21 March 2024
EMA/145924/2024
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bimzelx

International non-proprietary name: Bimekizumab

Procedure No. EMEA/H/C/005316/II/0020

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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List of abbreviations

AB	abscess
ABX	antibiotics
ADAb	antidrug antibody ADR adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AN	abscess and inflammatory nodule
AS	ankylosing spondylitis
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
bimekizumab-AI-1mL	bimekizumab-autoinjector-1mL
bimekizumab-SS-1mL	bimekizumab-safety syringe-1mL
BMI	body mass index
CI	confidence interval
CSR	clinical study report
CV	cardiovascular
CV-CAC	Cardiovascular Clinical Event Adjudication Committee
DDI	drug-drug interaction
DLQI	Dermatology Life Quality Index
DMC	Data Monitoring Committee
DT	draining tunnel
EAIR	exposure-adjusted incidence rate
EBE	empirical Bayes estimate
ECG	electrocardiogram
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EQ-5D-3L	Euro-Quality of Life 5-Dimensions, 3 levels
E-R	exposure-response
HAC	Hepatic Adjudication Committee
HADS	Hospital Anxiety and Depression Scale
HiSCR	Hidradenitis Suppurativa Clinical Response
HiSCR25, 50, 75, 90, 100	a ≥25%, ≥50%, ≥75%, ≥90%, ≥100% reduction in the total abscess and inflammatory nodule count with no increase from Baseline in abscess or draining tunnel count

HiSQOL	Hidradenitis Suppurativa Quality of Life
HLT	high level term
HR	hazard ratio
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
Hs-CRP	high-sensitivity C-reactive protein
HSSDD	Hidradenitis Suppurativa Symptom Daily Diary
HSSQ	Hidradenitis Suppurativa Symptom Questionnaire
IBD	inflammatory bowel disease
IBD-CAC	IBD Adjudication Committee
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
IHS4	International Hidradenitis Suppurativa Severity Score System
IIV	inter-individual variability
IL	interleukin
IMP	investigational medicinal product
IRT	interactive response technology
ISAP	Integrated Statistical Analysis Plan
IN	inflammatory nodule
ISS	Integrated Summary of Safety
ITP	Initial Treatment Period
LFT	liver function test
LS	least square
mAb	monoclonal antibody
MACE	major adverse cardiac event
MI	myocardial infarction
mNRI	modified non-responder imputation
MTP	Maintenance Treatment Period
NAb	neutralizing antibody
NAC	Neuropsychiatric Adjudication Committee
NAFLD	non-alcoholic fatty-liver disease
NEC	not elsewhere classified
nr-axSpA	nonradiographic axial spondylarthritis
OC	observed case

OLE	open-label extension
PBO	placebo
PD	pharmacodynamic(s)
PDILI	potential drug-induced liver injury
PGA	Physician Global Assessment
PFS	prefilled syringe
PHQ-9	Patient Health Questionnaire-9
PK	pharmacokinetic
PRO	patient-reported outcome
PsA	psoriatic arthritis
PSO	psoriasis
PSUR	Periodic Safety Update Report
PT	preferred term
RS	randomized set
Q2W	every 2 weeks
Q4W	every 4 weeks
QOL	quality of life
SAP	statistical analysis plan
sc	subcutaneous
SE	standard error
SFU	Safety Follow-up
SIB	suicidal ideation and behavior
SOC	system organ class
SUD	substance use disorder
TB	tuberculosis
TEAE	treatment-emergent adverse event
TN	True North
TSFD	time since first dose
TSQM-9	Treatment Satisfaction Questionnaire for Medication-9
ULN	upper limit of normal
VPC	visual predictive check

1. Background information on the procedure

1.1. Type II variation

Pursuant to Article 16 of Commission Regulation (EC) No 1234/2008, UCB Pharma S.A. submitted to the European Medicines Agency on 23 June 2023 an application for a variation.

The following variation was requested:

Variation requested		**Type**	**Annexes affected**
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderate to severe hidradenitis suppurativa (HS) in adults, based on final results from study HS0003 (BE HEARD I) and study HS0004 (BE HEARD II). These are phase 3, randomized, double blind, placebo controlled, multicenter, pivotal studies evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS. Further supportive data are based on the results of phase 2 study HS0001 and phase 3 currently ongoing open-label extension study HS0005. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated in accordance. Version 1.10 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.3.

The variation requested amendments to the Summary of Product Characteristics and Package Leaflet and to the Risk Management Plan (RMP).

Information on paediatric requirements

Pursuant to Article 8 of Regulation (EC) No 1901/2006, the application included (an) EMA Decision(s) P/0078/2021 on the agreement of a paediatric investigation plan (PIP) and on the granting of a (product-specific) waiver.

At the time of submission of the application, the PIP P/0078/2021 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the MAH did not submit a critical report addressing the possible similarity with authorised orphan medicinal products because there is no authorised orphan medicinal product for a condition related to the proposed indication.

Scientific advice

The MAH received Scientific Advice from the CHMP on 25 July 2019 (EMEA/H/SA/3306/4/2019/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP were:

Rapporteur: Finbarr Leacy Co-Rapporteur: Christophe Focke

Timetable	Actual dates
Submission date	23 June 2023
Start of procedure:	15 July 2023
CHMP Rapporteur Assessment Report	8 September 2023
PRAC Rapporteur Assessment Report	12 September 2023
CHMP Co-Rapporteur Assessment	20 September 2023
PRAC Outcome	28 September 2023
CHMP members comments	2 October 2023
Updated CHMP Rapporteur(s) (Joint) Assessment Report	5 October 2023
Request for supplementary information (RSI)	12 October 2023
CHMP Rapporteur Assessment Report	21 December 2023
PRAC Rapporteur Assessment Report	3 January 2024
PRAC members comments	n/a
PRAC Outcome	11 January 2024
CHMP members comments	15 January 2024
Updated CHMP Rapporteur Assessment Report	18 January 2024
Request for supplementary information (RSI)	25 January 2024
CHMP Rapporteur Assessment Report	6 March 2024
CHMP members comments	11 March 2024
Updated CHMP Rapporteur Assessment Report	14 March 2024
Opinion	21 March 2024

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Hidradenitis suppurativa (HS), also called 'acne inversa' or 'maladie de Verneuil', is a chronic, inflammatory, and recurrent skin condition characterised by painful, deep-seated, and inflamed lesions typically located in the intertriginous areas of the body (e.g., axillae, inguinal, and anogenital regions).

The therapeutic indication initially claimed by the MAH was:

Bimzelx is indicated for the treatment of adults with moderate to severe hidradenitis suppurativa.

The initially proposed dose regimen was:

The recommended dose for adult patients with hidradenitis suppurativa is 320 mg (given as 2 subcutaneous injections of 160mg each) every 2 weeks up to Week 16 and every 4 weeks thereafter.

Consideration should be given to discontinuing treatment in patients who have shown no improvement by 16 weeks of treatment.

Epidemiology and risk factors

HS is estimated to affect about 1% of the adult European population, with a female to male ratio of approximately 3:1. Most patients have mild or moderate disease with the majority typically having moderate disease, though severe disease has been reported in 4 to 28 % of patients. Risk factors for more severe disease include higher body mass index (BMI)/obesity, smoking and duration of disease.

Clinical presentation

The nodules are often inflamed, can progress to abscess (AB) formation, and may rupture to form fistulas and subsequent scarring. Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. The visible manifestations of disease among patients with HS impact interpersonal relationships, self-esteem, and perception of self-image and public image, resulting in depression and embarrassment. HS can progress to become a debilitating skin disease with disfiguring scarring; as a result, it has a high negative impact on patients' quality of life (QOL). HS is associated with significant comorbidity burden regardless of age, sex, racial, and disease severity group, which is beyond the skin manifestations, and includes metabolic, cardiovascular (CV), endocrine, gastrointestinal, rheumatologic, and psychiatric disorders, which collectively decrease the QOL of patients.

Management

Treatment modalities, as recommended by international guidelines (Dermatology Association, European HS Foundation, European Academy of Dermatology and Venereology, Swiss Consensus Group, Brazilian Society of Dermatology) include intralesional corticosteroids, topical clindamycin, oral tetracyclines, combination clindamycin and rifampicin therapy, biologics, and wide local excision. Specifically, the European treatment guideline for HS developed in 2015 suggests that the disease should be treated based on its individual subjective impact and objective severity. Locally recurring lesions can be treated by classical surgery or laser techniques, whereas medical treatment either as monotherapy or in combination with radical surgery is more appropriate for widely spread lesions. Medical therapy may include antibiotics (tetracyclines, clindamycin plus rifampicine), acitretin and biologics. Further treatment of HS depends on the extent and activity of the disease and include medical treatments, antiandrogen treatment in women, systemic retinoids, and metformin, as well as surgical treatments (e.g., radical excision, marsupialisation, and deroofing), and laser treatment.

Humira (adalimumab; a tumor necrosis factor-alpha inhibitor) and Cosentyx (secukinumab; an anti-human interleukin (IL)-17A antibody) are approved in the EU for the treatment of moderate to severe HS in adults (and adolescents for Humira) with an inadequate response to conventional systemic HS therapy.

Considering the limited treatment armamentarium, there is still an unmet medical need for additional systemic therapies.

2.1.2. About the product

Bimekizumab is a humanised IgG1/κ monoclonal antibody that selectively binds with high- affinity to IL-17A, IL-17F and IL-17AF cytokines, blocking their interaction with the IL-17RA/IL-17RC receptor complex. Bimekizumab (Bimzelx) was initially authorised in the EU on 25 June 2021 for the treatment of plaque psoriasis in adult patients (procedure EMEA/H/C/005316/0000). On 26 April 2023, new indications for psoriatic arthritis and axial spondyloarthritis were authorised (procedures EMEA/H/C/005316/0010 and EMEA/H/C/005316/0011, respectively).

2.1.3. The development programme/compliance with CHMP guidance/scientific advice

Scientific Advice (SA) related to the following aspects of the proposed clinical development programme in HS was provided by the CHMP in July 2019 (Procedure No.: EMEA/H/SA/3306/4/2019/II):

- Phase 3 study design including choice of dose regimens proposed for use in the Initial Treatment Period and the Maintenance Treatment Period,
- primary and secondary endpoints,
- study design
- size of safety database
- overall sufficiency of proposed development programme in HS

The MAH has generally followed recommendations provided in the scientific Advice. Compliance and deviations from SA are discussed in the relevant sections of the AR.

2.1.4. General comments on compliance with GCP

The Clinical trials were performed in accordance with GCP as claimed by the MAH. The MAH has also provided a statement confirming that all clinical trials conducted outside of the European Union meet the ethical requirements of Directive 2001/20/EC.

2.2. Non-clinical aspects

2.2.1. Introduction

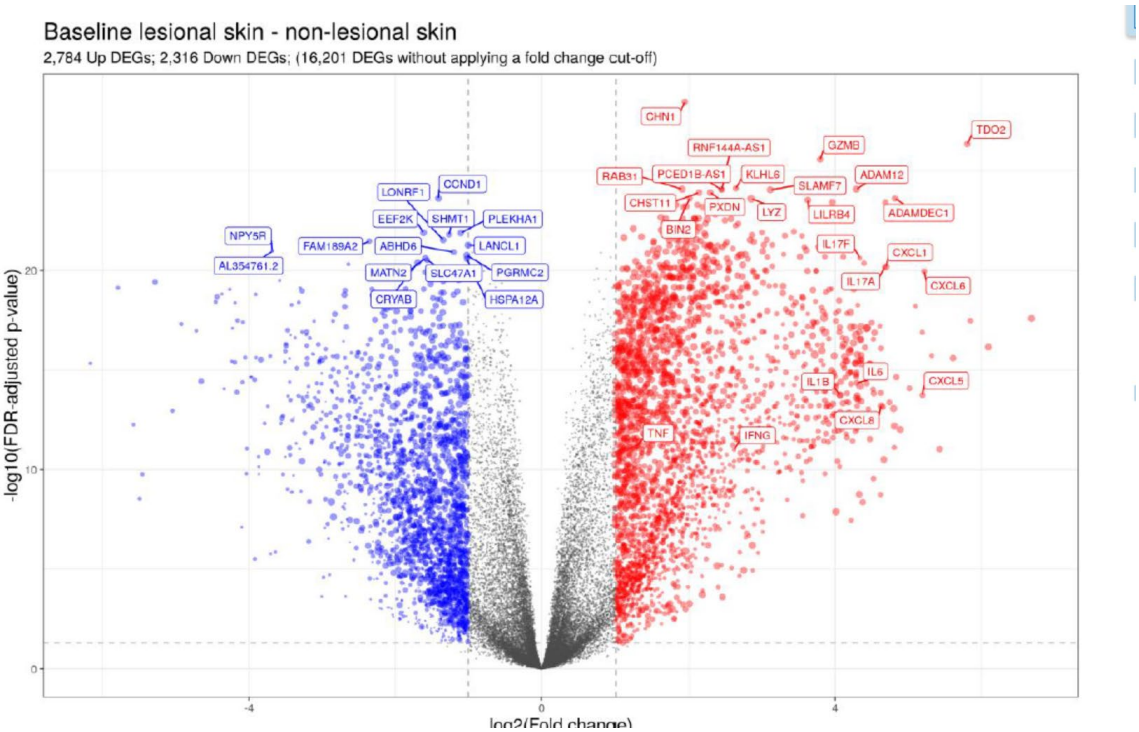
One additional *in vitro* pharmacology study has been submitted investigating the expression of IL-17F and IL-17A in HS tissues (study 40001864). Literature data has also been provided to support this extension of indication application.

2.2.2. Pharmacology

Primary pharmacodynamic studies

The MAH submitted one *in vitro* pharmacology study to support the scientific rationale for use of bimekizumab in HS. A non-GLP *in vitro* pharmacology study (40001864) was carried out with the aim of demonstrating expression of both IL-17A and IL-17F proteins in HS tissues in non-quantitative analysis by immunohistochemistry. Ten (10) patients (of both sexes) were included in the study. Lesional and non-lesional skin was obtained and compared with 10 patient-derived non-HS skin samples as a control. The study demonstrated abundant expression of both IL-17A and IL-17F in clinically normal peri-lesional skin in addition to lesional skin of patients with HS. Differential expression or quantitative analysis of IL-17F versus IL-17A was not reported in study 40001864. The data provided by the MAH suggests that inflammatory processes by both IL-17F and IL-17A are initiated in HS skin prior to formation of active lesions in peri-lesional skin. Since the IL-17 family of cytokines are implicated in pathogenesis of inflammatory skin diseases, mobilising neutrophils, recruitment of Th17 and myeloid cells and induction of pro-inflammatory cytokines by keratinocytes, this data suggests that inhibition of IL-17 may be a viable therapeutic target in HS. Literature data was submitted to support a 10-fold abundance of 1L-17F versus IL-17A in blood serum of 89 patients with HS. However, comparative assessment of IL-17F vs IL-17A abundance in tissue was not provided. Additional information was provided demonstrating that both IL-17F and IL-17A are more highly expressed in lesional versus non-lesional skin (RRUK1953).

Figure 1. Volcano plot of genes dysregulated between lesional and non-lesional skin at baseline



However, differential expression of IL-17F versus IL-17A in lesional tissue has not been assessed, nor discussed in study RRUK1953. A second study report submitted, RRUK2028, also demonstrates that both IL-17A and IL-17F are highly expressed in lesional and non-lesional skin, however without a quantitative comparison. No quantification of IL-17F and IL-17A were performed in the studies submitted.

The MAH provided a detailed evaluation of gene expression in skin biopsies of humans with moderate to severe HS demonstrating upregulation of genes inducing neutrophil migration, genes encoding for IL-1β,

IL-17A and IL-17F. Report 40001882 supports proof of concept that treatment with bimekizumab suppresses expression of neutrophil-associated cytokines in lesions. In primary dermal fibroblasts activated with Th17, bimekizumab reduced expression of genes associated with neutrophil activation and/or recruitment with higher efficiency than antibodies against IL-17A or IL-17F alone. The non-clinical *in vitro* study (4001864) also supports the scientific rationale for inhibition of IL-17A and IL-17F to suppress inflammatory responses associated with HS, versus inhibition of either alone.

2.2.3. Ecotoxicity/environmental risk assessment

According to the current CHMP guideline on environmental risk assessment (CHMP/SWP/4447/00 corr 2), for products containing vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids as active pharmaceutical ingredient(s), an ERA may consist of a justification for not submitting ERA studies, e.g., due to their nature they are unlikely to result in a significant risk to the environment. As a monoclonal antibody, bimekizumab falls within the scope of this provision.

