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ORIGINAL RESEARCH

Bimekizumab Pain Outcomes in Patients with Hidradenitis Suppurativa: Pooled 48-Week Results from BE HEARD I&II Phase 3 Randomized Clinical Trials

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ABSTRACT

***Introduction*:** Pain is a debilitating symptom of hidradenitis suppurativa (HS). Bimekizumab, a humanized IgG1 monoclonal antibody, selectively inhibits IL-17A and IL-17F. The impact of bimekizumab on pain outcomes in moderate to severe HS was assessed using pooled 48-week data from BE HEARD I&II (observed case and multiple imputation).

***Methods*:** Patients were randomized 2:2:2:1 to receive one of bimekizumab 320 mg every 2 weeks (Q2W); bimekizumab Q2W to Week 16, then every 4 weeks (Q4W) to Week 48; bimekizumab Q4W; or placebo to Week 16, then bimekizumab Q2W to Week 48. HS Symptom Daily Diary (HSSDD; baseline–Week 16) and HS Symptom Questionnaire (HSSQ; baseline, Weeks 16–48) assessed patient-reported skin pain. Mean scores, change from baseline (CfB), responder rates, shifts across pain severity categories, and association of HS Clinical Response (HiSCR) with pain outcomes were assessed.

***Results*:** A total of 1014 patients with moderate to severe HS were enrolled. Mean (standard deviation) age was 36.6 (12.2) years and 56.8% were women. Bimekizumab demonstrated rapid reductions in mean HSSDD worst

Prior presentation: Select data were previously presented at the British Association of Dermatologists congress 2024, American Academy of Dermatology congress 2024 and 2025, Symposium on Hidradenitis Suppurativa Advances congress 2024, Skin Inflammation & Psoriasis International Network congress 2025 and the European Academy of Dermatology and Venereology congress 2025.

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and average skin pain scores after 2 weeks. Greater reductions from baseline in HSSDD worst (mean CfB ± standard error, bimekizumab Q2W: − 1.9 ± 0.1; bimekizumab Q4W: − 1.5 ± 0.2) and average skin pain scores (bimekizumab Q2W: − 1.8 ± 0.1; bimekizumab Q4W: − 1.4 ± 0.2) were observed at Week 16 versus placebo (worst: − 0.7 ± 0.2; average: − 0.8 ± 0.2). Mean HSSQ skin pain showed similar improvements to Week 16; further reductions were seen to Week 48 in those continually receiving bimekizumab. Week 16 placebo switchers saw rapid improvements in HSSQ skin pain scores from Week 16 to Week 18, comparable to those continually receiving bimekizumab. Responses were maintained to Week 48 (bimekizumab Q2W/Q2W: − 2.9 ± 0.2; bimekizumab Q2W/Q4W: − 2.5 ± 0.2; bimekizumab Q4W/Q4W: − 2.8 ± 0.2; placebo/bimekizumab Q2W: − 2.5 ± 0.3). Many patients shifted from severe/very severe to lower severity HSSQ skin pain categories (mild/no pain). Improvements corresponded with higher HiSCR scores at Week 48.

Conclusions: Treatment with bimekizumab leads to rapid, continuous, and clinically meaningful reductions in skin pain.

Trial Registration: NCT04242446 (https://clinicaltrials.gov/study/NCT04242446); NCT04242498 (https://clinicaltrials.gov/study/NCT04242498).

An Infographic is available for this article.

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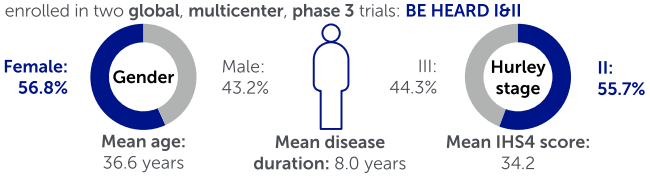
Adis
PEER-REVIEWED FEATURE

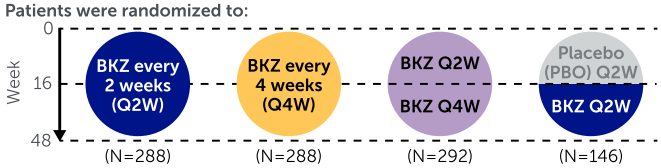
Participants and study design

1,014 patients with moderate to severe **hidradenitis suppurativa (HS)** were enrolled in two **global**, **multicenter**, **phase 3** trials: **BE HEARD I&II**



Bimekizumab (BKZ) is a humanized IgG1 monoclonal antibody targeting **interleukin (IL)-17F and IL-17A**

Patients were randomized to:



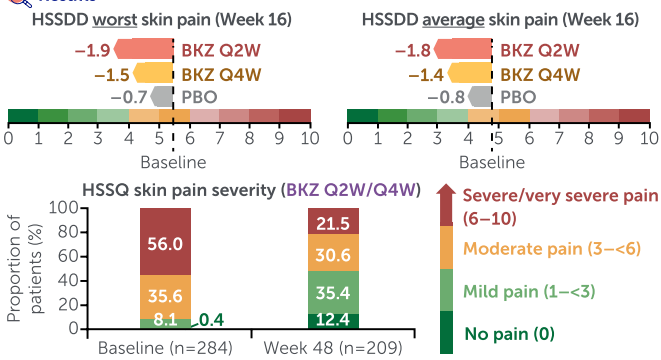
Methods

HS skin pain was evaluated using **two HS-specific, patient-reported instruments:**

HS Symptom Daily Diary (HSSDD)	HS Symptom Questionnaire (HSSQ)
Worst/average skin pain • Change from baseline • Responders	**Skin pain** • Change from baseline • Responders • Shifts in skin pain severity category
Recall period: 24 hours Baseline to Week 16 (daily)	**Recall period: 7 days** Baseline, Week 16, then every other week to Week 48

no skin pain — skin pain as bad as you can imagine

Results



Conclusions

Overall, BKZ demonstrated **rapid, sustained, and clinically meaningful improvements in HS skin pain**, in patients with moderate to severe HS to Week 48

Keywords: Bimekizumab; Hidradenitis suppurativa; Interleukin-17; Pain; Pain measurement; Monoclonal antibody

Key Summary Points

Why carry out this study?

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease, characterized by deep-seated lesions that result in significant, debilitating symptoms including pain [1–3], which negatively affects patients' quality of life.

What did the study ask?

