, respectively (Table 3). The vast majority of oral candidiasis cases were mild to moderate, resolved following standard anti-fungal therapy, and did not lead to discontinuation. Hypersensitivity reactions mostly related to the skin (dermatitis and eczema) occurred in 105 (21·3%) and 84 (16·8%) bimekizumab-treated patients in BE HEARD I and BE HEARD II (Table 3). There were no anaphylaxis events related to bimekizumab. The vast majority of hypersensitivity reactions were mild to moderate and did not lead to discontinuation; one serious case occurred.

In BE HEARD I and BE HEARD II, three and four bimekizumab-treated patients had adjudicated definite or probable inflammatory bowel disease, respectively, all of which were new-onset. Of these, one (BE HEARD I) and three (BE HEARD II) cases led to discontinuation. In the six (BE HEARD I) and two (BE HEARD II) patients with a previous history of inflammatory bowel disease, no flares were reported. Incidences of neutropenia, adjudicated major adverse cardiovascular events, and malignancies were low to week 48 (Table 3). Of adjudicated hepatic events, no elevations of aspartate aminotransferase or alanine aminotransferase >5× upper

limit of normal were adjudicated to be highly likely or definitely related to bimekizumab. Both studies exhaustively monitored and collected patient data related to suicidality and depression through questionnaires. Five (BE HEARD I) and one (BE HEARD II) events of adjudicated suicidal ideation and behaviour occurred overall, with no events of completed suicide (Table 3).

DISCUSSION

In the phase 3 BE HEARD I and BE HEARD II trials, bimekizumab significantly improved the signs of disease in patients with moderate to severe HS, compared with placebo at week 16, with responses maintained (HiSCR50) and improved (HiSCR75 and HiSCR90) to week 48.

The bimekizumab every 2 weeks group demonstrated significantly greater efficacy than placebo in the primary endpoint, HiSCR50, at week 16 in both BE HEARD I and BE HEARD II. Patients treated with bimekizumab every 4 weeks achieved statistical significance in BE HEARD II only, although similar response rates were observed with every 2 weeks dosing in BE HEARD I.

HiSCR50 was created for the seminal adalimumab trials and helped establish the concept of biological therapy in HS.[20] HiSCR50 has since been used as the primary endpoint in numerous HS clinical studies, however, as this outcome represents a 50% AN count improvement only, studies have begun measuring higher thresholds of clinical improvement reflecting deeper clinical responses in patients with HS as research advances.[25] Here, bimekizumab treatment demonstrated rapid and deep clinical responses, with greater proportions of patients treated with bimekizumab achieving the more stringent endpoints HiSCR75 and HiSCR90 versus placebo as early as week 4, and responses maintained over 48 weeks of treatment.

Other phase 3 HS programs suggest that continued treatment beyond a 12–16 week primary endpoint measure may lead to further improvement.[9] With bimekizumab treatment, clinical responses were sustained or improved over 48 weeks, with rapid improvements (within 4 weeks) observed in patients who switched from placebo to bimekizumab from week 16 onwards. Given the limited efficacy of current therapeutic options available for patients with HS, the rapid, deep, and maintained clinical response improvements offered by bimekizumab provide a potential additional treatment option; however, owing to the heterogeneous nature of the

disease, it must be acknowledged that clinical response may be affected by an individual patient's underlying disease aetiology, and thus IL-17F and IL-17A should not be considered as the only drivers of disease among patients with HS.[5, 26]

Across both trials, bimekizumab demonstrated improvements in patient-reported outcomes alongside clinical improvements. Clinically meaningful improvements in DLQI were observed at week 16 in bimekizumab treatment groups, but not with placebo. Pain was the highest ranked item in the HS Core Outcomes Set International Collaboration and is an important, albeit challenging and evolving, outcome measure in HS research.[6] Tools include patient-reported items such as the pain index and HSSDD.[19, 27] Rapid and clinically meaningful improvements in skin pain were observed, with improvements in HSSDD worst skin pain versus placebo at week 16 observed in patients who received bimekizumab every 2 weeks in BE HEARD I and II. Further data on signs of disease using the International HS Severity Score System (IHS4), and HS-specific health-related quality of life using the HS Quality of Life (HiSQoL©), were collected in the BE HEARD program and will be published in a dedicated manuscript.[28, 29]