2.2.4. Discussion on non-clinical aspects

The additional non-GLP *in vitro* pharmacology study (40001864) submitted by the MAH is considered supportive of the scientific rationale for this extension of indication in HS. These data together with existing non-clinical pharmacology studies submitted with the original MAA and available literature data, support the MAH's position that bimekizumab is likely to inhibit both IL-17A and IL-17F, which may provide enhanced suppression of inflammatory responses over inhibition of IL-17A alone. The MAH has not provided data on comparative expression of IL-17F versus IL-17A in skin samples of HS patients in the original study report submitted (400001864). While literature data suggests higher expression of IL-17F versus IL-17A based on quantitative analysis in sera of HS patients, evidence supporting these findings in lesional skin was not providedN.

Additional information, demonstrating that both IL-17F and IL-17A are more highly expressed in lesional versus non-lesional skin (RRUK1953) was provided, but differential expression of IL-17F versus IL-17A in lesional tissue was not assessed nor discussed in this study. Study RRUK2028 also demonstrates that both IL-17A and IL-17F are highly expressed in lesional and non-lesional skin, again without a quantitative comparison. Since comparative expression of IL-17A versus IL-17F in lesional skin has not been demonstrated in this report, the CHMP concluded that the proposed statement in section 5.1 of the SmPC suggesting that IL-17F is more highly expressed than IL-17A is unsupported by non-clinical data. Upon CHMP's request, the MAH agreed to remove this statement from SmPC section 5.1. Nevertheless, the MAH has demonstrated expression of both IL-17F and IL-17A in HS skin samples. The CHMP concluded that bimekizumab is anticipated to inhibit both IL-17F and IL-17A, to break the inflammatory loop in HS.

The MAH's ERA, providing a justification for not performing a detailed environmental risk assessment for bimekizumab, is acceptable to the CHMP.

2.2.5. Conclusion on the non-clinical aspects

From the non-clinical point of view, the extension of indication application is acceptable to the CHMP.

2.3. Clinical aspects

2.3.1. Introduction

GCP

The clinical trials were performed in accordance with GCP as claimed by the MAH.

The MAH has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Study number/clinical development phase/study design	Study Period	Number of study participants randomized			Maximum duration of active treatment
		BKZ	PBO	Active reference arm	
Primary efficacy studies					
HS0003/Phase 3/multicenter, randomized, double-blind, placebo-controlled study	ITP	320mg Q2W: 289 320mg Q4W: 144	72	NA	16 weeks
	MTP	PBO/320mg Q2W: 65 BKZ 320mg Q4W/Q4W: 125 BKZ 320mg Q2W/Q4W: 129 BKZ 320mg Q2W/Q2W: 129	0	NA	32 weeks
HS0004/Phase 3/multicenter, randomized, double-blind, placebo-controlled study	ITP	320mg Q2W: 291 320mg Q4W: 144	74	NA	16 weeks
	MTP	PBO/320mg Q2W: 69 BKZ 320mg Q4W/Q4W: 133 BKZ 320mg Q2W/Q4W: 130 BKZ 320mg Q2W/Q2W: 131	0	NA	32 weeks
Total exposure during primary efficacy studies [a]					
	ITP	320mg Q2W: 580 320mg Q4W: 288	146	NA	16 weeks
	MTP	PBO/320mg Q2W: 146 BKZ 320mg Q4W/Q4W: 288 BKZ 320mg Q2W/Q4W: 292 BKZ 320mg Q2W/Q2W: 288	0	NA	32 weeks

Study number/clinical development phase/study design	Study Period	Number of study participants randomized			Maximum duration of active treatment
		BKZ	PBO	Active reference arm	
Supporting efficacy studies					
HS0001/Phase 2/multicenter, Investigator-blind, study participant-blind, placebo-controlled study	Double-blind Treatment Period	640mg at Baseline followed by 320mg Q2W: 46	22	ADA: 22	12 weeks
Long-term studies					
HS0005/Phase 3/multicenter, OLE study	OLE	NA (study is ongoing)	NA	NA	100 weeks

ADA=adalimumab; AN=abscess and inflammatory nodule; BKZ=bimekizumab; CSR=clinical study report; $HiSCR_{90}$=≥90% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; IMP=investigational medicinal product; ISE=Integrated Summary of Efficacy; ITP=Initial Treatment Period; MTP=Maintenance Treatment Period; NA=not applicable; OLE=open-label extension; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

[a] In the MTP, the total exposure is based on the randomized treatment assignments.

The clinical studies supporting the bimekizumab HS clinical development program included a total of 3 efficacy and safety studies (HS0001, HS0003 and HS0004). These studies provided supportive data including PK, PD, and immunogenicity of bimekizumab in study participants with HS.

The dosing recommendation in HS was supported by knowledge concerning PK, exposure-response (ER), among other data, with respect to efficacy and impact of covariates on PK and ER. Therefore, the PK and the ER for the primary clinical endpoint HiSCR50 along with other hidradenitis suppurativa clinical response (HiSCR) rates were characterised in patients with HS by pharmacometric modelling.

2.3.2. Pharmacokinetics

Bioanalytical methods

The bioanalytical methods used for analyses of plasma bimekizumab concentrations, anti bimekizumab antibody (ADAb) assessments, and anti bimekizumab neutralising antibody (Nab) determination in clinical studies relevant to the HS indication have been fully validated.

Pharmacokinetics

The PK of bimekizumab was different in participants with HS compared with healthy participants and participants with PSO, PsA or axSpA. Overall, lower median plasma concentrations, normalising for dosing regimen, were observed in participants with HS compared with other populations.

Compared with PSO, PsA, and axSpA, CL/F was 31% higher and V/F was 18% higher for a 90kg participant with HS; the t½ for a 90kg individual was 20 days in participants with HS. However, bimekizumab exhibited dose proportional, linear PK across dose regimens as evidenced by clinical study data and population PK modelling across the bimekizumab clinical program to date.

Immunogenicity

The prevalence of pre-existing anti-drug-antibodies (ADAb) in the HS Phase 3 population was low and within the expected prevalence range. Overall and relative to placebo at Week 16, clinically meaningful response rates were observed for both HiSCR50 and HiSCR75 regardless of ADAb and neutralising anti-drug-antibody (NAb) status. However, response rates were higher for ADAb- and NAb-negative participants receiving bimekizumab 320mg Q2W at Week 16 compared with ADAb- and NAb-positive participants, while no trends were observed for the bimekizumab Q4W treatment arm. Similar trends were observed at Week 48 for ADAb-negative participants, but not for NAb-negative participants. There was no indication of a reduced HiSCR50/75 response with increasing ADAb titers (as determined at 'trough'/pre-dose timepoints) at Week 16 or Week 48. ADAb and NAb positivity had no clinically meaningful impact on the safety profile of bimekizumab in HS study participants. Also see section 2.5 on clinical safety.

2.3.3. Pharmacodynamics

Pharmacodynamic assessments included HiSCR as a clinical endpoint, and no additional biomarkers (PD endpoints) were assessed in the Phase 3 E-R analysis.

2.3.4. PK/PD modelling

Population PK and exposure-response analyses of bimekizumab in adults with HS

The aim of this analysis was to support the posology of bimekizumab in HS by means of characterising the population PK and Exposure-Response (ER) of bimekizumab in adults with HS.

Data

The data for this analysis originate from 3 clinical studies: one Phase 2 study (HS0001) and the two Phase 3 studies (HS0003, HS0004) in patients with moderate to severe HS. In HS0001, patients were administered 320 mg bimekizumab q2w with a loading dose of 640 mg over 12 weeks of treatment. In the Phase 3 studies, patients were administered 320 mg bimekizumab every other week (Q2W) or every fourth week (Q4W). Treatment duration was 12 weeks in HS0001 and 48 weeks (initial treatment period 16 weeks, maintenance treatment period 32 weeks) in studies HS0003 and HS0004. Bimekizumab was administered as subcutaneous (SC) injections.

All blood samples were drawn prior to dosing at the given study visit. Study HS0001: pre-dose and at Weeks 2, 4, 8, 12. Studies HS0003, HS0004: pre-dose and at Weeks 1, 2, 4, 8, 12, 16, 18, 20, 24, 36, 48. Observation records with bimekizumab plasma concentration values below the lower limit of quantification (LLOQ) were retained in the derived data file, with the values set to LLOQ/2. The number of below limit of quantification (BLQ) observations relative to the total number of bimekizumab plasma observation records in the derived data file was low and no alternative modelling approaches for handling these observations were deemed necessary.

The data analysed in the ER HiSCR analysis comprised of the response variables 50% improvement from baseline in hidradenitis suppurativa clinical response (HiSCR50), 75% improvement from baseline in hidradenitis suppurativa clinical response (HiSCR75), 90% improvement from baseline in hidradenitis suppurativa clinical response (HiSCR90) and 100% improvement from baseline in hidradenitis suppurativa clinical response (HiSCR100) derived from the collected lesion count data. ER HiSCR assessments were performed in studies HS0003 and HS0004: pre-dose and at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48.

Methods

The starting population PK model was an existing bimekizumab population PK model developed from data in patients with PSO, PSA and axSpA. The modelling analysis of the bimekizumab PK data from subjects with HS were performed using NONMEM. Body weight was included *a priori* as a mechanistic covariate on CL/F and apparent volume of distribution (V/F). Additional potential covariate-parameter relationships were evaluated on CL/F using the stepwise covariate model building procedure (SCM) with adaptive scope reduction (ASR). The evaluated covariates included ADAb and NAb status as a combined covariate, prior use of biologics, disease severity (Hurley stage II and III), age, sex, race and geographical region. The impact of covariates on model parameters and on derived secondary PK exposure metrics was illustrated using Forest plots. If the estimated covariate effect and 95% CI fell completely within the 0.8 to 1.25 boundaries for all PK metrics evaluated, the parameter-covariate relationship was discarded.

The ER structural model was based on a population ER model previously developed to describe the ER relationship between bimekizumab plasma concentration and ASAS (assessment of spondyloarthritis international society) response. The modelling analysis of the HiSCR data from subjects with HS was performed using NONMEM, applying a proportional odds model, which simultaneously described the time course of the probabilities of non-response, HiSCR50, HiSCR75, HiSCR90 and HiSCR100. Potential covariate-parameter relationships were evaluated using the SCM procedure with ASR. The evaluated covariates included body weight (WT), body mass index (BMI), age, sex, race, smoking status, duration of disease, disease severity (Hurley stage II and III), abscess and inflammatory nodule (AN) counts, prior use of biologics, antibiotic use at baseline entry, geographical region, high-sensitivity C-reactive protein (hs-CRP), ADAb and NAb status (as a combined covariate).

Simulations were performed based on the final PK and ER models to illustrate the clinical impact of i) the most influential covariates identified in the models, and ii) of the treatment regimens of interest. The

simulations were performed for the following treatment regimens, (i) 320 mg q4w until Week 48, (ii) 320 mg q2w until Week 48, (iii) 320 mg q2w until Week 16, then switch to 320 mg q4w until Week 48.

Results

- **Bimekizumab PK**

The parameter estimates of the final bimekizumab PK model are presented in Table 1. The t1/2 based on these parameter estimates is 19.7 days (subject weighing 95 kg). The t1/2 for subjects at the 5th and 95th percentile of the WT distribution (corresponding to 62 and 142 kg) are 22.7 and 17.2 days, respectively.

Table 1. Parameter estimates of the final bimekizumab PK model

		Final model		
Run		129		
OFV		32881.60		
Condition number		10.19		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
CL/F[a]	(L/day)	0.512	1.47	
V/F[b]	(L)	14.5	1.18	
k_a	(1/day)	0.499	4.04	
WT on CL/F[a]		1.12	3.96	
Prior biologics on CL/F[c]		0.121	23.9	
Hurley stage III on CL/F[c]		0.182	13.0	
WT on V/F[b]		0.782	5.17	
IIV CL/F	(CV)	0.239	4.33	20.1
IIV V/F	(CV)	0.192	7.72	32.6
IIV F_{rel}	(CV)	0.274	4.06	14.8
IIV RUV	(CV)	0.317	7.07	11.6
Proportional RUV	(CV)	0.111	2.86	4.96
Additive RUV	(SD, µg/mL)	0.871	10.3	4.96

The RSE for IIV and RUV parameters are reported on the approximate SD scale.
The equations of the covariate effects are described in detail in Appendix 3.1.5.1.
[a]Parameter estimate is for a subject weighing 95 kg (updated to the median of WT in the PK analysis data set) with no prior biologics use and in Hurley stage II.
The equation for the typical values of CL/F with respect to WT is $CL/F = 0.512 \cdot (\frac{WT}{95})^{1.12}$.
[b]Parameter estimate is for a subject weighing 95 kg (updated to the median of WT in the PK analysis data set).
The equation for the typical values of V/F is $V/F = 14.5 \cdot (\frac{WT}{95})^{0.782}$
[c]The effects of disease severity (Hurley stage III) and Prior biologics use on CL/F are calculated as a proportional change (1+ final model value), compared to the corresponding reference categories.

Diagnostic plots for the final population PK model are presented in Figure 2 and Figure 3. Prediction-corrected visual predictive checks are presented in Figure 4 and Figure 5.

Figure 2. Observed versus predicted concentrations for the final bimekizumab PK model , coloured by treatment group. Data are presented on linear scale (left) and logarithmic scale (right). Lines connect points from the same subject. See Section 4.4 for smooth characteristics.

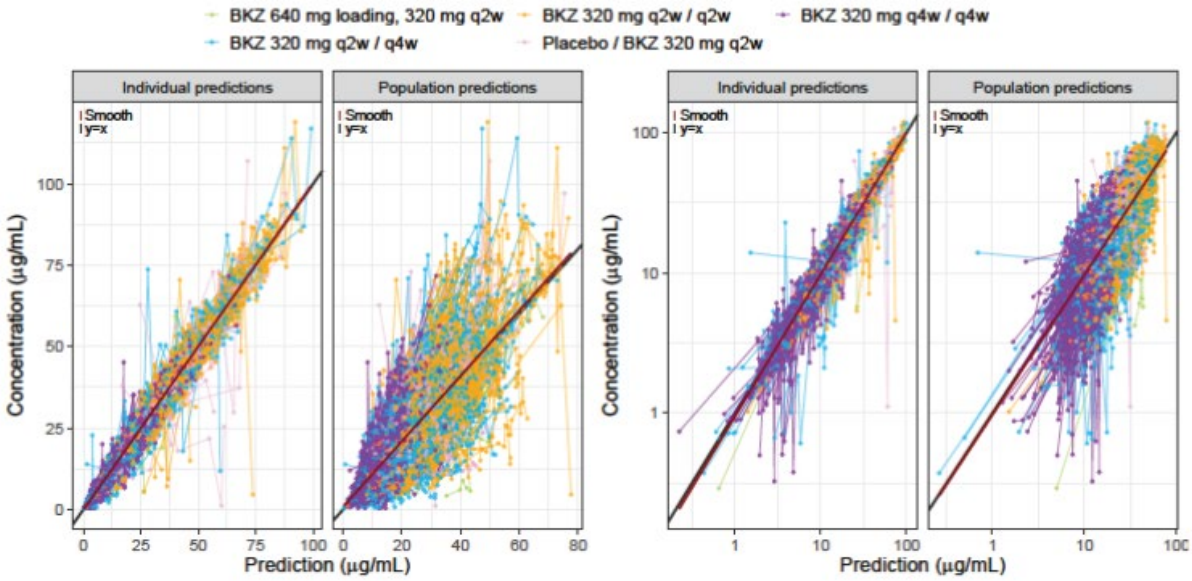


Figure 3. CWRES versus PRED for the final bimekizumab PK model, coloured by treatment group. Data are presented on linear scale (left) and linear-log scale (right). Lines connect data points from the same subject.