This study assessed the impact of bimekizumab on pain outcomes in patients with moderate to severe HS, utilizing the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD) and the Hidradenitis Suppurativa Symptom Questionnaire (HSSQ), in the BE HEARD I&II trials.

What was the study's conclusion?

Bimekizumab demonstrated rapid, sustained, and clinically meaningful improvements in skin pain versus placebo in patients with hidradenitis suppurativa

What has been learned from the study?

Bimekizumab, a humanized IgG1 monoclonal antibody, which inhibits interleukin (IL)-17F in addition to IL-17A, is a treatment that reduces pain, which is one of the most burdensome symptoms in patients with moderate to severe HS.

DIGITAL FEATURES

This article is published with digital features, including an Infographic, to facilitate understanding of the article. To view digital features for this article, go to https://doi.org/10.6084/m9.figshare.30126976.

INTRODUCTION

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease, characterized by deep-seated lesions that result in significant, debilitating symptoms [1–3]. Disease-associated pain is considered one of the most burdensome HS symptoms, with 83.6% of patients with HS reporting pain in the last 24 h and a 2-point increase in pain intensity having a similar impact as progressing from Hurley stage I to III, negatively impacting quality of life [4–8]. Therefore, reducing pain is essential for enhancing the quality of life of patients with HS. The Hidradenitis Suppurativa Core Outcomes Set International Collaboration (HiSTORIC) concluded, through a consensus process, that pain is to be measured and reported in HS clinical trials as its own domain [9, 10].

Pain associated with HS can be caused by three processes: (i) nociceptive pain, occurring when signaling molecules at sites of tissue injury or potential tissue injury induce pain, likely resultant from inflammation; (ii) neuropathic pain, arising from peripheral or central somatosensory nervous system dysfunction, proposed to be caused by chronic inflammation resulting in peripheral neuroplastic changes, and (iii) nociplastic pain, arising in the absence of tissue damage or nervous system dysfunction [11–17]. In addition, central sensitization (CS)—a process characterized by increased responsiveness of central neural pathways—has been suggested to contribute to persistent pain in chronic inflammatory conditions such as HS and autoimmune and inflammatory rheumatic diseases [18, 19]. CS is influenced by ongoing inflammatory signals, as seen with elevated cytokines like interleukin (IL)-17 [20, 21]. Two studies report that IL-17 could have an important role in nociceptive and neuropathic pain, by activating key signaling pathways that upregulate pro-nociceptive mediators, cytokines and other inflammatory factors impacting neuron sensitivity [20, 21]. In skin affected by HS, higher levels of IL-17 were reported compared with healthy skin, with increasing serum levels correlating with increasing HS disease severity [22]. Upregulation of both IL-17A and IL-17F has been observed in

HS lesional tissue [23]. Limiting IL-17 activity has been demonstrated to significantly reduce hyperalgesia in murine models [21, 24, 25]. Dual inhibition of both IL-17A and IL-17F has been reported in vitro to more effectively suppress inflammatory cytokine responses, including attenuation of Th17-induced HS-associated genes and neutrophil migration, compared to inhibition of IL-17A alone [23, 26, 27].

Historically, treatment of HS had been mostly unsuccessful and restricted to symptom management. Current treatment options now include drug therapy to address inflammation, surgical interventions, adjuvant therapies, and lifestyle modifications [28]. In particular, the recent approvals of biological therapies, including the TNFα inhibitor adalimumab, the IL-17A inhibitor secukinumab and more recently, the IL-17A and IL-17F inhibitor bimekizumab, has provided new and effective treatment modalities for patients with higher disease severity [28]. Bimekizumab is a humanized IgG1 monoclonal antibody that selectively inhibits IL-17F in addition to IL-17A [26]. The efficacy and safety of bimekizumab have been demonstrated in two phase 3 clinical trials, BE HEARD I (NCT04242446) and II (NCT04242498), in patients with moderate to severe HS [29]. In these trials, the primary endpoint, a reduction in total abscess and inflammatory nodule count of at least 50% from baseline with no increase from baseline in abscess or draining tunnel count (HS Clinical Response [HiSCR50]) at Week 16, was met in patients treated with bimekizumab every 2 weeks (Q2W; both trials) and every 4 weeks (Q4W; BE HEARD II only) [29]. In these trials, bimekizumab was well tolerated by patients with moderate to severe hidradenitis suppurativa and bimekizumab treatment produced rapid, deep, and maintained clinically meaningful improvements in physician-assessed and patient-reported outcome measures to Week 48. The safety profile of bimekizumab in BE HEARD I and II was consistent with other approved indications [29–33].

To effectively measure HS pain, both the assessment measure and the response interpretation of an endpoint must be HS-disease relevant, validated, and fit for purpose. BE HEARD I and II utilized the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD) and Hidradenitis Suppurativa Symptom Questionnaire (HSSQ) to assess the impact of bimekizumab on patient-reported symptoms, including pain. HSSDD and HSSQ are HS-specific instruments developed in line with US Food and Drug Administration (FDA) guidance [34, 35]. Both demonstrated good construct validity, including known-groups validity, as well as good responsiveness and test–retest reliability [36]. Clinically meaningful within-patient improvement thresholds and severity bands have also been derived for each item score for both instruments to guide interpretation [36]. Here, the impact of bimekizumab on pain outcomes in patients with moderate to severe HS is reported using pooled data from two phase 3 clinical trials, BE HEARD I and II.

METHODS

Study Design and Patients

BE HEARD I (NCT04242446) and II (NCT04242498) were randomized, double-blinded, placebo-controlled, global, multicenter phase 3 studies. Across the two studies, 1014 patients (BE HEARD I [$n = 505$]; BE HEARD II [$n = 509$]) were enrolled from February 2020 to October 2021. Data were pooled for these analyses. The pooling approach was supported by the similarities between the study populations and the consistency in the magnitude of changes in the outcomes of interest as previously reported [29].

Full study design details, including eligibility criteria and protocol, for BE HEARD I and II have previously been reported [29]. To summarize, adult patients with a diagnosis of HS for ≥ 6 months were enrolled. Eligible patients had moderate to severe disease, 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 and demonstrated inadequate response to systemic antibiotics for HS. Patients using a stable dose (as needed use not accepted) of antibiotics for 28 days before baseline were allowed to continue. Exclusion criteria included patients with > 20 draining tunnels at baseline, another

active skin disease or condition that may interfere with HS assessment, or HS therapies which would preclude bimekizumab treatment.