Systemic antibiotics are frequently used as first-line therapy, for flares or as co-treatment for HS.[30] They are commonly evaluated as adjuvant therapy in HS clinical trials, though methodology to calculate efficacy in the presence of systemic antibiotic use is not standardised. In BE HEARD I and II, systemic antibiotic use consistent with HS treatment guidelines was permitted as rescue therapy for flaring disease.[30] Patients who took any systemic antibiotic for any indication, including for non-HS indications, were treated as non-responders at subsequent visits for the primary analysis at week 16 (mNRI [All-ABX]), which is likely to underestimate the efficacy of bimekizumab for HS, since patients responding well who receive systemic antibiotic therapy for reasons not related to HS are considered non-responders. In the supportive post-hoc analyses, patients treated with systemic antibiotics identified as rescue therapy for HS by the investigator were treated as non-responders at subsequent visits for the evaluation of endpoints over time (mNRI [HS-ABX]). Despite the stringent nature of the analysis, the studies demonstrated high levels of maintained response over time. In contrast, long-term (52-week) data reported from the SUNSHINE and SUNRISE trials of secukinumab in HS reported OC data only from weeks 18–52.[9]

The safety profile of bimekizumab in BE HEARD I and II was consistent with other indications, and with other IL-17A inhibitors in development for HS.[9, 17, 22-24] Moreover, over 48 weeks, the most common TEAEs were similar between bimekizumab treatment groups. Candidiasis and inflammatory bowel disease are associated with IL-17 inhibition.[31, 32] Candidiasis incidence was higher among patients who received bimekizumab treatment compared to those who received placebo. Oral candidiasis events were generally mild to moderate, resolved following standard therapy, and did not lead to discontinuation. Across 1,014 patients randomised in BE HEARD I and II, incidence of safety topics of interest, such as inflammatory bowel disease and suicidal ideation and behaviour, were aligned with study population expectations.[5] Adjudicated definite or probable inflammatory bowel disease occurred in three and four patients on bimekizumab, respectively, with no flares in patients with a previous history of inflammatory bowel disease. Although paradoxical HS reactions have been reported following treatment with both anti-TNF and anti-IL-17A-only agents,[33] these were not an issue in the BE HEARD I and II trials.

Limitations of the BE HEARD I and II trials include the relatively short initial 16-week placebo-controlled period, which may affect the interpretability of later efficacy results, and the lack of an active comparator across 48 weeks of treatment. In addition, evaluation of treatment efficacy in the presence of rescue systemic antibiotic use poses a challenge; methodology used to calculate efficacy rates under these conditions has not yet been standardised across trials in HS. Other limitations also include subtle differences in the following: body weight was lower in the bimekizumab arms versus placebo in BE HEARD II, there was a slightly higher proportion of Black patients in BE HEARD I, and a higher proportion of patients from Central and Eastern Europe in BE HEARD II. More generally in clinical trials for patients with HS, a patient's underlying disease severity or multifactorial aetiology of underlying disease may lead to variability in observed efficacy and subsequent interpretation of results.[26] Subsequent studies are warranted, including collection of real-world evidence for bimekizumab use in patients with HS, considerations for precision medicine approaches in HS, Network Meta-Analyses to help inform future clinician decision making, and concomitant medical and surgical therapy use. HS head-to-head comparator studies are lacking. While numerically greater proportions of patients achieved HiSCR50 by week 48 in BE HEARD I and II compared to other long-term phase 3 trials in HS (using OC), further research is needed to formally

compare these outcomes owing to the heterogeneity in trial populations and differing analysis methods used across studies.[9, 10]

These two phase 3 trials of bimekizumab demonstrated rapid, deep, and maintained clinically meaningful responses through week 48 for patients with HS, across physician-reported and patient-reported outcome measures. Bimekizumab was well-tolerated in patients with moderate to severe HS. These studies support bimekizumab, which targets IL-17F in addition to IL-17A, as a promising new therapeutic option for moderate to severe HS.