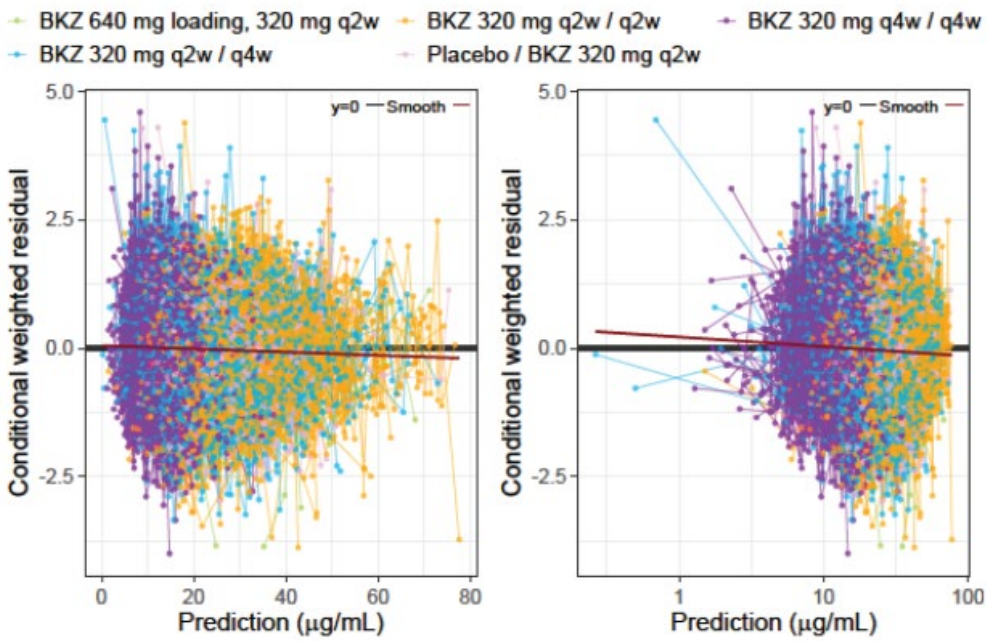


Figure 4. Prediction-corrected visual predictive check of BKZ plasma concentrations versus time after dose, for the bimekizumab PK analysis data set, using the final bimekizumab PK model. Data are presented on a semi-logarithmic scale. Time points associated with BLQ observations were included in the VPC. The observed data are indicated by open circles.

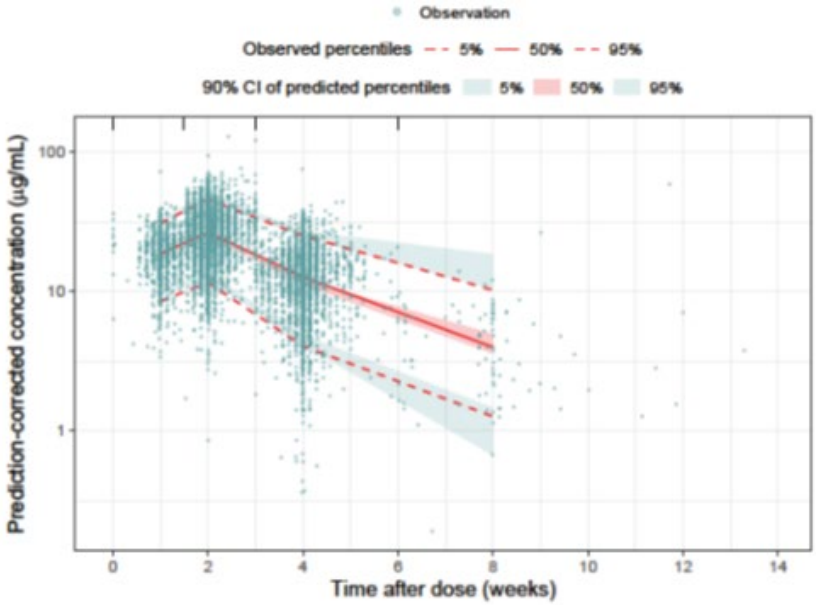
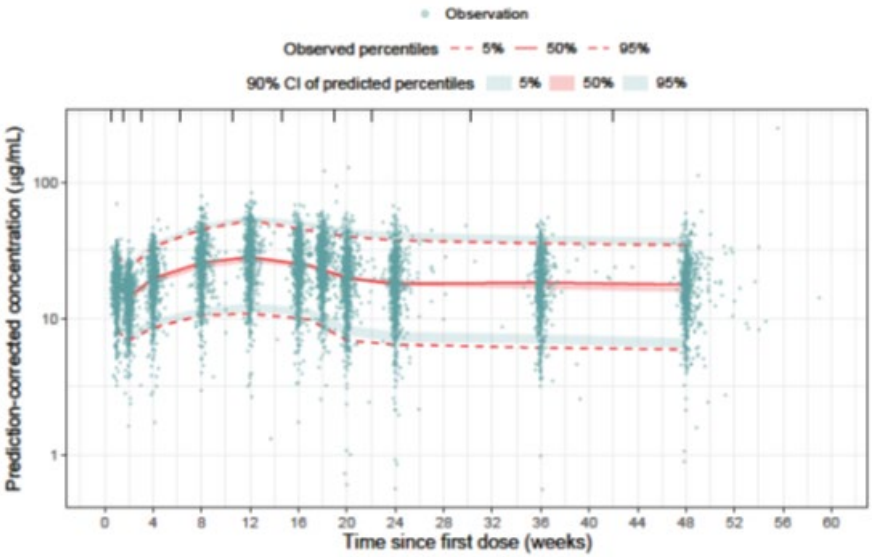


Figure 5. Prediction-corrected visual predictive check of BKZ plasma concentrations versus time since first dose, for the bimekizumab PK analysis data set using the final bimekizumab PK model. Data are presented on a semi-logarithmic scale. Time points associated with BLQ observations were included in the VPC. The observed data are indicated by open circles.



Compared with results from the previous population PK analysis of PSO, PsA and axSpA data, this analysis indicates, for a 70 kg subject, higher CL/F (27% increase), higher V/F (17% increase) and shorter t1/2 (8% decrease) in subjects with HS. The half-life for a 70 kg subject was 23.7 days in a subject with PSO, PsA and axSpA as compared with 21.8 days for a subject with HS.

A forest plot illustrating the influence, or lack of influence, of covariates on AUCt,ss, Cmax,ss, Cmin,ss and t1/2, following dosing of bimekizumab Q4W is presented in Figure 6. The steady-state Cmin,ss following 320 mg bimekizumab dose Q4W and Q2W was predicted to be 41% and 38% lower,

respectively, for a subject weighing 142 kg, compared to a typical subject weighing 95 kg. The steady-state Cmin,ss following 320 mg bimekizumab dose Q4W and Q2W was predicted to be 71% and 65% higher, respectively, for a subject weighing 62 kg, compared to a typical subject weighing 95 kg.

*Figure 6. Forest plots illustrating the effects of covariates on secondary bimekizumab PK parameters ($AUC_{t,ss}$, $C_{max,ss}$, $C_{min,ss}$ and $t_{1/2}$), conditioned on a typical reference subject, based on the final bimekizumab PK model, following dosing of bimekizumab 320 mg **q4w**. Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CIs; these values are calculated based on 200 sample parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference subject (for whom covariate characteristics are provided above the plot) are shown by the solid vertical lines with the associated 90% CIs reflecting uncertainty in the estimated PK parameters; the dashed vertical lines indicate the 80%-125% margins relative to the reference subject. For categorical covariates, the impact of each category is shown, compared to the reference group. For WT, the impact at the 5%, 25%, 75% and 95% percentiles is shown, compared to the median of the covariate.*

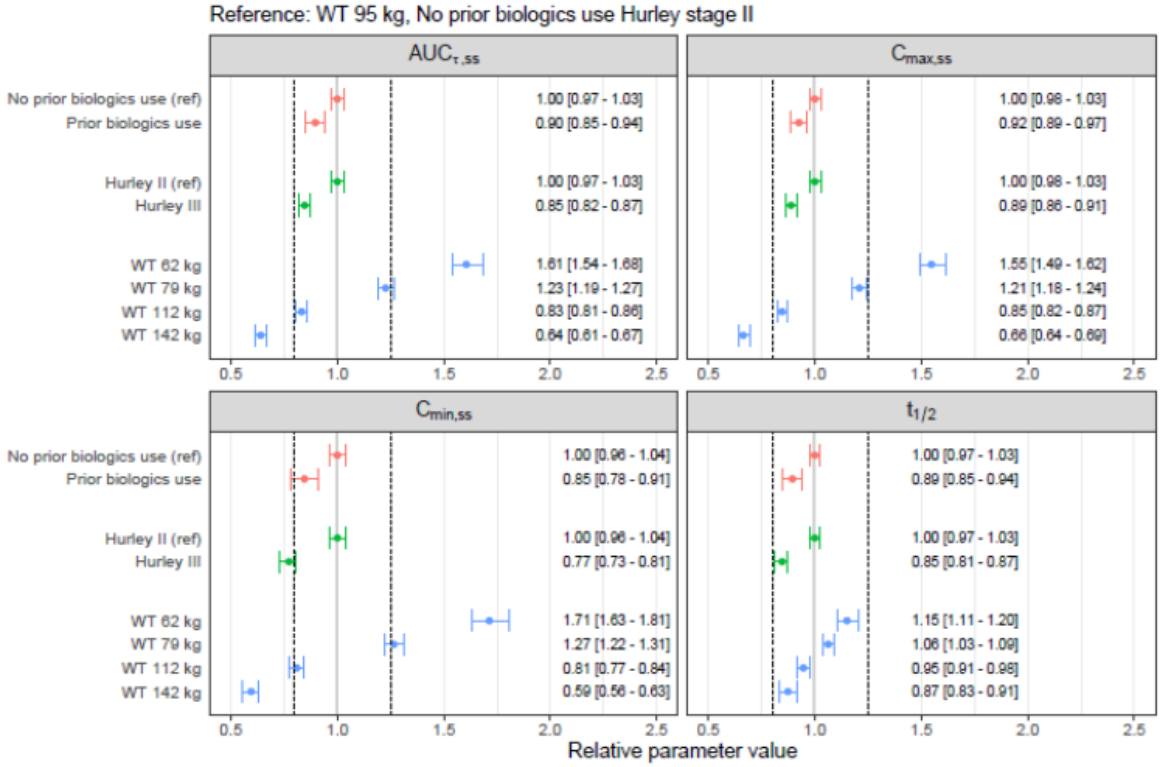


Table 2. Presents the predicted bimekizumab PK metrics stratified by dosing regimen and body weight category

Dosing regimen/WT	n[a]	$AUC_{\tau,ss}$[b,c] (µg · day/mL)	$C_{max,ss}$[b] (µg/mL)	$C_{min,ss}$[b] (µg/mL)	t_{max}[b] (days)	$t_{1/2}$[b] (days)	AR[b]
320 mg q4w							
<120 kg	798	629 [272 - 1480]	30.9 [14.7 - 66.3]	13.4 [3.98 - 37.2]	4.66 [4.16 - 4.95]	18.0 [9.23 - 34.5]	1.52 [1.14 - 2.32]
>=120 kg	202	370 [164 - 955]	19.5 [9.59 - 43.7]	7.22 [2.39 - 20.5]	4.56 [4.07 - 4.86]	15.3 [8.41 - 27.3]	1.39 [1.11 - 1.97]
320 mg q2w							
<120 kg	798	629 [272 - 1480]	50.7 [23.0 - 114]	36.5 [14.4 - 91.8]	3.66 [3.46 - 3.77]	18.0 [9.23 - 34.5]	2.40 [1.54 - 4.07]
>=120 kg	202	370 [164 - 955]	30.7 [14.3 - 74.8]	20.7 [8.30 - 58.2]	3.62 [3.41 - 3.74]	15.3 [8.41 - 27.3]	2.13 [1.46 - 3.35]

[a]: n corresponds to the number of simulated patients.
[b]: Median [2.5th-97.5th percentiles]
[c]: $AUC_{\tau,ss}$ corresponds to AUC over the dosing interval.

- **ER HiSCR**

The final ER model was a proportional odds model that simultaneously estimated the probabilities to be non-responder, HiSCR50-75 responder, HiSCR75-90 responder, HiSCR90-100 responder and HiSCR100 responder. The probability of response was a function of the baseline probability, time (placebo response), bimekizumab concentrations, the previous HiSCR observation and IIV. All study participants were, per definition, non-responders at baseline and the probability of not being a non-responder at baseline was fixed to an extremely low value. Consequently, this parameter had no impact on the probability of response. The placebo response increased in a log-linear manner with time. The active drug model constituted of an Emax function of the individual predicted bimekizumab concentration. The impact of the previous HiSCR observation was included by Markov elements showing an increasing probability to respond with increasing HiSCR response at the previous observation. IIV terms were supported on the probability of response and on the Emax parameter. The final model included the effect of smoking status and baseline AN counts on the overall probability. In the assessment of covariates, the effect of smoking status was the most important. There was no effect of the other covariates explored. The parameter estimates of the final ER HiSCR placebo and drug model are presented in Table 3.

Table 3. Parameter estimates of the final HiSCR response model

Table 23: Parameter estimates of the final HiSCR response model

	Final model			
Run		213		
OFV		24284.0		
Condition number		105.8		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
BL_{50} (θ_1)		-30.0	(FIX)	
DBL_{75} (θ_2)		-1.54	2.10	
DBL_{90} (θ_3)		-1.54	2.21	
DBL_{100} (θ_4)		-0.702	3.61	
Placebo slope	1/day	8.45E+04	(FIX)	
Drug EC_{50}	µg/mL	0.956	32.4	
Drug E_{max}		2.74	3.47	
Markov element,0-3 placebo ($\theta_{corr_{0,placebo}}$)		-1.06	(FIX)	
Markov element,0 (θ_{corr_0})		-2.53	3.29	
Markov element,1 (θ_{corr_1})		-1.61	5.27	
Markov element,2 (θ_{corr_2})		-1.04	7.83	
Markov element,3 (θ_{corr_3})		-0.552	18.5	
Baseline AN counts on overall probability		-0.0115	28.8	
Non-smoking on overall probability		0.498	20.7	
IIV overall probability	(SD)	1.23	5.94	20.0
IIV E_{max}	(CV)	0.914	12.3	49.9

BL_{50}, DBL_{75}, DBL_{90}, DBL_{100} probabilities are reported on the logit scale.
The RSE for IIV parameters are reported on the approximate SD scale.
The probabilities of response on the logit scale (LP) are calculated as followed:

$$LP_{50} = BL_{50} + \log(1 + Placeboslope \cdot 1000000) \cdot time) + \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + \theta_{corr_{0,placebo}} + Markov,drug + baselineANcounts \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + Non-smoking & \text{if non-smoker} \end{cases} + IIV_{response}$$

$$LP_{75} = BL_{50} + DBL_{75} + \log(1 + Placeboslope \cdot 1000000) \cdot time) + \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + \theta_{corr_{0,placebo}} + Markov,drug + baselineANcounts \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + Non-smoking & \text{if non-smoker} \end{cases} + IIV_{response}$$

$$LP_{90} = BL_{50} + DBL_{75} + DBL_{90} + \log(1 + Placeboslope \cdot 1000000) \cdot time) + \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + \theta_{corr_{0,placebo}} + Markov,drug + baselineANcounts \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + Non-smoking & \text{if non-smoker} \end{cases} + IIV_{response}$$

$$LP_{100} = BL_{50} + DBL_{75} + DBL_{90} + DBL_{100} + \log(1 + Placeboslope \cdot 1000000) \cdot time) + \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + \theta_{corr_{0,placebo}} + Markov,drug + baselineANcounts \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + Non-smoking & \text{if non-smoker} \end{cases} + IIV_{response}$$

Markov,drug was one of the parameters θ_{corr_0}, θ_{corr_1}, θ_{corr_2}, θ_{corr_3}, depending of the previous HiSCR observation.

VPCs did not show any major model misspecification (Figure 7). However, the pattern of the proportion of transitions (moving from one responder category to another between two visits) are not fully matched with the observed data (Figure 8), mainly shown as a slight under-prediction of staying in the same responder category.

Figure 7. Visual predictive check of the proportion of non-responders and HiSCR$_{50}$ responders, HiSCR$_{75}$ responders, HiSCR$_{90}$ responders and HiSCR$_{100}$ responders, versus nominal TSFD, for the final placebo and drug HiSCR response model, stratified by treatment. The red points represent the observed proportion of study participants in the analysis data set, the red line connects the dots and the blue line and shaded areas represent the median and the 90% CI of model predictions. Observations at visits Weeks 10, 14, 18, 22, 26, 30, 34, 38, 42, 46 (visits not planned for HiSCR recording) are not included in this figure.