The 48-week trials consisted of a 16-week placebo-controlled initial treatment period (Weeks 0–16) followed by a 32-week maintenance treatment period (Weeks 16–48). Patients were randomized 2:2:2:1 to receive one of bimekizumab 320 mg every 2 weeks (Q2W); bimekizumab Q2W to Week 16, then every 4 weeks (Q4W) to Week 48; bimekizumab Q4W; or placebo to Week 16, then bimekizumab Q2W to Week 48.

Data Collection

Patient and disease characteristics were recorded at baseline. Lesion counts were collected at selected visits enabling the derivation of HiSCR throughout the studies. Patients completed electronic patient-reported outcome questionnaires, including the HSSDD and HSSQ that captured pain severity (Supplementary Fig. 1). From baseline to Week 16, HSSDD assessments were undertaken daily by patients (Supplementary Fig. 1). HSSDD is an HS-specific, five-item instrument used to assess patients' perception of the core symptoms of HS (worst and average skin pain, smell or odor, drainage or oozing from HS lesions and itch at its worst) experienced in the past 24 h. For worst skin pain, patients were asked to rate their skin pain from HS lesions "at its worst" in the past 24 h; for average skin pain, patients were asked to rate their skin pain from HS lesions "on an average" in the past 24 h. Symptoms were rated using an 11-point Numeric Rating Scale (NRS) from 0 ("no symptom") to 10 ("symptom as bad as you can imagine"). HSSDD item scores were derived as the weekly averages of the daily scores from a given week if ≥ 4 daily values were available, otherwise the item score was reported as missing. For HSSDD worst and average skin pain item scores, a 3- to 4-point decrease has been described as a clinically meaningful within-patient improvement [36].

HSSQ assessments were undertaken at baseline, Week 16, then every other week to Week 48 (Supplementary Fig. 1). HSSQ is a HS-specific four-item instrument used to assess patient-perceived severity of HS symptoms over the previous 7 days. Items measured are skin pain, smell or odor, drainage or oozing from HS lesions, and itch. Patients were asked to appraise symptoms using an 11-point NRS (0–10), with a higher score indicating a more severe symptom. Using thresholds previously derived by receiver operating characteristic analysis, severity of skin pain was categorized to none (0), mild (1–2), moderate (3–5), severe/very severe (6–10) [36].

Outcomes

The outcomes reported herein were secondary or exploratory endpoints for BE HEARD I and II. Secondary endpoints have been noted below; all other endpoints were exploratory. To assess the overall changes in skin pain following bimekizumab treatment, mean scores and absolute change from baseline scores were calculated for HSSDD worst and average skin pain to Week 16, and HSSQ skin pain to week 48 (Supplementary Fig. 1). Here, we define "rapid" as a response in 2 weeks or less.

Absolute change from baseline in HSSDD worst skin pain score at Week 16 was assessed as a statistically controlled, ranked secondary endpoint. To evaluate the efficacy of bimekizumab on pain outcomes, responder rates over time were calculated for HSSDD worst and average skin pain. HSSDD worst skin pain response at Week 16, defined as a ≥ 3-point reduction from baseline among patients with a baseline HSSDD score ≥ 3, was assessed as a ranked secondary endpoint. To address the lack of literature consensus, additional thresholds of ≥ 30% reduction and ≥ 1-point reduction (often referred to as NRS30) and ≥ 4-point reduction, from a baseline score ≥ 3 and ≥ 4, respectively, were assessed for HSSDD worst skin pain. HSSDD average skin pain response was also assessed and defined as a ≥ 30% and ≥ 1-point reduction from baseline among patients with a baseline score ≥ 3. HSSQ skin pain responders were assessed every other Week from Weeks 16–48 and defined as a ≥ 30% reduction and ≥ 1-point reduction from baseline in patients with a baseline HSSQ score ≥ 3. HSSQ

skin pain categories are reported at baseline, Week 16, and Week 48.

To determine the association of clinical efficacy of bimekizumab with skin pain outcomes, the change from baseline in HSSQ skin pain to Week 48 was evaluated by mutually exclusive HiSCR bands: HiSCR < 50, HiSCR50–< 75, HiSCR75–< 90 and HiSCR90–100. Patients were pooled regardless of treatment and were stratified by achievement of mutually exclusive response levels at Week 48. The association between HSSDD and HiSCR was not assessed.

Statistical Analysis

These analyses were descriptive and post hoc in nature, and the data in this article are presented using the observed case (OC) for dichotomous outcomes, or multiple imputation (MI) methods for continuous outcomes. The Supplementary Materials also report dichotomous data, including the more stringent modified non-responder imputation (mNRI; Supplementary Figs. 2–3) as a sensitivity analysis.

OC is defined as data analyzed as observed; missing data and intercurrent events were not considered. mNRI included patients who experienced the intercurrent events of discontinuation due to lack of efficacy or adverse events, or received systemic antibiotics identified as rescue medication for HS by the principal investigator. These patients were considered non-responders, and missing data were subsequently imputed using MI. MI for continuous outcomes included patients who experienced the aforementioned intercurrent events and all other missing data; these patient data were set to missing after the intercurrent event and subsequently imputed using MI.

Details of the sample size calculation for the BE HEARD trials have been previously reported [29]. All analyses were performed using SAS © version 9.4 or later (SAS Institute, Cary, NC, USA). Error is reported using standard error (SE) for estimated outcomes (MI) or standard deviation (SD). 95% confidence intervals (CI) are reported for dichotomous outcomes to describe the variability and uncertainty around observed estimates. No formal hypothesis testing or inferential statistics were conducted and, as such, p values were not calculated.

Ethical Approval

The study protocol, amendments, and patient informed consent were reviewed by a national, regional, or Independent Ethics Committee (IEC) or Institutional Review Board (IRB). This study was conducted in accordance with the applicable regulatory and International Conference on Harmonisation Good Clinical Practice requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved. Ethics approval was obtained from the relevant institutional review boards at participating sites. All patients provided written informed consent in accordance with local requirements.

RESULTS

Patient Disposition and Baseline Characteristics

Overall, 720 patients completed treatment to Week 48 from BE HEARD I (n = 333) and II (n = 387) [29]. Baseline characteristics were similar across treatment groups (Table 1). In accordance with the inclusion criteria, no patients were classified as Hurley stage I at baseline; 55.7% of patients were Hurley stage II and 44.3% were Hurley stage III (Table 1).