CONTRIBUTORS

Substantial contributions to study conception and design: **ABK**, **GBEJ**, **CS**, **JSK**, **EP**, **JRI**, **AG**, **ABG**, **JCS**, **FGB**, **EJGB**, **HF**, **RR**, **PJ**, **PD**, **EM**, **LP**, **CM**, **MB**, and **CCZ**; substantial contributions to analysis and interpretation of the data: **ABK**, **GBEJ**, **CS**, **JSK**, **EP**, **JRI**, **AG**, **ABG**, **JCS**, **FGB**, **EJGB**, **HF**, **RR**, **PJ**, **PD**, **EM**, **LP**, **CM**, **MB**, and **CCZ**; drafting the article or reviewing it critically for important intellectual content: **ABK**, **GBEJ**, **CS**, **JSK**, **EP**, **JRI**, **AG**, **ABG**, **JCS**, **FGB**, **EJGB**, **HF**, **RR**, **PJ**, **PD**, **EM**, **LP**, **CM**, **MB**, and **CCZ**; final approval of the version of the article to be published: **ABK**, **GBEJ**, **CS**, **JSK**, **EP**, **JRI**, **AG**, **ABG**, **JCS**, **FGB**, **EJGB**, **HF**, **RR**, **PJ**, **PD**, **EM**, **LP**, **CM**, **MB**, and **CCZ**; **ABK**, **RR**, **PJ**, **PD**, **EM**, **LP**, and **MB** accessed and verified the data. All authors had access to all the included data in the study and had final responsibility for the decision to submit for publication.

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DATA SHARING

Underlying data from this manuscript may be requested by qualified researchers six months after product approval in the USA and Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymised 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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FIGURE TITLES AND LEGENDS

Figure 1. Trial profiles

The BE HEARD I (A) and BE HEARD II (B) trial profiles to week 48. [a]In BE HEARD I, two screen failure participants were excluded from the enrolled set due to the termination of a site without obtaining principal investigator signatures on March 17, 2021.

Figure 2. HiSCR responses over time to week 16

The rates of HiSCR50 (A, B) and HiSCR75 (C, D) over time to week 16 in BE HEARD I and BE HEARD II. mNRI (All-ABX): patients who took any systemic antibiotic (new or increased dose) or who discontinued due to an adverse event or lack of efficacy were treated as non-responders at all subsequent visits. Other missing data were imputed via MI; primary, pre-specified analysis method. ABX=antibiotics; AN=abscess and inflammatory nodule; BHI=BE HEARD I; BHII=BE HEARD II; BKZ=bimekizumab; DT=draining tunnel; HiSCR=Hidradenitis Suppurativa Clinical Response; HiSCR50/75=≥50/75% reduction from baseline in the total AN count with no increase from baseline in abscess or DT count; mNRI=modified non-responder imputation; Q2W=every 2 weeks; Q4W=every 4 weeks.

Figure 3. HiSCR responses over time to week 48

The rates of HiSCR50 (A, B) and HiSCR75 (C, D) over time to week 48 in BE HEARD I and BE HEARD II. OC: all available data after an intercurrent event were summarised as recorded in the database, and all missing data were left missing. AN=abscess and inflammatory nodule; BHI=BE HEARD I; BHII=BE HEARD II; BKZ=bimekizumab; DT=draining tunnel; HiSCR=Hidradenitis Suppurativa Clinical Response; HiSCR50/75=≥50/75% reduction from baseline in the total AN count with no increase from baseline in abscess or DT count; OC=observed case; Q2W=every 2 weeks; Q4W=every 4 weeks.