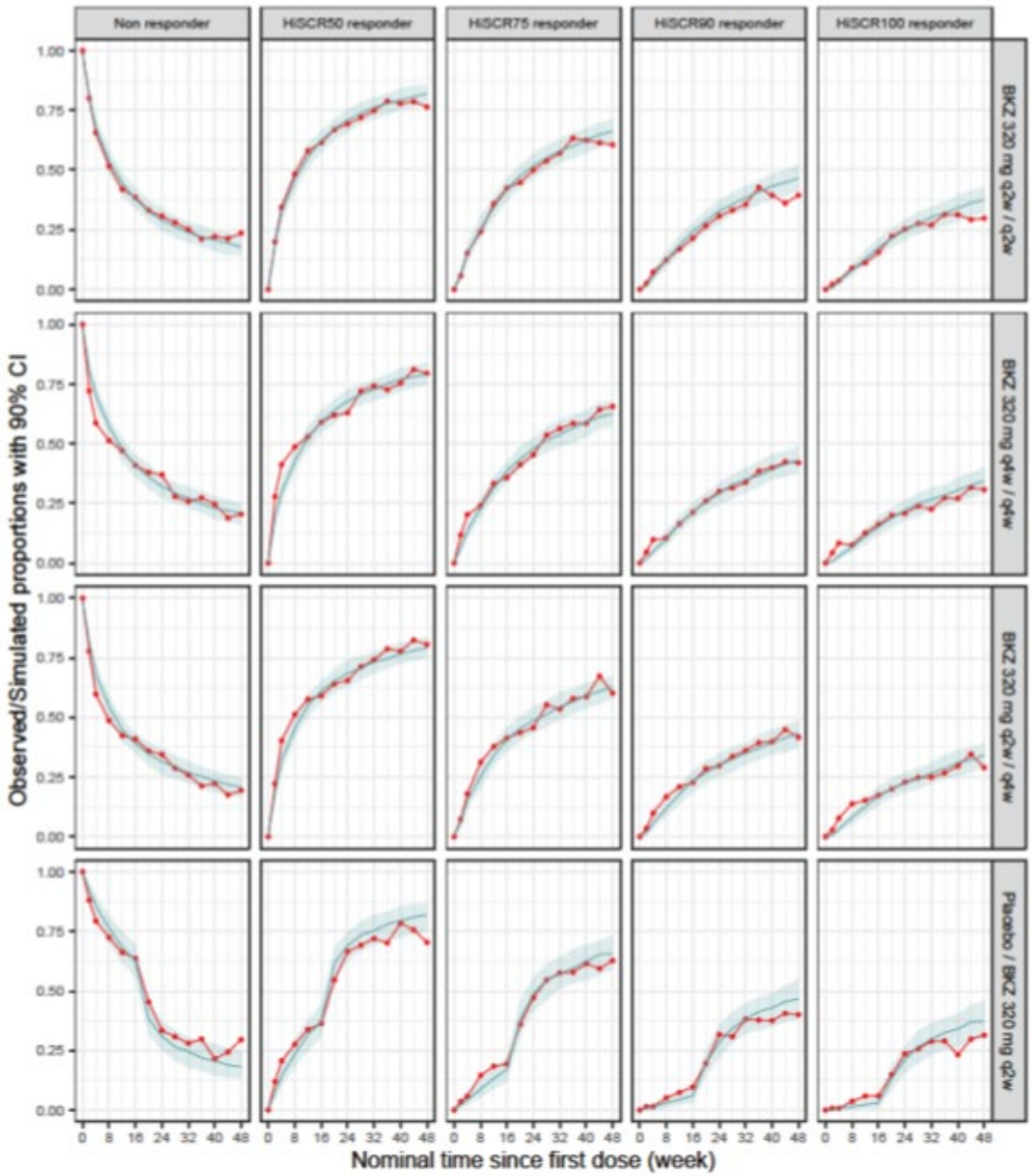
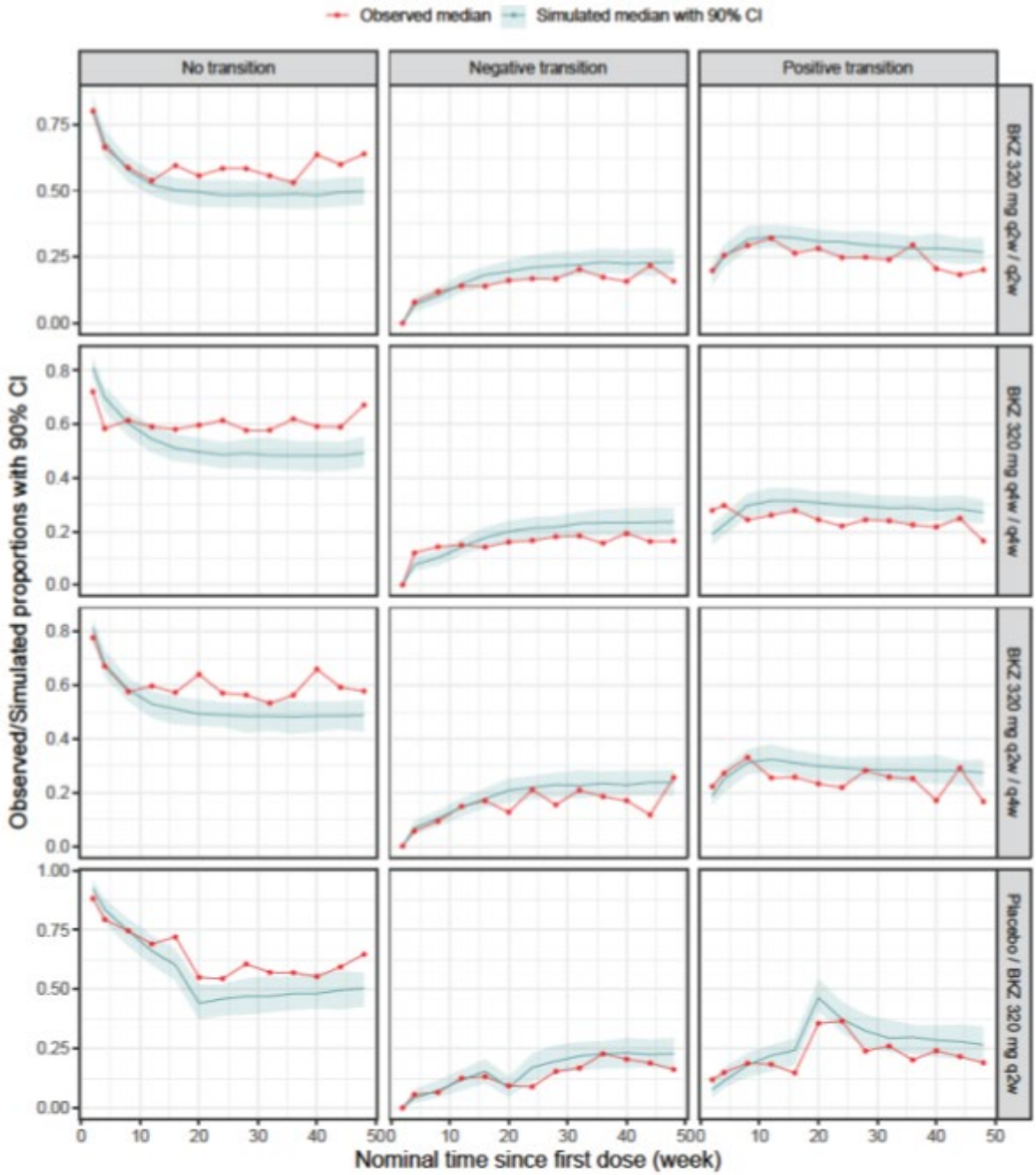


Figure 8. Visual predictive check of the proportion of study participants with no HiSCR transition, negative HiSCR transition, and positive HiSCR transition from the previous visit, versus nominal TSFD, for the final placebo and drug HiSCR response model, stratified by treatment.



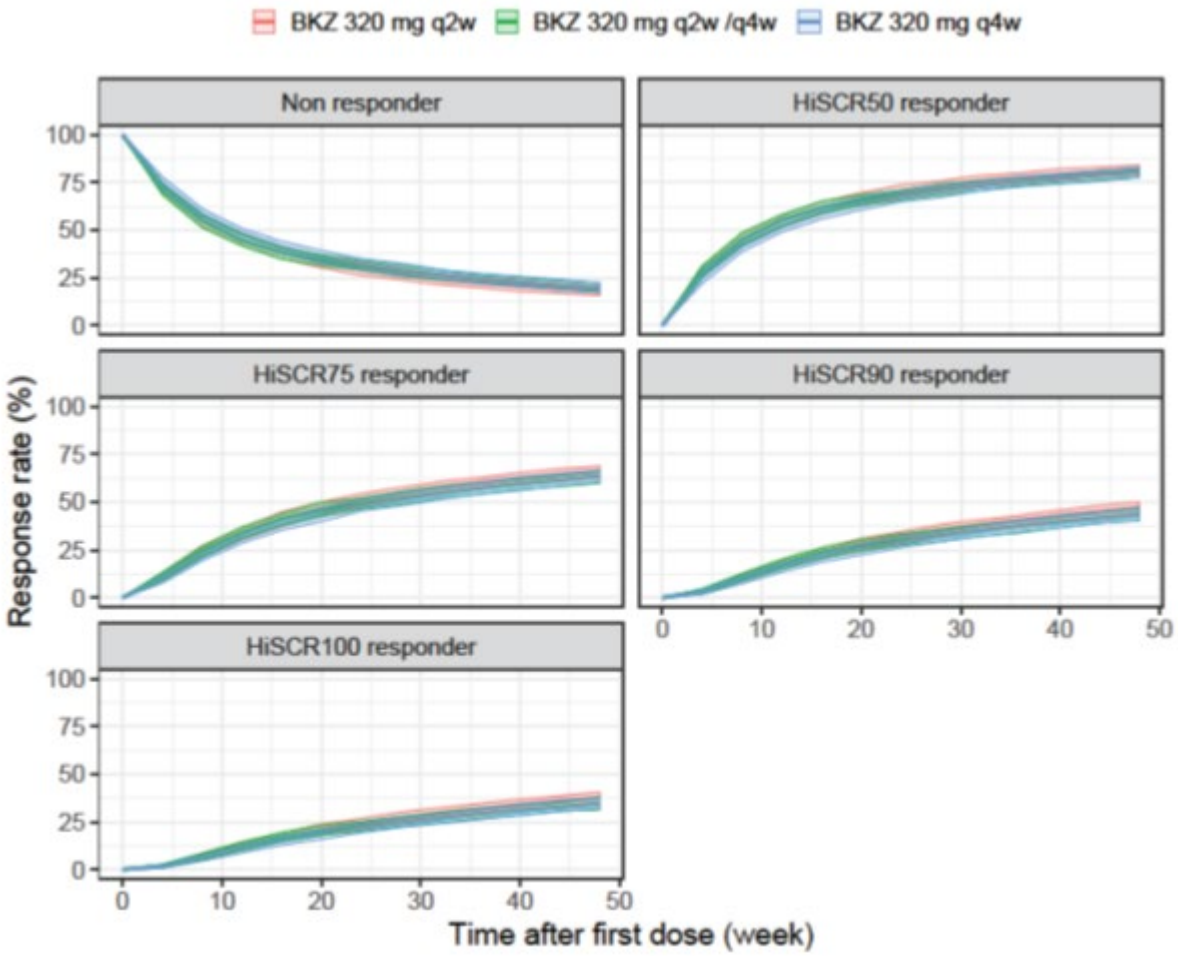
The estimated EC50 was 0.956 mg/mL. The concentration resulting in 90% of maximum effect (EC90) was derived at 8.60 mg/mL, a concentration that is lower than what was observed in 80% of the subjects at nominal time 16 weeks after the first dose (all treatments) as follows. The observed 5th, 10th, 20th percentiles and median concentrations at nominal time Week 16 were 4.89, 7.26, 11.7 and 24.7, respectively, which illustrates that with the studied treatments the majority of the subjects are close to Emax.

Simulations were performed to illustrate the impact of changes in bimekizumab treatment, CL/F parameters, and PK and ER covariates, on the HiSCR. Three treatment regimens were simulated: (i) 320 mg Q4W until Week 48, (ii) 320 mg Q2W until Week 48, (iii) 320 mg Q2W until Week 16, then switch to 320 mg Q4W until Week 48.

The simulated proportions of non-responders, HiSCR50 responders, HiSCR75 responders, HiSCR90 responders, and HiSCR100 responders versus time since first dose (TSFD), following the three dosing regimens are provided in Figure 9, and illustrates similar outcome following dosing of bimekizumab 320 mg Q4W and Q2W. The 95% prediction interval (PI), for the HiSCR50 response rate at Week 16 and 48 for the 320 mg Q4W dose were 55.9-62.1 and 77.7-82.8, respectively. Corresponding PIs for the 320 mg Q2W were 59.1-64.9 and 79.4-84.2.

In the simulations the median predicted (observed) proportion of HiSCR50 responders at Week 16 were 62% (61%) and 59% (59%) following dosing of 320 mg bimekizumab Q2W and Q4W, respectively. The corresponding proportions at Week 48 were 82% (77%) (Q2W) and 81% (79%) (Q4W). The median predicted (observed) proportion of HiSCR75 responders at Week 16 were 41% (42%) and 38% (36%) following dosing of 320 mg bimekizumab Q2W and Q4W, respectively. The corresponding proportions at Week 48 were 66% (61%) (Q2W) and 64% (61%) (Q4W).

Figure 9. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects versus nominal TSFD, colored by dosing regimen. The lines and the shaded areas represent the median and 95% PI response rates, respectively



With respect to the identified ER covariates, non-smokers had higher probability to be a responder compared with current/previous smokers (Figure 10 and Figure 11). The 95% PI, for the HiSCR50 response rate for non-smokers at Week 16 and 48 for the 320 mg Q4W dose were 60.8-70.0 and 80.8-87.8, respectively. Corresponding PIs for previous/current smokers were 51.1-60.2 and 73.8-81.0. An increasing count of AN resulted in a lower probability to be a responder (Figure 12 and Figure 13), specifically for the two highest deciles.

Figure 10. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects at Week 16 versus smoking status, colored by dosing regimen. The lines and the error bars represent the median and 95% PI response rates, respectively

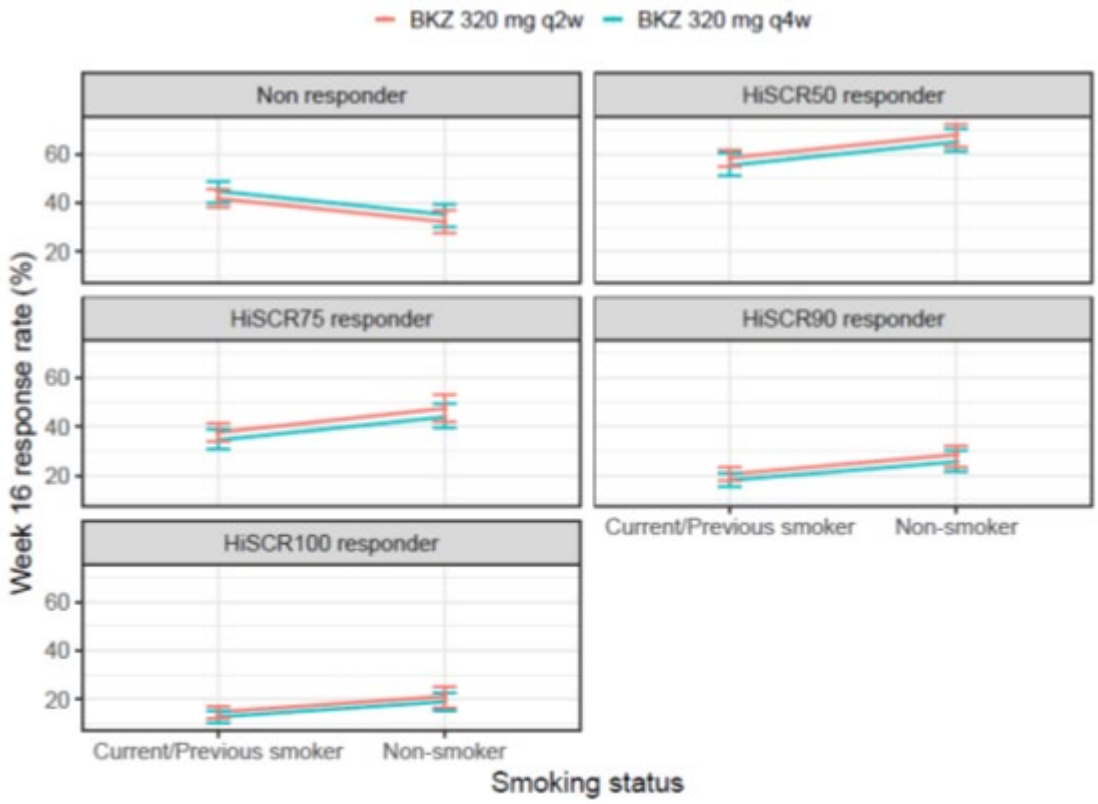


Figure 11. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects at Week 48 versus smoking status, colored by dosing regimen. The lines and the error bars represent the median and 95% PI response rates, respectively