At baseline, HSSDD worst skin pain, HSSDD average skin pain, and HSSQ skin pain mean scores were comparable across treatment groups (Table 2). HSSDD completion rates ranged from 79.5 to 86.8% at baseline, 68.5–71.2% at week 8, and 61.8–66.9% at week 16. HSSQ completion rates ranged from 97.3 to 99.0% at baseline, to 88.9–92.5% at Week 16 and 67.0–71.6% at Week 48.

Overall Pain Outcomes

Bimekizumab treatment resulted in substantial reductions in skin pain compared to placebo at Week 16. Mean absolute HSSDD worst and

Table 1 Baseline characteristics

	BKZ Q2W/Q2W *N* = 288	BKZ Q2W/Q4W *N* = 292	BKZ Q4W/Q4W *N* = 288	PBO/BKZ Q2W *N* = 146	All patients *N* = 1014
Age (years), mean (SD)	36.8 (12.4)	37.0 (12.4)	35.8 (11.6)	37.3 (12.8)	36.6 (12.2)
Sex, female, *n* (%)	152 (52.8)	174 (59.6)	175 (60.8)	75 (51.4)	576 (56.8)
Racial group, White, *n* (%)	232 (80.6)	233 (79.8)	224 (77.8)	119 (81.5)	808 (79.7)
Racial group, Black, *n* (%)	32 (11.1)	31 (10.6)	34 (11.8)	13 (8.9)	110 (10.8)
BMI (kg/m^2), mean (SD)	32.7 (8.6)	32.7 (7.9)	33.8 (7.9)	33.1 (8.3)	33.1 (8.1)
Duration of disease (years), mean (SD)	7.6 (7.4)	8.3 (7.7)	7.3 (7.3)	9.8 (9.4)	8.0 (7.8)
Hurley stage,[a] *n* (%)					
II	166 (57.6)	160 (54.8)	160 (55.6)	79 (54.1)	565 (55.7)
III	122 (42.4)	132 (45.2)	128 (44.4)	67 (45.9)	449 (44.3)
Prior biologic use, *n* (%)	59 (20.5)	56 (19.2)	47 (16.3)	29 (19.9)	191 (18.8)
Baseline antibiotic use,[b] *n* (%)	29 (10.1)	28 (9.6)	18 (6.3)	11 (7.5)	86 (8.5)
IHS4 Score,[c] mean (SD)	33.4 (25.4)	36.0 (34.0)	35.0 (34.0)	30.6 (21.8)	34.2 (30.2)
Total DLQI score, mean (SD)	11.2 (6.5)	10.8 (6.7)	11.7 (7.4)	12.2 (7.1)	11.4 (6.9)
HiSQOL total score, mean (SD)	24.8 (12.7)	24.5 (13.1)	25.8 (13.9)	26.4 (14.1)	25.2 (13.4)

BKZ bimekizumab, *BMI* body mass index, *DLQI* Dermatology Life Quality Index, *IHS4* International Hidradenitis Suppurativa Severity Score System, *HiSQOL* Hidradenitis Suppurativa Quality of Life, *OC* observed case, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SD* standard deviation

[a]Values are derived based on lesion count data

[b]Values are derived from concomitant medication data

[c]IHS4 categories: mild (≤ 3), moderate (4–10), and severe disease ≥ 11) [49]

average skin pain scores reflected rapid reductions in pain, by 2 weeks, compared with placebo (Supplementary Fig. 4a–b). At Week 16, patients treated with bimekizumab had greater reductions from baseline in absolute HSSDD worst skin pain score (mean ± SE: bimekizumab Q2W: − 1.9 ± 0.1; bimekizumab Q4W: − 1.5 ± 0.2) compared with patients who received placebo (− 0.7 ± 0.2). HSSDD average skin pain demonstrated comparable results (bimekizumab Q2W: − 1.8 ± 0.1; bimekizumab Q4W: − 1.4 ± 0.2; versus placebo: − 0.8 ± 0.2) (Table 2).

From baseline to Week 16, absolute HSSQ skin pain scores also showed greater improvements in bimekizumab-treated groups compared with placebo (Table 2 and Supplementary Fig. 4c). From Week 16 to Week 48, a further reduction in HSSQ skin pain scores was seen in those treated with bimekizumab from baseline (Table 2 and Supplementary Fig. 4c). In patients who switched from placebo to bimekizumab at Week 16, absolute HSSQ skin pain score rapidly improved (between Weeks 16 and 18) to levels observed in patients randomized to bimekizumab at baseline, and remained at similar levels to Week 48 (Table 2 and Supplementary Fig. 4c).

Table 2 Baseline and absolute change from baseline scores in HSSDD worst and average skin pain to week 16 and HSSQ skin pain to Week 48 (MI)

	HSSDD worst and average skin pain			HSSQ skin pain			
	BKZ Q2W *N* = 580	BKZ Q4W *N* = 288	PBO *N* = 146	BKZ Q2W/Q2W *N* = 288	BKZ Q2W/Q4W *N* = 292	BKZ Q4W/Q4W *N* = 288	PBO/BKZ Q2W *N* = 146
Baseline, mean ± SE							
HSSDD worst skin pain	5.4 ± 0.1	5.6 ± 0.2	5.4 ± 0.2				
HSSDD average skin pain	4.7 ± 0.1	4.9 ± 0.2	4.8 ± 0.2				
HSSQ skin pain				5.8 ± 0.1	5.8 ± 0.1	5.8 ± 0.1	5.8 ± 0.2
Week 16 change from baseline, mean ± SE							
HSSDD worst skin pain	− 1.9 ± 0.1	− 1.5 ± 0.2	− 0.7 ± 0.2				
HSSDD average skin pain	− 1.8 ± 0.1	− 1.4 ± 0.2	− 0.8 ± 0.2				
HSSQ skin pain				− 2.5 ± 0.2	− 2.0 ± 0.2	− 1.7 ± 0.2	− 0.8 ± 0.2
Week 48 change from baseline, mean ± SE							
HSSQ skin pain				− 2.9 ± 0.2	− 2.5 ± 0.2	− 2.8 ± 0.2	− 2.5 ± 0.3

Randomized set, *N* = 1014. HSSDD baseline scores are computed as the average of the closest consecutive 7 days to the baseline visit with at least four non-missing daily scores in the 2 weeks prior to the baseline visit, not including the baseline visit itself. MI: patients who discontinued study treatment due to lack of efficacy or adverse events, or who took systemic antibiotics as rescue medication for HS as defined by the principal investigator, were considered missing and subsequently imputed using MI. HSSDD absolute change from baseline in worst skin pain score at Week 16 is a statistically controlled, ranked secondary endpoint for BE HEARD I and II, all others are exploratory endpoints