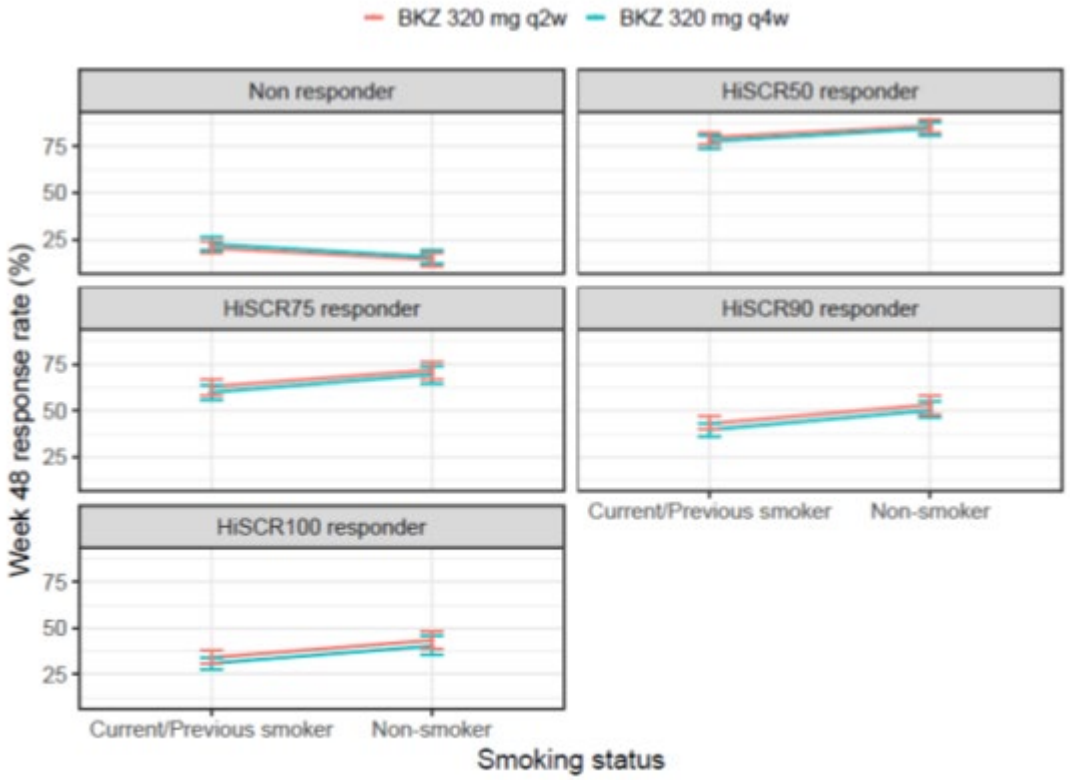


Figure 12. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects at Week 16 versus baseline AN deciles, colored by dosing regimen. The lines and the error bars represent the median and 95% PI response rates, respectively

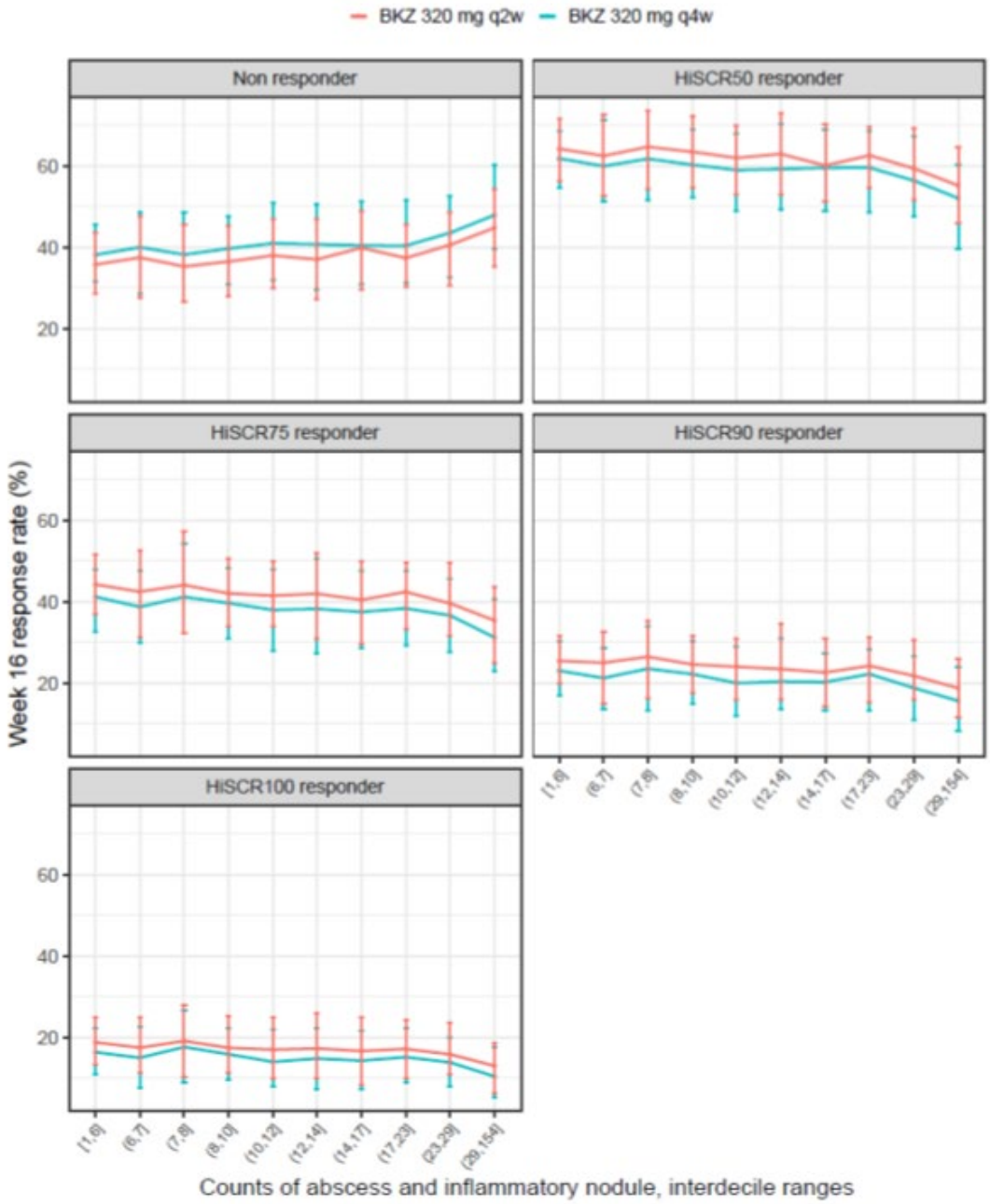
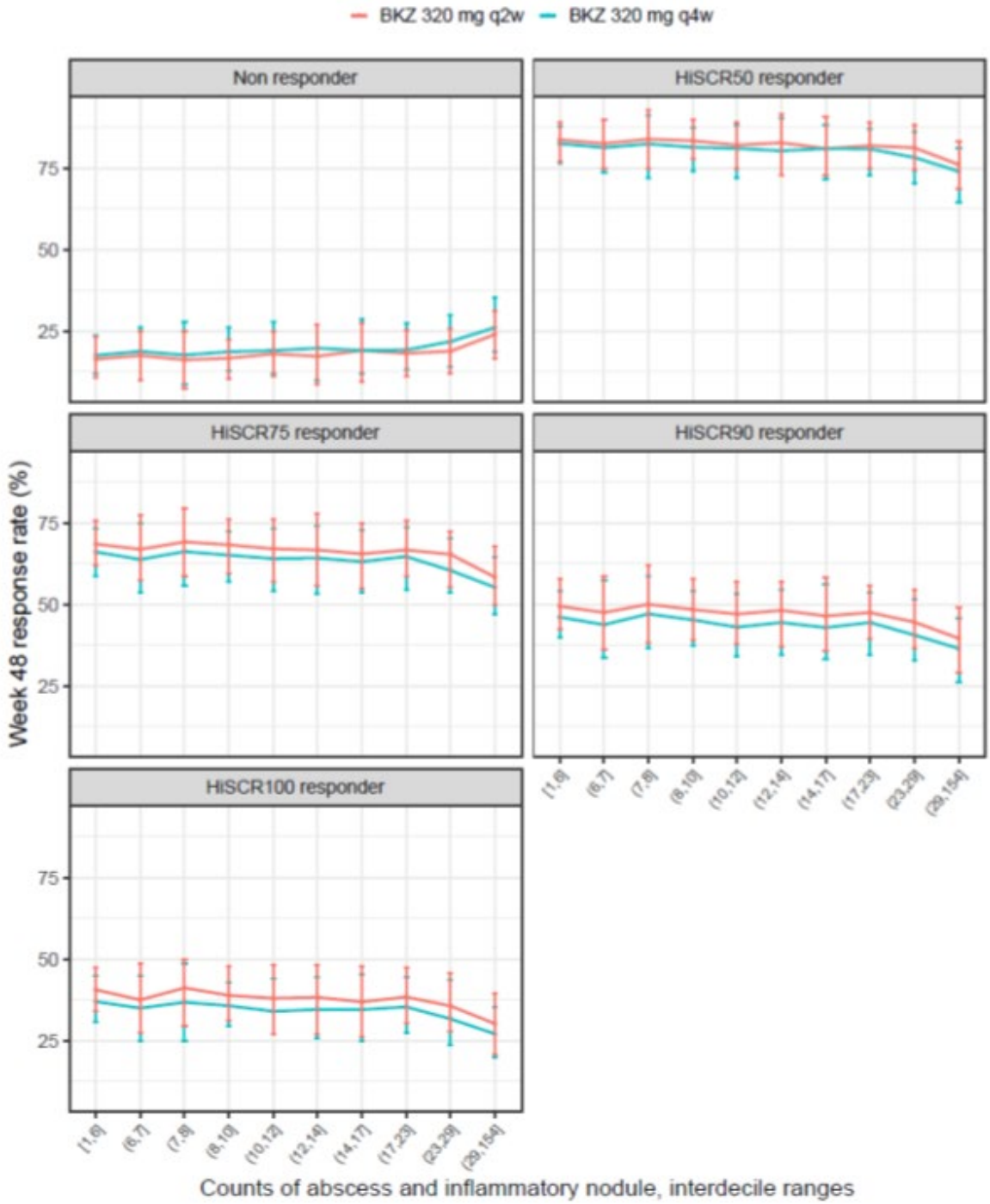


Figure 13. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects at Week 48 versus AN deciles, coloured by dosing regimen. The lines and the error bars represent the median and 95% PI response rates, respectively



The identified PK covariates had a minor impact on the response rates. Despite the marked effect on PK metrics of the most important PK covariate, the impact on response rates over the body weight distribution was not pronounced (Figure 14 and Figure 15).

Figure 14. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects at Week 16 versus WT deciles, colored by dosing regimen. The lines and the error bars represent the median and 95% PI response rates, respectively

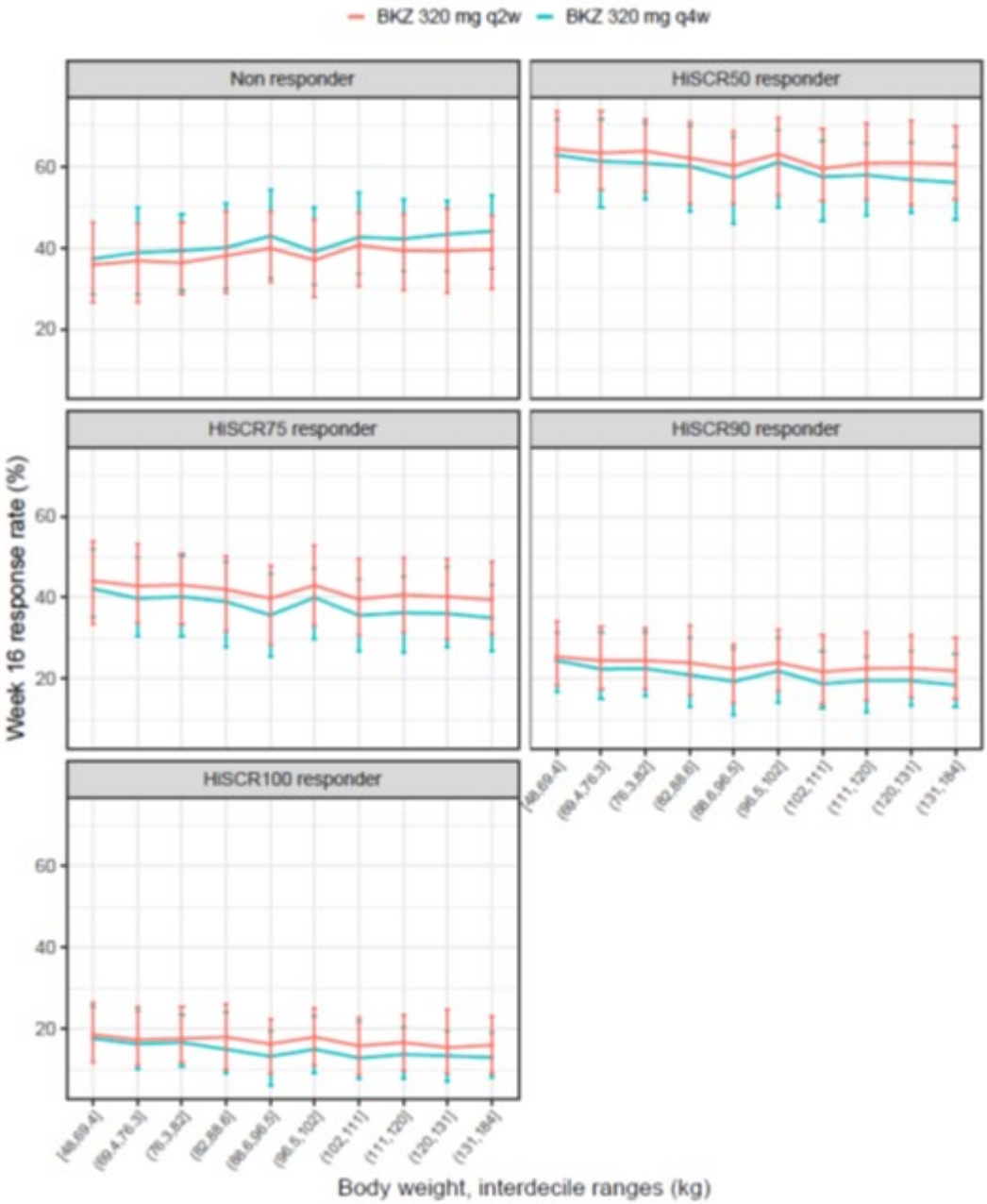
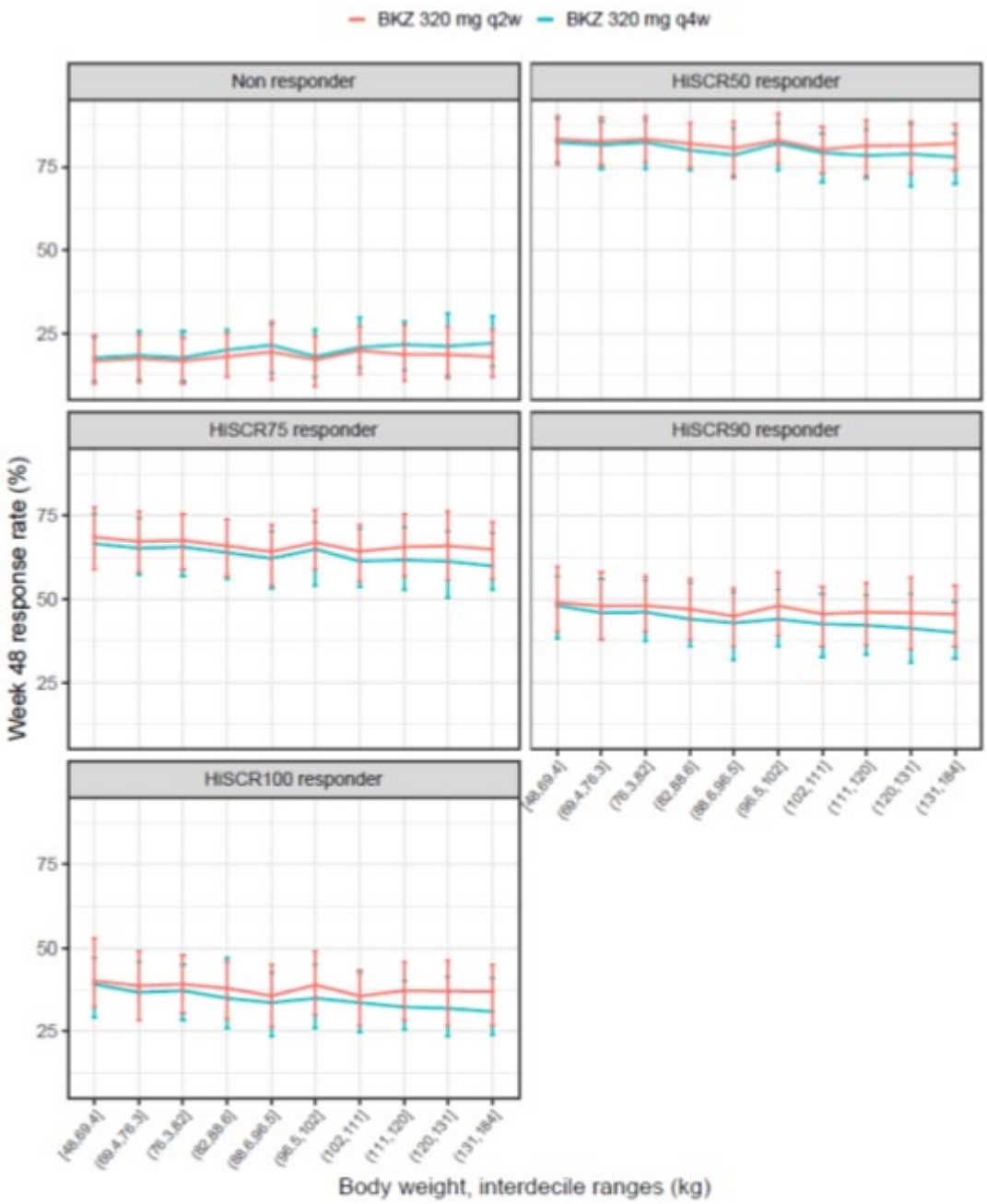


Figure 15. Predicted percentage of non-responder, HiSCR$_{50}$ responder, HiSCR$_{75}$ responder, HiSCR$_{90}$ responder and HiSCR$_{100}$ responder subjects at Week 48 versus WT deciles, colored by dosing regimen. The lines and the error bars represent the median and 95% PI response rates, respectively



Overall, there appears to be no specific sub-group that would benefit from a different dosing regimen than the rest of the HS population.