BKZ bimekizumab, *HSSDD* Hidradenitis Suppurativa Symptom Daily Diary, *HSSQ* Hidradenitis Suppurativa Symptom Questionnaire, *MI* multiple imputation, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *SE* standard error

HSSDD and HSSQ Skin Pain Responder Rates

A treatment effect was observed in both HSSDD worst and average skin pain after one dose of bimekizumab, demonstrated by numerically greater responder rates (as early as Week 2) for both the bimekizumab Q2W and Q4W groups compared to placebo (Fig. 1a–c, Supplementary Fig. 2a–e). At Week 16, using a threshold of ≥ 3-point reduction from a baseline HSSDD worst skin pain score ≥ 3 (a ranked secondary endpoint), responder rates were 38.9% for the bimekizumab Q2W group and 34.0% for the Q4W group, versus 11.8% for placebo (Fig. 1a). When using the less stringent threshold of ≥ 30% reduction and ≥ 1-point reduction from a baseline score ≥ 3 (Fig. 1b), responder rates were greater, as expected. Similarly, the pattern persisted with the ≥ 4-point reduction threshold, though overall responder rates were lower (Supplementary Fig. 2a). Comparable results were observed for HSSDD average skin pain response, both using a ≥ 30% reduction and ≥ 1-point reduction from a baseline score ≥ 3 (Fig. 1c).

HSSQ skin pain responder rates demonstrated greater clinically meaningful improvements,

defined as a ≥ 30% reduction and ≥ 1-point reduction from baseline in patients with a baseline HSSQ score ≥ 3, at Week 16 in the bimekizumab groups compared with placebo (Fig. 1d). Following switch from placebo to bimekizumab at Week 16, the proportion of responders rapidly increased; by Week 18, this group reached similar responder rates to those continually treated with bimekizumab from baseline (Fig. 1d). Across all treatment groups, responder rates were maintained or further improved from Week 16 to Week 48 (Fig. 1d), with similar trends also observed across analysis types (Supplementary Fig. 3).

Shifts in Pain Severity Categories

A large proportion of patients shifted from severe/very severe to lower severity HSSQ skin

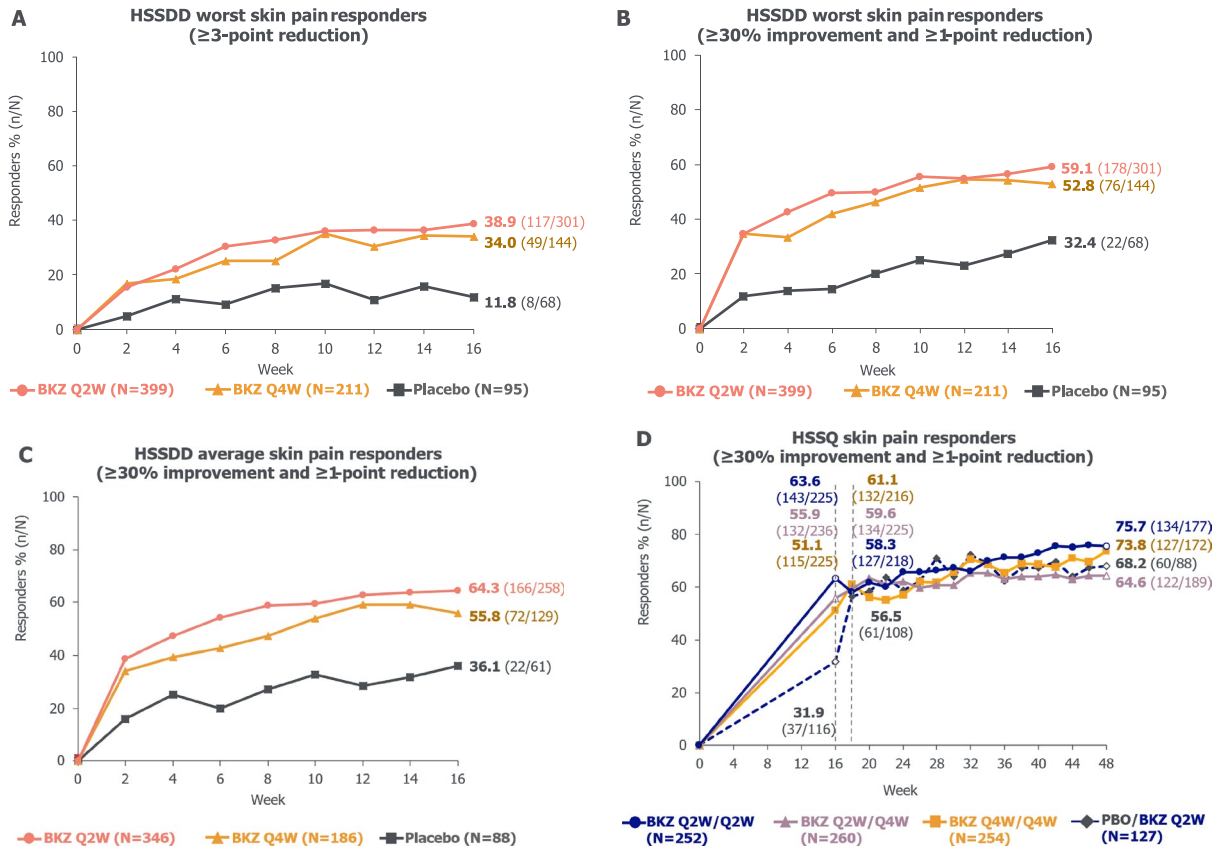


Fig. 1 Responder rates over time: HSSDD worst (**A** ≥ 3-point reduction from baseline, **B** ≥ 30% improvement and ≥ 1-point reduction from baseline) and HSSDD average (**C** ≥ 30% improvement and ≥ 1-point reduction from baseline) and HSSQ skin pain (**D** ≥ 30% improvement and ≥ 1-point reduction from baseline) (OC). Randomized set, $N = 1014$. Patients included in HSSDD analyses had a baseline HSSDD worst or average skin pain score of ≥ 3. HSSDD worst skin pain response, defined as a ≥ 3-point reduction from a baseline HSSDD worst skin pain score of ≥ 3, is a statistically controlled, ranked secondary endpoint at week 16, all others were exploratory. HSSQ responders were defined as a ≥ 30% reduction and ≥ 1-point reduction from baseline in patients with a baseline HSSQ score ≥ 3. Individual symptom items were scored 0–10 at baseline and from weeks 16–48. HSSQ skin pain responder analysis was an exploratory endpoint. OC, *n*/*N*: denominator represents the number of patients with non-missing HSSDD or HSSQ data in the given week, and percentages are calculated accordingly. *BKZ* bimekizumab, *HSSDD* Hidradenitis Suppurativa Symptom Daily Diary, *HSSQ* Hidradenitis Suppurativa Symptom Questionnaire, *OC* observed case, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks

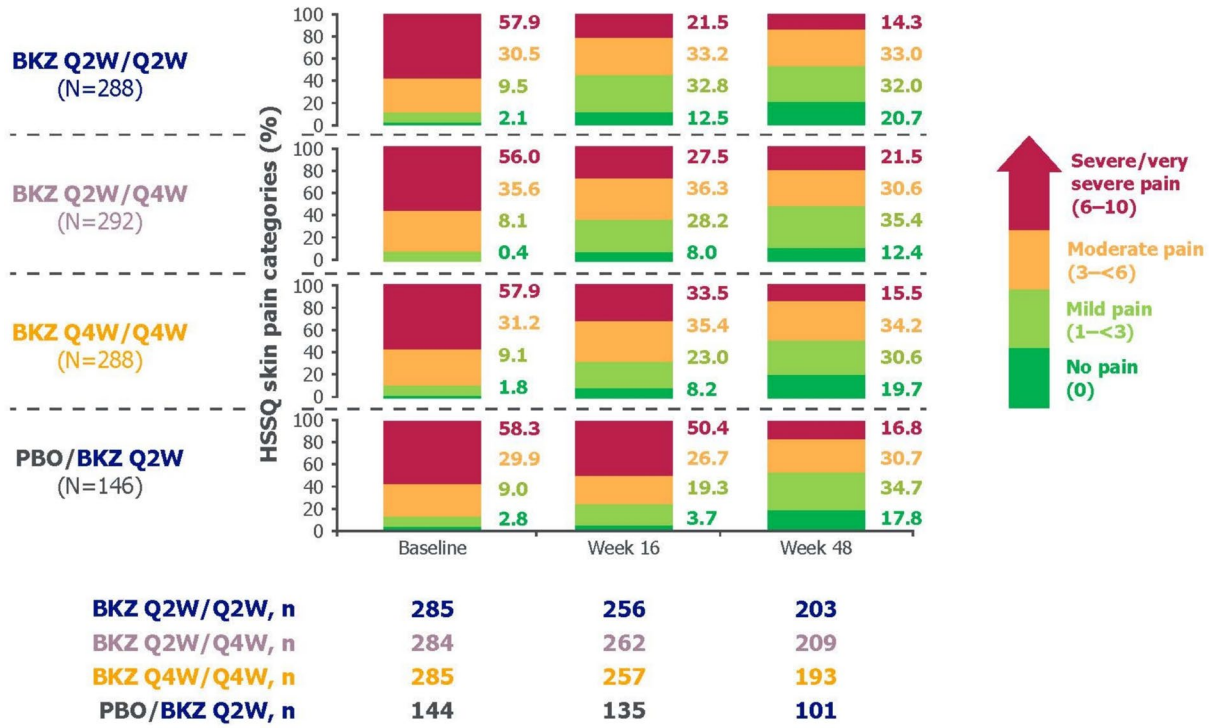


Fig. 2 HSSQ skin pain categories at baseline, Week 16, and Week 48 (OC). Change in HSSQ skin pain severity category was an exploratory endpoint. *n* represents the number of participants with a non-missing measurement at that week. *BKZ* bimekizumab, *HSSQ* Hidradenitis Suppurativa Symptom Questionnaire, *OC* observed case, *PBO* placebo, *Q2W* every 2 weeks, *Q4W* every 4 weeks

pain categories over 48 weeks across all treatment groups (Fig. 2). By Week 48, 12.4–20.7% of patients reported no pain (HSSQ skin pain score of 0). Sankey plots, shown in Supplementary Fig. 5–6, show the movement of patients between HSSQ skin pain categories from baseline to Week 16, and from Week 16 to Week 48. Additionally, the shifts in the distribution of HSSQ skin pain scores (NRS 0–10) over these time periods can be seen in Supplementary Fig. 7.

Association of HiSCR and HSSQ Skin Pain

At Week 48, achievement of increasingly stringent levels of HiSCR correlated with greater improvements in HSSQ skin pain across all treatment groups (Fig. 3). Specifically, patients with HiSCR < 50, the least stringent threshold, experienced a mean (95% CI) improvement of − 1.5 (− 1.9, − 1.1), while those in the HiSCR90–100 category, the most stringent threshold, demonstrated greater improvements of − 3.8 (− 4.1, − 3.5) (Fig. 3).

DISCUSSION

Pain is one of the most detrimental symptoms of HS, profoundly impacting patients' quality of life, due to its chronic and intense nature [1, 3, 8]. A cross-sectional study of emergency department visits in the United States found that 69.9% of patients with HS rated their pain as severe and 40.1% rated their pain as 10 on a 0–10 scale, concurring with a frequently reported unmet need for pain control [37, 38]. It is therefore important that new HS treatments relieve pain, as prioritized by the HiSTORIC group [3, 6, 9, 10]. IL-17 plays an important role in the pathogenesis of various types of pain and