2.3.5. Discussion on clinical pharmacology

The bioanalytical methods used for analyses of plasma bimekizumab concentrations, ADAb assessments and Nab determination in clinical studies relevant to the present HS submission, were adequately validated.

Population PK analysis

The starting model for this analysis was based on a previously developed bimekizumab popPK model developed from data in patients with PSO, PSA and axSpA. The methods used for model development and evaluation are considered acceptable. Data exclusions were detailed and acceptable.

The final model was a one-compartment model with first-order absorption without lag time and first-order elimination. Compared with results from the previous popPK analysis of PSO, PsA and axSpA data, this analysis indicates, for a 70 kg subject, higher CL/F (27% increase), higher V/F (17% increase) and shorter t1/2 (8% decrease) in subjects with HS.

All retained covariates were further evaluated for their effect sizes (estimated ratios) in relation to the typical individual in the data set. If the estimated ratio and 95% CI corresponding to both the 5th and 95th percentiles (continuous covariates) or all the subgroups (categorical covariates) were within the 0.8–1.25 range, the covariate effect was concluded to have a non-meaningful impact on bimekizumab PK. The covariate was therefore dropped from the final popPK model. The MAH has thus adequately discussed the covariates selected in the final popPK model.

The final model included body weight, prior use of biologics and disease severity on CL/F, as well as body weight on V/F. Body weight had the greatest impact on bimekizumab PK.

The impacts of the remaining covariates on PK parameters and steady-state exposures (prior use of biologics and disease severity) were relatively small.

All PK parameters (fixed and random effects) in the final model were estimated with good precision (RSE<24%). The IIV terms were associated with acceptable shrinkage values: 20%, 33% and 15% for CL/F, V/F and Frel, respectively. The goodness of fit plots showed that the model adequately described the observed data. The pcVPCs showed that the model captured the global trend and the variability of the concentration vs time data reasonably well. Overall, the final model is deemed adequate for deriving individual PK parameters (EBEs) and PK exposure metrics to be used in the subsequent ER modelling analysis.

Based on popPK analyses and using a reference bodyweight of 90 kg, the bimekizumab apparent clearance and volume of distribution, respectively, in patients with HS were estimated to be approximately 31 and 18 % higher than for the PSO, PSA and axSpA indications, with an estimated half-life in HS of 20 days. Consequently, the median steady state trough concentration at a dose of 320 mg every 4 weeks was approximately 40 % lower in HS compared to other indications. SmPC section 5.2 has been updated accordingly.

Exposure-response HiSCR analysis

The final ER HiSCR model was a proportional odds model. The probability of being a non-responder/responder was a function of the baseline probability, time (placebo response), bimekizumab concentrations, the previous HiSCR observation and IIV. The placebo response increased in a log-linear manner with time. The active drug model consisted of an Emax function of the individual predicted bimekizumab concentration.

The concentration resulting in 90% of maximum effect (EC90) was derived at 8.60 mg/mL, a concentration that is lower than what was observed in 80% of the subjects at nominal time 16 weeks after the first dose (all treatments) as follows. The observed 5th, 10th, 20th percentiles and median concentrations at nominal time Week 16 were 4.89, 7.26, 11.7 and 24.7, respectively, which indicates that with the studied treatments most of the subjects are close to Emax.

The ER model provided an adequate description of the observed HiSCR data, as shown in the VPC plots. However, the model did not fully capture the observed proportion of transitions from one responder

category to another between 2 visits. This limitation of the model was acknowledged by the MAH and considered to have no consequence for the predictions of responder rates. This is agreed by the CHMP. As such, the CHMP concluded that the ER model is adequate for its purpose in the present application.

Simulations assessing three dosing regimens (320 mg Q4W until Week 48; 320 mg Q2W until Week 48; 320 mg Q2W until Week 16, then switch to 320 mg Q4W until Week 48) predicted similar HiSCR for Initial (16 weeks) and Maintenance treatment periods for both 320 mg bimekizumab Q4W and Q2W dosing. In the simulations the median predicted (observed) proportion of HiSCR50 responders at Week 16 were 62% (61%) and 59% (59%) following dosing of 320 mg bimekizumab Q2W and Q4W, respectively. The corresponding proportions at Week 48 were 82% (77%) (Q2W) and 81% (79%) (Q4W). The median predicted (observed) proportion of HiSCR75 responders at Week 16 were 41% (42%) and 38% (36%) following dosing of 320 mg bimekizumab Q2W and Q4W, respectively. The corresponding proportions at Week 48 were 66% (61%) (Q2W) and 64% (61%) (Q4W). Overall, these findings support the proposed dosing regimen of 320 mg Q2W until Week 16, then 320 mg Q4W thereafter, as outlined in SmPC section 4.2.

Of the covariates explored, the final model only included the effect of smoking status and baseline AN counts on the overall probability. The simulations predicted that non-smokers had a higher probability to respond (~10% higher) compared with smokers/previous smokers and that subjects with high baseline AN counts (>20) had a lower probability to respond (~ 10% lower) compared with those with lower baseline AN counts. It is agreed that the impact of these covariates on response rates was minor. Therefore, a higher dose is not warranted for smokers/previous smokers or subjects with high baseline AN counts.

Of the identified PK covariates, the CHMP agreed that prior use of biologics and disease severity, had a minor impact on response rates. Despite the marked effect of body weight on bimekizumab exposure, the PK/PD simulation data and clinical data do not support a separate posology for overweight patients. As such, the CHMP agreed that the recommended posology of 320 mg Q2W followed by 320 mg Q4W after Week 16 is appropriate for all HS patients, including those with body weight >100 kg. Results from study HS0005 will likely provide additional information on dosing recommendations in (overweight) patients. The MAH agreed to re-evaluate the dosing recommendation in overweight patients once results from study HS0005 become available and amend the PI accordingly if needed.

2.3.6. Conclusions on clinical pharmacology

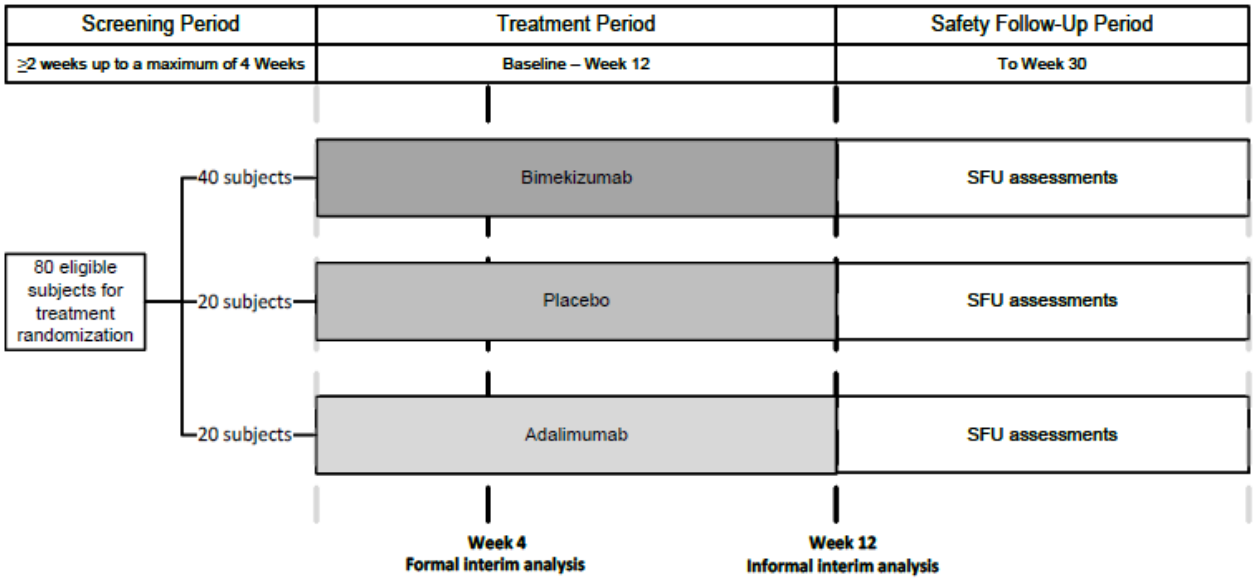
The clinical pharmacology package supports the extension of indication to HS patients and the proposed dosing frequency of 320 mg Q2W followed by 320 mg Q4W after week 16 for all HS patients.

2.4. Clinical efficacy

2.4.1. Dose response study

HS0001 was a phase 2 multicentre, randomised, investigator-blind, study participant-blind, placebo-controlled, active reference arm study to assess the efficacy, safety, and PK of bimekizumab in eligible adult study participants with moderate to severe HS.

Figure 16. Schematic diagram for HS0001



IMP=investigational medicinal product; SFU=Safety Follow-Up

Note: The first administration of IMP occurred at Baseline (Visit 2). The final dose of IMP was at Week 10; the primary efficacy variable was assessed at Week 12. The SFU Period commenced from a study participant's final dose of IMP.

Note: In order to maintain the blind throughout the study, a double-dummy approach was applied using placebo injections such that all study participants received the same number of injections at each corresponding visit.

Note: The Week 4 formal interim analysis was replaced with an informal interim analysis in Protocol Amendment 1.

Statistical Methods

A dose response study in a Bayesian framework was designed such that an informative prior based on a Beta function provided at least 99% probability that the chance of responses from bimekizumab are greater than placebo by at least 97.5% with a sample size of N=80. Both vague and informative priors were used in the analysis.

Results

Table 4. Disposition and discontinuation reasons (RS) (HS0001)

Disposition	PBO N=22 n (%)	ADA N=22 n (%)	BKZ N=46 n (%)	All Participants N=90 n (%)
Randomized	22 (100)	22 (100)	46 (100)	90 (100)
Completed study	18 (81.8)	17 (77.3)	38 (82.6)	73 (81.1)
Completed Week 4	20 (90.9)	21 (95.5)	46 (100)	87 (96.7)
Completed Week 12	19 (86.4)	18 (81.8)	42 (91.3)	79 (87.8)
Discontinued study	4 (18.2)	5 (22.7)	8 (17.4)	17 (18.9)
Primary reason for discontinuation				
AE	0	0	1 (2.2)	1 (1.1)
Lack of efficacy	0	0	0	0
Protocol violation	0	0	0	0
Consent withdrawn (not due to AE)	3 (13.6)	3 (13.6)	2 (4.3)	8 (8.9)
Lost to follow up	1 (4.5)	0	5 (10.9)	6 (6.7)
Other	0	2 (9.1)	0	2 (2.2)

ADA=adalimumab; AE=adverse event; BKZ=bimekizumab; PBO=placebo; RS=Randomized Set
Note: A study participant was defined as completing the study if all visits up to Visit 12 (Week 30) were completed. A study participant was defined as completing Week 4 and Week 12, respectively, if adequate efficacy data were available in the database to calculate the primary efficacy variable at the respective visit.

Study participant demographics

The mean age of study participants was 36.7 years overall (range: 18 to 69 years); the mean ages of study participants in the placebo and bimekizumab groups were similar (40.7 and 37.4 years, respectively) and were higher than the adalimumab group (31.1 years). The majority of study participants were female (69.3%), white (69.3%), and not of Hispanic or Latino ethnicity (88.6%). Overall, the mean weight was 97.60 kg, and the mean BMI was 34.76 kg/m2. Study participants were predominantly from the US, Australia, and Russia (50.0%, 21.6%, and 12.5%, respectively).

Baseline characteristics

The mean duration of disease was 9.04 years (range: 0.2 to 38.2 years). Based on the HS Physician Global Assessment (PGA), the majority of study participants had very severe lesions (62.5%), followed by moderate lesions (31.8%), and severe lesions (4.5%); 1 study participant (1.1%) had mild lesions and no study participants had clear or minimal lesions at Baseline.

Overall, approximately half of study participants had Baseline Hurley Stage II or Stage III (48.9% and 51.1%, respectively), and most of the study participants had erythema scores of 2 or 3 at Baseline (44.3% and 46.6%, respectively). The mean modified Sartorius score was 101.6 overall.

Overall, the mean International Hidradenitis Suppurativa Severity Score System (IHS4) score was 43.1 (indicating severe disease), and the mean PGA of skin pain scores (average and worst pain in the last 24 hours) were 4.1 and 5.2, respectively. Overall, the mean total DLQI score was 12.6, and the mean EQ-5D-3L index and visual analog scale (VAS) scores were -0.2550 and 63.5, respectively. Overall, the mean total HADS-A and HADS-D scores were in the normal range (5.0 and 3.2 respectively [normal range: 0 to 7]).

Total lesion counts at Baseline by Baseline Hurley Stage were generally balanced across treatment groups and were reflective of a population with moderate to severe HS. Overall, study participants in the

bimekizumab group had a lower mean abscesses and inflammatory nodules (AN) count (14.5) compared with the placebo and adalimumab groups (22.1 and 20.0, respectively).

Similarly, study participants in the bimekizumab group had a lower overall mean inflammatory nodules (IN) count (9.8) compared with the placebo and adalimumab groups (16.4 and 15.8, respectively). Overall, AN and DT (fistula/sinus tract) counts were similar across treatment groups.

Prior and concomitant diseases

The most frequently reported conditions/diseases at Baseline by PT were hypertension (21.6%), drug hypersensitivity and asthma (15.9% each), and depression (12.5%). No study participants had Baseline Inflammatory bowel disease (IBD) reported as a comorbidity (e.g., Crohn's disease (CD) or ulcerative colitis).

Prior medication

The most frequently reported prior HS medications by ATC Level 1 code overall were dermatologicals (70.5%), anti-infectives for systemic use (63.6%), and various (22.7%). The incidence of prior HS medication use was generally balanced across treatment groups (range: 91.3% to 100%). The incidence of prior HS medication use in each ATC Level 1 code was generally balanced across treatment groups with the exception of dermatologicals, which were reported at a lower incidence in the bimekizumab group (58.7%) compared with the placebo and adalimumab groups (85.7% and 81.0%, respectively).

Concomitant medications

The most frequently reported concomitant HS medications by ATC Level 1 code overall were dermatologicals (69.3%), various (23.9%) and musculo-skeletal system and anti-infectives for systemic use (14.8% each). The incidence of concomitant HS medication use in each ATC Level 1 code was generally balanced across treatment groups with the exception of dermatologicals, which were reported at a lower incidence in the bimekizumab group (60.9%) compared with the placebo and adalimumab groups (76.2% and 81.0%, respectively).

Rescue medication

A total of 17 study participants (19.3%) took rescue medication during the study (Week 0 to Week 30). A higher incidence of study participants in the adalimumab group (38.1%) required rescue medication compared with the placebo and bimekizumab groups (14.3% and 13.0%, respectively). Anti-infectives for systemic use were the most frequently reported rescue medications used during the study by ATC Level 1 code (12.5%). The most frequently reported rescue medications used during the study by PT were adalimumab (4.5%) and tramadol (3.4%).

Pharmacokinetic results

Geometric mean trough plasma concentrations of bimekizumab increased through Week 8 and were within the expected concentration ranges at each visit, although the median concentrations were lower than anticipated based on other indications. The geometric mean plasma bimekizumab concentration then decreased at Week 12 and was not calculable at the safety follow up (SFU) Visit.