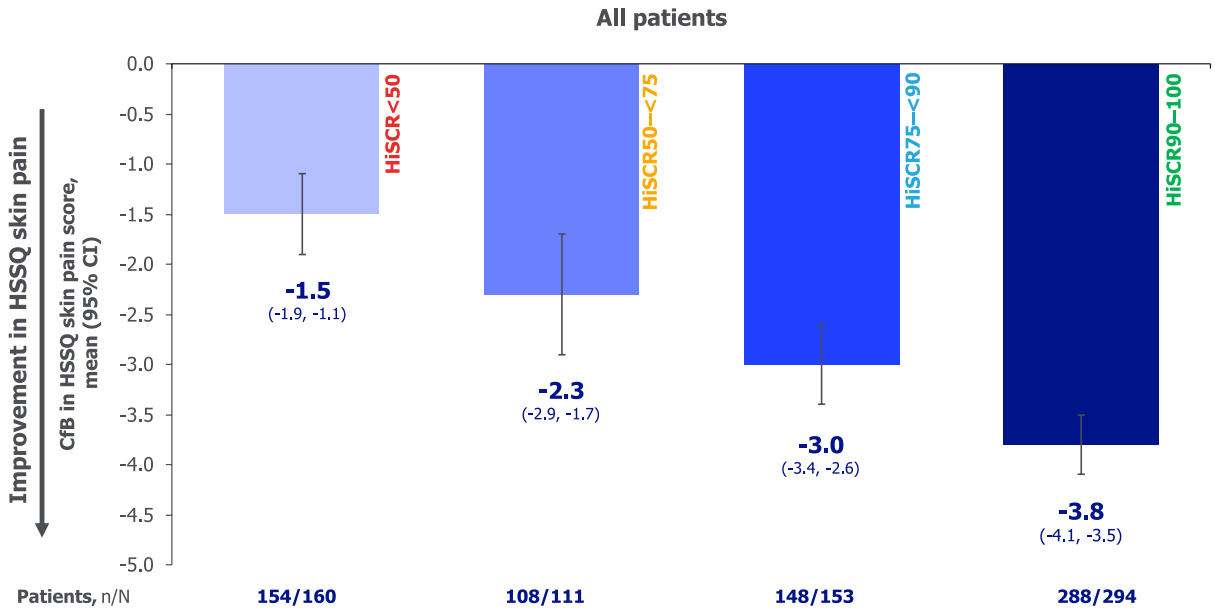


Fig. 3 HSSQ skin pain score improvement from baseline by HiSCR bands at Week 48 (OC). Association of HSSQ skin pain score improvement and HiSCR bands was an exploratory endpoint. OC, *n*/*N*: denominator represents pooled number of patients with a non-missing HSSQ score and achievement of the HiSCR, regardless of treatment and stratified by achievement of the mutually exclusive response levels at Week 48. *CfB* change from baseline, *CI* confidence intervals, *HiSCR* HS Clinical Response, *HiSCR50/75/90/100* 50/75/90/100% reduction in total abscess and inflammatory nodule count from baseline with no increase from baseline in abscess or draining tunnel count, *HSSQ* Hidradenitis Suppurativa Symptom Questionnaire, *OC* observed case

may represent a key therapeutic target in HS [21, 24, 25, 39].

Measurement of pain outcomes and severity thresholds varies across trials. Previous HS clinical trials used measures like the PGA of skin pain on a continuous numeric rating scale (NRS30), with thresholds of 30% or more reduction and reduction of two or more units from BL [40], 30% reduction and at least 1 unit reduction from BL in skin pain (10-point scale) [41] and NRS15 and HS Quality of Life (HiSQOL) score[42]. There is a gap in previous work, including use of HS-specific measures and the need for a more robust set of validated thresholds for what is considered a responder, in line with recent FDA guidance [34, 35, 43]. In the BE HEARD trials, these gaps were addressed with the use of HS-specific measures of pain (HSSDD and HSSQ) and the use of responder thresholds aligned with FDA guidance [29, 34–36, 43]. HSSDD and HSSQ underwent thorough psychometric assessment and interpretation threshold derivation [36]. The data reported here demonstrate bimekizumab efficacy in improving pain; in particular, at Week 16 about a third of patients treated with bimekizumab reach the robust clinically meaningful within-patient improvement threshold of 3- to 4-point decrease in HSSDD. Overall, we believe the HSSDD and HSSQ outcomes will be of benefit to the HS research and clinical communities to assess HS pain improvements.

Here, bimekizumab treatment produced rapid pain improvement, as early as 2 weeks after treatment initiation, which was sustained or further improved up to 48 weeks. Results were consistent across treatment groups, including patients who switched from placebo to bimekizumab treatment at Week 16. Patients with HS had greater improvements in pain when they achieved more stringent HiSCR thresholds over 48 weeks, demonstrating that lesion improvement after bimekizumab treatment translates into greater pain outcomes. Further exploration of the association between clinical response and

patient-reported outcomes is of key interest for future study.

Both worst and average skin pain (from HSSDD), assessed to week 16, have been reported throughout this publication. Results were similar across treatment groups and outcomes. While no formal statistical analyses were undertaken between HSSDD worst and average pain scores, the results suggest that future studies may not require the inclusion of both outcomes. Interestingly, HSSQ skin pain scores, not specifically measuring worst or average pain, were numerically greater than HSSDD skin pain scores. This is most likely associated with different recall periods (the past 7 days for HSSQ versus the past 24 h for HSSDD).

This pain-focused analysis has several limitations. First, there is no consensus on the most suitable method or tool for measuring pain severity in patients with HS, with multiple instruments and pain responder definitions reported across the literature [6, 44–48]. Consequently, treatment comparison across studies is difficult. Although this study utilized new instruments, both HSSQ and HSSDD have undergone psychometric assessment [36]. To compare pain outcomes across clinical studies, future research requires agreement on the use of a HS disease-specific, validated, and fit-for-purpose instrument, as is currently done for lesion-based endpoints. Second, restrictions on analgesic use in the context of controlled clinical trials limits the ability to assess whether bimekizumab-related reduction in skin pain leads to decreased usage. Future studies in a real-world setting should be conducted to explore potential associations between pain reduction following bimekizumab treatment and the reduction in usage of HS-specific analgesics, including opioids. Additionally, we were not able to account for pain medication usage in these analyses; use of prescribed or over-the-counter pain medication could cause a decrease in pain, independent of bimekizumab treatment.

Another limitation is the use of OC analyses for binary data throughout this report, which can potentially overestimate treatment effects. However, mNRI data reported within the Supplementary Materials, which incorporated intercurrent events, demonstrated similar findings. Further, although multiple imputation was used to handle missing pain score data, we recognize that this approach does not replicate the actual values that would have been observed in the absence of missing data. Instead, it produces plausible estimates based on patterns within the available data, which may limit the extent to which the imputed values accurately represent true counterfactual outcomes. The timings of HSSDD assessments (daily for the first 16 weeks) and HSSQ assessments (baseline, Week 16, then every other week to Week 48), chosen to minimize patient burden, prevents the direct comparison of the kinetics for the first 16 weeks to the kinetics of the following 16 weeks. Finally, longer-term data are needed to show how skin pain results are sustained in the context of a chronic and relapsing disease.

CONCLUSIONS

Patients with hidradenitis suppurativa (HS) suffer under a heavy burden of pain. The results here report exploratory and post hoc analyses up to 48 weeks using pooled data from two phase 3 clinical trials of patients with moderate to severe HS, BE HEARD I and II. Using validated, disease-specific measures of pain, these findings showed that treatment with bimekizumab leads to rapid, continuous, and clinically meaningful reductions in skin pain.

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Data Availability. Underlying data from this manuscript may be requested by qualified researchers six months after product approval in the US and/or Europe, or global development is discontinued, and 18 months after trial completion. Investigators may request access to anonymized individual patient-level data and redacted trial documents, which may include: analysis-ready 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.

Declarations

Conflict of Interest. **John R. Ingram**: Received a stipend as Editor-in-Chief of the British Journal of Dermatology and an authorship honorarium from UpToDate; consultant for AbbVie, Boehringer Ingelheim, ChemoCentryx, Citryll, Incyte, MoonLake Immunotherapeutics, Novartis, UCB and Union Therapeutics; has served on advisory boards for Insmed, Kymera Therapeutics and Viela Bio; co-copyright holder of HiSQOL © and HS-IGA; his department receives income from copyright of the Dermatology Life Quality Instrument (DLQI) and related instruments. **Hideki Fujita**: Received honoraria or fees for serving on advisory boards, as a speaker and as a consultant, as well as grants as an investigator from AbbVie, Amgen, Boehringer Ingelheim, Bristol Myers Squibb, Daiichi Sankyo, Eisai, Eli Lilly, Janssen, Japan Blood Products Organization, JMEC, Kaken Pharmaceutical, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Nihon Pharmaceutical, Novartis, Otsuka Pharmaceutical, Sanofi, Sato Pharmaceutical, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, UCB and Ushio. **Alice B. Gottlieb**: Received research/educational grants from Bristol-Myers Squibb, Janssen, MoonLake Immunotherapeutics and UCB (all paid to Mount Sinai School of Medicine until May 1, 2025). Sub I at

UT Southwestern on studies from Bristol-Myers Squibb, Janssen, and UCB. Received honoraria/speaker fees as an advisory board member and consultant for Bristol Myers Squibb, Eli Lilly and Company, Janssen, Novartis, Oruka, Sanofi, SunPharma, Takeda, Teva and UCB. **Hadar Lev-Tov**: Consultant for Novartis and UCB. **Errol Prens**: Consultant, advisory board member, speaker for, and received honoraria from Almirall, Janssen-Cilag, GSK, MoonLake Immunotherapeutics, Novartis, and UCB. Department has received investigator-initiated grant support from AbbVie, Celgene, CHDR, Citryll, Janssen-Cilag, Kymera, and UCB. **Christopher J. Sayed**: Investigator for AbbVie, AstraZeneca, ChemoCentryx, Incyte, InflaRx, Novartis and UCB; consultancy fees from AbbVie, Alumis, AstraZeneca, InflaRx, Incyte, Logical Images, MoonLake Immunnotherapeutics, Sandoz, Sanofi, Sonoma Biotherapeutics and UCB; speaker for AbbVie and Novartis. **Vivian Y. Shi**: On the board of directors for the Hidradenitis Suppurativa Foundation (HSF), advisor for the National Eczema Association, stock shareholder of Learn Health and has served as an advisory board member, investigator, speaker, and/or received research funding from AbbVie, Altus Lab/cQuell, Alumis, Aristea Therapeutics, Boehringer Ingelheim, Burt's Bees, Dermira, Eli Lilly and Company, Galderma, Genentech, GpSkin, Incyte, Kiniksa, LEO Pharma, Menlo Therapeutics, MYOR, Novartis, Pfizer, Polyfins Technology, Regeneron, Sanofi Genzyme, Skin Actives Scientific, Sun Pharma, Target-PharmaSolutions and UCB. **Jacek C. Szepietowski**: Consultant and advisory board member of AbbVie, LEO Pharma, Novartis, Pierre Fabre, Sanofi Genzyme, Trevi Therapeutics; speaker for AbbVie, Almirall, Eli Lilly, LEO Pharma, Novartis, Pfizer, Pierre Fabre, Sanofi-Genzyme, and UCB; investigator for AbbVie, Amgen, Bristol Myers Squibb, Galapagos, Galderma, Incyte, InflaRX, Janssen, Kiniksa, Kymab Limited, Menlo Therapeutics, Merck, Novartis, Pfizer, Regeneron Pharmaceuticals, Trevi Therapeutics, and UCB. **Kenzo Takahashi**: Received honoraria or fees for a speaker from AbbVie, Amgen, Janssen, Kaken Pharmaceutical, Kyowa Kirin, LEO Pharma, Maruho, Mitsubishi Tanabe, Sun Pharma, Taiho Pharmaceutical, Torii Pharmaceutical, UCB and Ushio, and fees as a consultant from AbbVie, Earth Corporation, Kaken Pharmaceutical, Mitsubishi Tanabe, and UCB. Department participated in trials for AbbVie, Boehringer Ingelheim, Eli Lilly, Janssen, Kaken Pharmaceutical, Kyowa Kirin Corporation, Novartis, Sanofi, and UCB. **John W. Frew**: Conducted advisory work for AbbVie, Boehringer Ingelheim, ChemoCentryx, Janssen, Kyowa Kirin, LEO Pharma, Pfizer, Regeneron and UCB; participated in trials for Boehringer Ingelheim, CSL, Eli Lilly and Company, Pfizer, and UCB; received research support from Ortho Dermatologics and Sun Pharma. **Jérémy Lambert, Leah Davis, Tae Oh, Robert Rolleri, Marie-Hélène Saintmard**: Employees and shareholders of UCB. **Lauren A.V. Orenstein**: On the board of directors for the Hidradenitis Suppurativa Foundation (HSF); consultant and/or advisory board member for ChemoCentryx, Novartis, and UCB; received grant funding from Pfizer.

Ethical Approval. The study protocol, amendments, and patient informed consent were reviewed by a national, regional, or Independent Ethics Committee (IEC) or Institutional Review Board (IRB). This study was conducted in accordance with the current version of the applicable regulatory and International Conference on Harmonisation (ICH)-Good Clinical Practice (GCP) requirements, the ethical principles that have their origin in the principles of the Declaration of Helsinki, and the local laws of the countries involved. Ethics approval was obtained from the relevant institutional review boards at participating sites. All patients provided written informed consent in accordance with local requirements.

Consent. All the results presented in this article are in aggregate form, and no personally identifiable information was used for this study.

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