Figure 17. Spaghetti Plot of Individual Plasma Concentrations of Bimekizumab vs Actual time. Analysis Set: Pharmacokinetic Per-Protocol Set

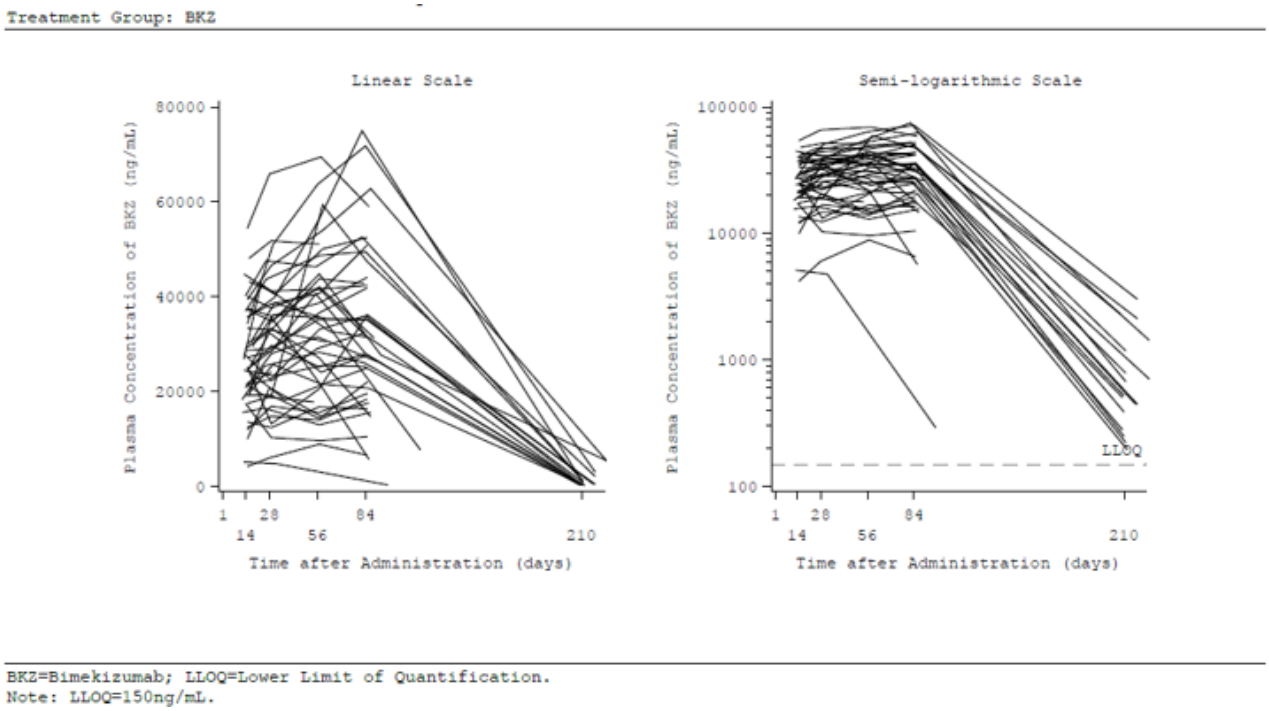
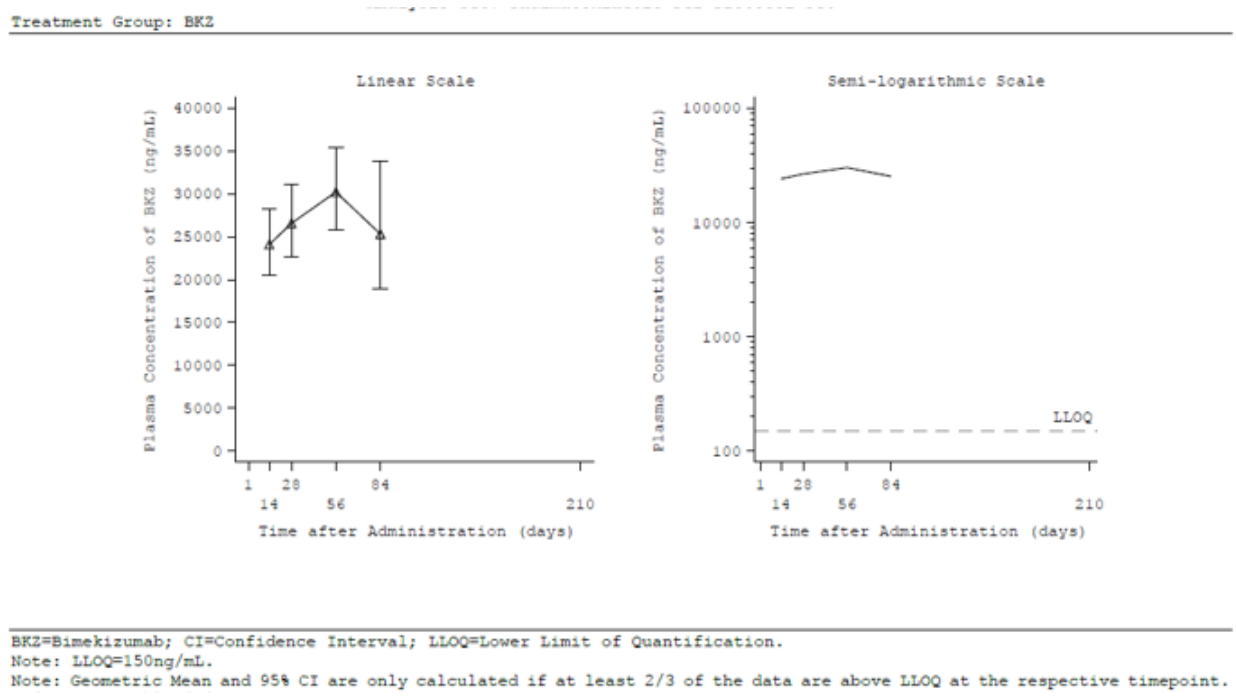


Figure 18. Geometric Mean (95% CI) Plasma Concentrations of Bimekizumab vs Scheduled Time. Analysis Set: Pharmacokinetic Per-Protocol Set



Immunogenicity results

Two study participants (4.3%) out of the 46 study participants in the bimekizumab group were confirmed ADAb positive at Baseline and were not considered treatment-emergent ADAb positive. One study participant was considered pre-ADAb positive and treatment-emergent reduced, and the other study participant was positive at pre-dose only. During the Treatment Period, 6 study participants were

treatment emergent ADAb positive and an additional 2 study participants were only ADAb positive at the SFU. Of the 6 study participants who were treatment-emergent ADAb positive during the Treatment Period, 3 study participants were considered transient and 3 study participants were considered persistent (when the SFU was taken into account). Overall, 9 study participants (19.6%) in the bimekizumab group were confirmed ADAb positive at any point during the study.

The first ADAb treatment-emergent positive sample was seen at Week 2 in 1 study participant. There were no apparent trends in the status of ADAb positivity and the efficacy of bimekizumab in this study.

Efficacy results

Primary analysis of the primary efficacy variable

The primary analysis compared week 12 HiSCR between the bimekizumab and placebo arms using a Bayesian analysis and the per-protocol set. Proof-of-concept was to be declared in this study if the estimated posterior probability of the difference in HiSCR rates between bimekizumab and placebo treatment groups at Week 12 using the Bayesian logistic regression model was ≥97.5%. The results from the primary efficacy analysis of HiSCR at Week 12 indicated that this predefined success criterion was met (i.e. a posterior probability of 99.8% was observed), with statistical evidence in favour of the true HiSCR rate being higher in the bimekizumab group compared with the placebo group at Week 12.

Table 5. Bayesian analysis of HiSCR at Week 12 using informative prior distributions and NRI (PPS)

Posterior Response Rate (%)	**PBO N=3000**	**BKZ N=3000**
Mean (SD)	26.1 (6.8)	57.3 (7.4)
Median	25.7	57.4
95% credible interval	13.8, 40.5	42.4, 71.4
95% HPD	12.9, 39.2	42.6, 71.6
Posterior Difference from PBO (%)		
Mean (SD)	31.2 (10.1)	
95% credible interval [a]	11.0, 50.4	
95% HPD	11.2, 50.5	
Pr [Diff>0%] (%)	99.8	

ADA=adalimumab; BKZ=bimekizumab; CI=confidence interval; Diff=difference; HiSCR=Hidradenitis Suppurativa Clinical Response; HPD=highest posterior density; N=number of simulated posterior samples; NRI=nonresponder imputation; PBO=placebo; PPS=Per-Protocol Set; Pr=probability; SD=standard deviation

Note: Results were based on a Bayesian logistic regression model where the number of responders was assumed to follow a binomial distribution. Treatment and Baseline Hurley Stage were included as predictors in the model.

Note: Pr[Diff > 0%] (%) = probability that the BKZ response rate was greater than the PBO response rate.

Note: Study participants with missing data at Week 12 (due to early discontinuation or other reason) were considered as nonresponders for the analysis.

[a] 95% credible and HPD intervals are presented for the BKZ vs PBO comparison, and 60% credible and HPD intervals are presented for the BKZ vs ADA comparison (Table 8-2).

Supportive analyses

Bayesian analysis of HiSCR at Week 12 – comparison to adalimumab

A comparison was made between the HiSCR rates in the bimekizumab and adalimumab treatment groups in order to assess whether any improvements in response rate observed with bimekizumab treatment are comparable to the current standard-of-care treatment.

Table 6. Bayesian analysis of HiSCR at Week 12 using informative prior distributions and NRI - comparison of BKZ to ADA (PPS)

Posterior Response Rate (%)	ADA N=3000	BKZ N=3000
Mean (SD)	59.5 (7.7)	57.3 (7.4)
Median	59.7	57.4
95% credible interval	44.2, 73.9	42.4, 71.4
95% HPD	44.6, 74.2	42.6, 71.6
Posterior Difference from ADA (%)		
Mean (SD)	-2.2 (10.6)	
60% credible interval	-11.2, 6.6	
60% HPD	-10.9, 7.0	
Pr[Diff>0%] (%)	42.1	

ADA=adalimumab; BKZ=bimekizumab; Diff=difference; HiSCR=Hidradenitis Suppurativa Clinical Response; HPD=highest posterior density; N=number of simulated posterior samples; NRI=nonresponder imputation; PPS=Per-Protocol Set; Pr=probability; SD=standard deviation.
Note: Results were based on a Bayesian logistic regression model where the number of responders was assumed to follow a binomial distribution. Treatment and Baseline Hurley Stage were included as predictors in the model.
Note: Pr[Diff > 0%](%) = probability that the BKZ response rate was greater than the ADA response rate.
Note: Study participants with missing data at Week 12 (due to early discontinuation or other reason) were considered as nonresponders for the analysis.

Other supportive analyses

The estimated HiSCR rate at Week 12 was higher in the bimekizumab group (56.9% [95% CI:41.4%, 71.2%]) compared with the placebo group (23.7% [95% CI: 10.2%, 45.8%]), with an odds ratio of 4.3 (95% CI: 1.3, 13.9). This indicated that the odds of a response following treatment with bimekizumab were 4.3 times higher compared with treatment with placebo. These results are consistent with those observed in the primary Bayesian analysis of HiSCR at Week 12 using NRI for the PPS.

Table 7. Analysis of HiSCR at Week 12 – NRI frequentist analysis (PPS)

Statistic	PBO	BKZ
n	20	44
Response rate (%)	23.7	56.9
95% CI for response rate	10.2, 45.8	41.4, 71.2
Odds ratio vs PBO	-	4.3
95% CI for odds ratio	-	1.3, 13.9

BKZ=bimekizumab; CI=confidence interval; HiSCR=Hidradenitis Suppurativa Clinical Response; NRI=nonresponder imputation; PBO=placebo; PPS=Per-Protocol Set.
Note: Results were based on a longitudinal generalized estimating equation model for a binary outcome, controlling for Baseline. Hurley Stage and including treatment, visit, and a treatment by visit interaction term. An unstructured covariance matrix was used for this analysis.
Note: Study participants with missing data at a visit due to early discontinuation were considered as nonresponders in the analysis. Study participants with missing HiSCR at a visit not due to discontinuation were treated as missing at random in the model.

A formal statistical analysis was only performed for the primary efficacy variable and all other efficacy variables were summarised descriptively.

Patient's Global Assessment (PGA) of skin pain at Week 12

Change and percentage change from Baseline in PGA of skin pain over time. Overall, both the bimekizumab and placebo groups had moderate pain at its worst in the last 24 hours at Baseline (mean scores of 4.7 and 5.6, respectively). Greater mean reductions from Baseline in PGA scores for pain at its worst were observed in the bimekizumab group compared with the placebo group beginning at Week 2 and consistently at each visit through Week 12.

At Week 12, the overall proportion of study participants with at least a 30% reduction and at least a 1-unit reduction from Baseline in the PGA of skin pain at Week 12 was higher in the bimekizumab group (64.3%) compared with the placebo group (36.8%).

Lesion counts

Greater reductions from Baseline in mean relevant lesion counts (comprising the HiSCR) were observed in the bimekizumab group compared with the placebo group beginning at Week 2 and consistently through Week 12.

Disease flare

The incidence of disease flare at any time during the Treatment Period was lower in the bimekizumab group (4 study participants [8.7%]) compared with the placebo group (11 study participants [52.4%]). A lower incidence of disease flare was observed in the bimekizumab group compared with the placebo group beginning at Week 2 and consistently at each visit through Week 12.

IHS4

Overall, the mean reduction from Baseline in IHS4 scores was substantially greater in the bimekizumab group compared with the placebo group beginning at Week 2 and consistently at each visit through Week 12.

HS-Physician's Global Assessment

Overall, more study participants in the bimekizumab group shifted from very severe to less severe categories, and more study participants shifted to clear, minimal and mild compared with the placebo group.

DLQI

Overall, greater improvements in study participants' HRQoL (reductions in total DLQI score indicate improvement), as measured by the mean change from Baseline in total DLQI score, were observed in the bimekizumab group compared with the placebo group beginning at Week 2 and consistently through Week 12.

Depth of response

For the modified Hidradenitis Suppurativa Clinical Response (mHiSCR), the mHiSCR75 and mHiSCR90 responder rates were higher for the bimekizumab group compared with the placebo group beginning at Week 2 and consistently through Week 12. Study participants who received bimekizumab also had a greater depth of response than study participants who received adalimumab, with higher mHiSCR75 and mHiSCR90 responder rates at all timepoints from Week 4 through Week 12.

2.4.2. Main studies

HS0003 and HS0004: Phase 3, randomised, double blind, placebo controlled, multicenter, pivotal studies evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS.

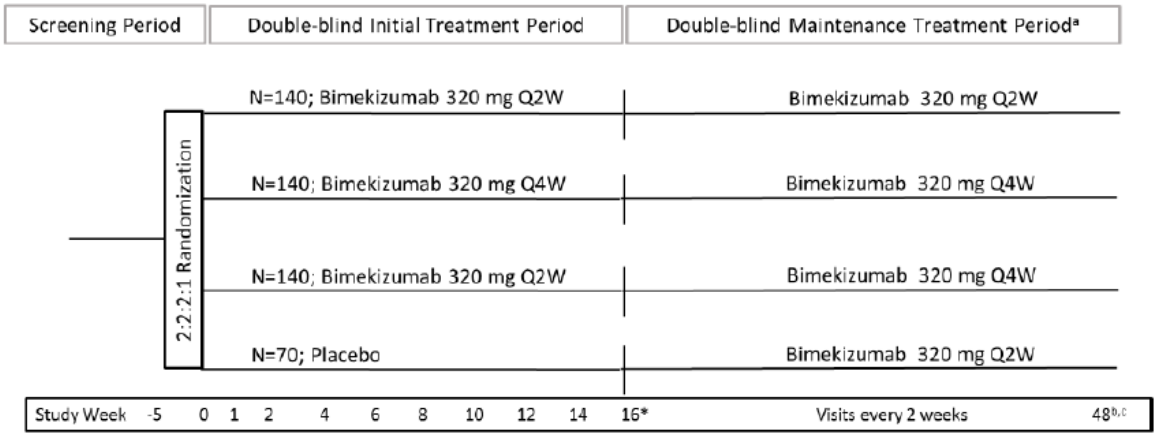
The clinical efficacy is supported by two pivotal Phase 3 studies of identical design, HS0003 and HS0004**.** Both studies were randomised, double-blind, placebo controlled parallel group multicentre study evaluating the efficacy of bimekizumab 320mg every 4 weeks (Q4W) and every 2 weeks (Q2W) in the treatment of moderate to severe HS. The double-blind 16-week initial treatment period (ITP) and the double-blind 32-week (Weeks 16 to 48) maintenance treatment period (MTP) have been completed for both the HS0003 and HS0004 studies. The 20-week SFU Period for HS0003 is ongoing as of the Week 48 data cut-off (14 November 2022). For both studies, the MAH provides analyses for all 48 weeks of efficacy data.

As both studies were identical in design and the MAH has conducted analyses pooling results from the two studies, the Methods and Results sections present the studies together, with differences between the studies highlighted as relevant. The results of both Phase 3 pivotal studies are presented individually; in addition, data from pooled analysis for HS0003 and HS0004 are presented as supportive data.

Methods

HS0003 and HS0004 had identical designs and were conducted at non-overlapping study sites. The overall study design consisted of a Screening Period (≥14 days to ≤5 weeks), a double-blind, 48-week Treatment Period comprising a 16-week ITP and 32-week MTP; and a 20-week SFU Period following the final injection of investigational medicinal product (IMP) if study participants did not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment.

Figure 19. Schematic diagram for HS0003 and HS0004



AN=abscess and inflammatory nodule; $HiSCR_{50}$=a ≥50% reduction in the total abscess and inflammatory nodule count with no increase from Baseline in abscess or draining tunnel count; IMP=investigational medicinal product; Q2W=every 2 weeks; Q4W=every 4 weeks; SFU=Safety Follow-up

*Week 16=primary endpoint ($HiSCR_{50}$ bimekizumab versus placebo)

[a] Study participants should discontinue from the study from Week 32 on if no partial response is achieved (partial response is defined as ≥25% improvement in AN count relative to Baseline [Week 0] lesion values,)

[b] Study participants achieving improvement of at least 25 % in AN count continue in HS0005 (Extension Study).

[c] 20-week SFU (from last IMP injection) for any study participant who discontinues from study prior to Week 48, or who does not continue in HS0005.

Pooling strategy

As the studies were identical in design, efficacy data during the placebo-controlled periods of HS0003 and HS0004 were combined in a pool designated as Pool E1 to investigate efficacy in selected subgroups, as well as to yield estimates of the treatment effect of bimekizumab vs placebo with greater precision based on this combined population from Baseline to Week 16. HS0001 was excluded from this pool due to the shorter duration of the placebo-controlled period (12 weeks vs 16 weeks), and also due to the loading dose regimen that was not mirrored in the Phase 3 studies. An integrated analysis of data from the two Phase 3 studies (HS0003 and HS0004) was prespecified in the SAP for the integrated summary of efficacy (ISE).

Efficacy data for the double-blind 48-week treatment periods of HS0003 and HS0004, i.e., including both the ITP and the MTP, were combined in a pool designated as Pool E2. Pool E2 was used to evaluate the long-term efficacy data for the Q2W and Q4W bimekizumab arms from Baseline through to Week 48. This pool was also used to investigate the effect of reducing the dosing regimen from bimekizumab 320mg Q2W to Q4W, as well as to show the onset and maintenance of treatment effect for participants originally randomised to placebo, and switched to bimekizumab 320mg Q2W for Week 16 to 48.

Study participants

The following main eligibility criteria were applied in both pivotal studies HS0003 and HS0004:

Main inclusion criteria:

1. Male and female subjects ≥ 18 years of age.
2. Diagnosis of HS ≥ 6 month prior to baseline.
3. HS lesions present in at least 2 distinct anatomic areas (e.g., left and right axilla), 1 of which must have been at least Hurley Stage II or Hurley Stage III at both the Screening and Baseline Visits.
4. Subjects with moderate to severe HS defined as:
    - A total of ≥ 5 inflammatory lesions, (i.e., number of abscesses plus number of inflammatory nodules).
5. Study participant must have had a history of inadequate response to a course of systemic antibiotics for treatment of HS at the Screening Visit.

Main exclusion criteria:

1. Draining tunnel count ≥ 20 at baseline.
2. Other active skin disease or condition that may interfere with assessment of HS.
3. Study participant had a diagnosis of sarcoidosis, systemic lupus erythematosus, or active IBD.
4. Study participant had a primary immunosuppressive condition, including taking immunosuppressive therapy following an organ transplant, or had a splenectomy.
5. History of lymphoproliferative disease or any known malignancy or history of malignancy of any organ system treated or untreated within the past 5 years.
6. Study participant had an active infection or history of infection(s) as follows:
    - Any infection requiring systemic treatment within 14 days prior to Baseline,

- A serious infection, defined as requiring hospitalisation or intravenous anti-infective(s), within 2 months prior to the Baseline Visit,
- A history of opportunistic, recurrent, or chronic infections that, in the opinion of the Investigator, might have caused this study to be detrimental to the study participant. Opportunistic infections were infections caused by uncommon pathogens (e.g., Pneumocystis jirovicii, cryptococcosis), or unusually severe infections caused by common pathogens (e.g., cytomegalovirus, herpes zoster).

7. Female study participant who was breastfeeding, pregnant, or planned to become pregnant during the study or within 20 weeks following the final dose of IMP.

Treatments

The IMPs used in this study were bimekizumab and placebo.

- Bimekizumab was supplied as a solution for injection (160mg/mL) in a pre-filled 1mL syringe for subcutaneous (sc) injection.
- Placebo was supplied as a solution for injection containing 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of US Pharmacopoeia/European Pharmacopoeia quality in a pre-filled 1mL syringe for sc injection.

Study participants were randomised in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 4 treatment sequences as follows:

• Bimekizumab 320mg every 2 weeks (Q2W) from Weeks 0 to 48

• Bimekizumab 320mg every 4 weeks (Q4W) from Weeks 0 to 48

• Bimekizumab 320mg Q2W to Week 16, continuing on 320mg Q4W from Weeks 16 to 48

• Placebo to Week 16, continuing on bimekizumab 320mg Q2W from Weeks 16 to 48

For analyses during the Initial Treatment Period, bimekizumab 320mg Q2W participants were pooled from the bimekizumab 320mg Q2W/Q2W and bimekizumab 320mg Q2W/Q4W groups.

Dosing Scheme

Week / Dose assignment	Initial Treatment Period (Weeks after first dose)									Maintenance Treatment Period (Weeks after first dose)														
	Baseline 0	2	4	6	8	10	12	14	16	18	20	22	24	26	28	30	32	34	36	38	40	42	44	46
Bimekizumab 320mg Q2W/Q2W	●●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●
Bimekizumab 320mg Q4W/Q4W	●●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○
Bimekizumab 320mg Q2W/Q4W	●●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○	● ●	○ ○
Placebo/bimekizumab 320mg Q2W	○○	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○	○ ○	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●	● ●

Q2W=every 2 weeks; Q4W=every 4 weeks
Note: A bimekizumab 160mg injection is depicted by a black circle (●). A placebo injection is depicted by a white circle (○).

The following concomitant treatments and medications were permitted during the study:

- Wound care: Concomitant use of wound care dressings on HS wounds was allowed; however, options were limited to alginates, hydrocolloids, and hydrogels.
- Lesion care: Concomitant use of saline, water, and/or Vaseline (petroleum jelly) was allowed for care of skin lesions and use of these were recorded in the eCRF.

- Analgesic therapy: Study participants were required to wash out of all analgesics for HS-related pain 14 days prior to Baseline. Study participants on a stable (scheduled) dose of a non-opioid analgesic for HS-related pain, or for a non-HS medical condition (e.g., osteoarthritis, neuropathic pain), could continue the analgesic. If HS-related or non–HS-related pain worsened after Baseline, the study participant could initiate analgesic therapy at any time. For HS-related pain, permitted analgesics were limited to ibuprofen at a dose of up to 800mg orally every 6 hours, not to exceed 3.2g/24 hours and/or acetaminophen/paracetamol as per local labeling.

• Antibiotic therapy:

For study participants entering the study in the antibiotic strata, they had to be on a stable dose and regimen of doxycycline, minocycline, or an equivalent systemic tetracycline for 28 days prior to Baseline (Visit 2). The dose and regimen should have remained stable throughout study participation, but at least through Week 16. Antibiotics taken on an as needed (PRN) basis were not considered as a stable dose. After Week 16, participants could receive an antibiotic if required in the judgement of the Investigator.

• Rescue medication.

There were no absolute restrictions on the use of rescue medications for study participants whose HS deteriorated during the study. Interventions could include analgesics for a limited period of time, intralesional injections of triamcinolone, and/or incision and drainage of the abscess. A total of 2 protocol-allowed interventions were permissible during the Initial Treatment Period (from Baseline Visit to Week 16). Analgesic rescue treatment was not included in the number of protocol-allowed interventions. An intervention could occur on maximally 2 different lesions at the same visit, or on the same lesion at 2 different study visits. The same lesion could not be treated 2 times at the same visit. If a study participant required more than 2 interventions within the first 16 weeks of the study, then the study participant should have been discontinued from the study.

During the Maintenance Treatment Period (Weeks 16 to 48), a maximum of 2 interventions every 4 weeks were permitted. Do not include analgesic rescue treatment in the number of protocol-allowed interventions. An intervention could occur on 2 different lesions at the same visit or on the same lesion at 2 different study visits. Within each 4-week period, the same type of intervention could not be used 2 times on the same lesion. If a study participant required more than 2 interventions within a 4-week period, or had 2 of the same interventions on the same lesion within that period, then the study participant should have been discontinued from the study.

Objectives

The **primary objective** of the studies was to evaluate the efficacy of bimekizumab in study participants with moderate to severe HS.

The **secondary objectives** of the study were as follows:

- To evaluate the efficacy of bimekizumab on other measures of disease activity in study participants with moderate to severe HS.
- To evaluate the safety of bimekizumab in study participants with moderate to severe HS.

The **other objectives** of the study were as follows:

- To evaluate the efficacy of bimekizumab on Hidradenitis Suppurativa Clinical Response (HiSCR), other HS Scores, and other clinical measures of disease activity at various timepoints in study participants with moderate to severe HS.

- To evaluate the efficacy of bimekizumab on abscesses, nodules, and draining tunnels at various timepoints in study participants with moderate to severe HS.
- To evaluate the efficacy of bimekizumab on patient-reported outcome (PRO) measures at various timepoints in study participants with moderate to severe HS.
- To evaluate the effect of bimekizumab on other safety measures at various timepoints in study participants with moderate to severe HS.
- To evaluate the PK of bimekizumab in study participants with moderate to severe HS.
- To evaluate the immunogenicity of bimekizumab (i.e., antidrug/antibimekizumab antibody [ADAb]) in study participants with moderate to severe HS.

Outcomes/endpoints

Primary efficacy endpoint

The primary efficacy endpoint is the HiSCR50 (defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule [AN] count with no increase from Baseline in abscess or draining tunnel count) at Week 16.

Secondary efficacy endpoints

The secondary efficacy endpoints were defined as:

- HiSCR75 response (defined as at least a 75% reduction from Baseline in the total AN count with no increase from Baseline in abscess or draining tunnel count) at Week 16.
- Flare by Week 16 (**Study HS0004 only**).
- Absolute change from Baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 16.
- Absolute change from Baseline in Skin Pain score at Week 16, as assessed by the 'worst skin pain' item (11-point numeric rating scale) in the HS Symptom Daily Diary (HSSDD).
- Skin pain response based on the threshold for clinically meaningful change (defined as at least a 3-point decrease from Baseline in HSSDD weekly worst skin pain score) at Week 16 among study participants with a score of ≥3 at Baseline.

The other efficacy endpoints were defined as:

- Time to response of HiSCR25, HiSCR50, HiSCR75, HiSCR90.
- Absolute change from Baseline in International Hidradenitis Suppurativa Severity Score System (IHS4).
- Change from Baseline in the HS-Physician's Global Assessment 6-point scale.
- HiSCR25, HiSCR50, HiSCR75, HiSCR90, at both Weeks 16 and 48.
- Time to loss of response of HiSCR50, HiSCR75, HiSCR90, and HiSCR100 in Week 16 responders.
- Change and percentage change from Baseline in lesion counts (abscess count, inflammatory nodule count, AN count, and draining tunnel count).
- Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline) at both Weeks 16 and 48.

- Skin pain response based on the threshold for clinically meaningful change (defined as at least a 3-point decrease from Baseline in HSSDD weekly worst skin pain score) among study participants with a score of ≥3 at Baseline.
- Absolute change from Baseline in DLQI Total Score.
- Absolute change from Baseline in Hidradenitis Suppurativa Quality of Life (HiSQOL) domain scores (symptoms, psychosocial, activities and adaptations) and Total score.
- Absolute change from Baseline in each of the other HS Symptoms - itch, drainage or oozing of HS lesions, and smell or odor.

Endpoint definitions used in the pivotal studies primary and secondary ranked endpoints.

Lesion count

The lesion count was defined as an assessment of all the various skin 'appearances' that were termed 'lesions' in HS study participants. The lesion count included the following:

- Abscesses (circumscribed collection of purulent exudate frequently associated with swelling and other signs of inflammation, such as fluctuance, tenderness, and pain).
- Draining tunnels (fistulas/sinus tracts) (pathologic passageway connecting to the skin surface from dermis or sc tissue/pathologic passageway that developed into a channel to the skin surface that drained serous or purulent fluid, either spontaneously or by gentle palpation).
- Non-draining tunnels (fistulas/sinus tracts) (pathologic passageway connecting to the skin surface from dermis or sc tissue/pathologic passageway that developed into a channel to the skin surface that did not drain serous or purulent fluid).
- Noninflammatory nodules (nontender or minimally tender, non-erythematous nodules).
- Inflammatory nodules (a tender, erythematous, well-defined nodule. The lesion had no evidence of fluctuance. A pyogenic granuloma lesion was considered an inflammatory nodule; a papule or pustule was not considered an inflammatory nodule).
- Scars of HS lesions (enlargement or overgrowth of a scar so that it extended above the surrounding skin surface). The data collected from the lesion count was used for the derivation of study variables including, but not limited to HiSCR25, HiSCR50, HiSCR75, HiSCR90, HiSCR100, HS Physician's Global Assessment, AN count, and IHS4.

HiSCR

The HiSCR was defined by status of abscesses, inflammatory nodules and draining tunnels; defined as a ≥50% reduction from Baseline in the total AN count, with no increase from Baseline in abscess or draining tunnel count. HiSCR has been labelled HiSCR50 in this application. The HiSCR75, HiSCR90, and HiSCR100 were also evaluated in this study. These measures of clinical response differ from HiSCR50 only in the percent decrease in AN count from Baseline.

DLQI

The DLQI is a skin disease-specific questionnaire aimed at the evaluation of how symptoms and treatment affect participants' health-related quality of life (HRQoL), with a recall period of 7 days. This instrument asks participants about symptoms and feelings, daily activities, leisure, work and school, personal relationships, and treatment. The DLQI Total Score ranges from 0 to 30 with higher scores indicating lower HRQoL. In other dermatological/skin conditions, a 4-point change in the DLQI Total Score (DLQI response) has been reported to be meaningful for the participant (within-patient minimal clinically

important difference [MCID]); while a DLQI total absolute score of 0 or 1 indicates no impact of the disease on HRQoL.

HSSDD

The 5 items on the HS Symptom Daily Diary (HSSDD) assess patients' perception of the core symptoms of HS experienced in the past 24 hours: pain, smell or odor, drainage or oozing from HS lesions, and itch on an 11-point numeric rating scale (NRS). Two items assess skin pain (ie, worst skin pain and average skin pain). The remaining 3 items assess smell or odor, itch at its worst, and amount of drainage or oozing from HS lesions.. The HSSDD was completed daily by the study participants at the end of the day on an electronic hand-held device from the start of Screening through the Week 16 Visit.

Flare

Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline).

Sample size

A total of 490 study participants were planned to be randomly assigned in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 4 treatment sequences as follows into each study (HS0003 and HS0004):

- Bimekizumab 320mg every 2 weeks (Q2W) from Weeks 0 to 48
- Bimekizumab 320mg every 4 weeks (Q4W) from Weeks 0 to 48
- Bimekizumab 320mg Q2W to Week 16, continuing on 320mg Q4W from Weeks 16 to 48
- Placebo to Week 16, continuing on bimekizumab 320mg Q2W from Weeks 16 to 48

For analyses during the Initial Treatment Period, bimekizumab 320mg Q2W participants were pooled from the bimekizumab 320mg Q2W/Q2W and bimekizumab 320mg Q2W/Q4W groups.

Randomisation

An IRT system was used for assigning eligible study participants to a treatment regimen at Baseline based on a predetermined production randomisation and/or packaging schedule provided by the MAH (or designee). The randomisation schedule was produced by the IRT vendor. The IRT generated individual assignments for kits of IMP, as appropriate, according to the visit schedule.

Blinding (masking)

In order to maintain the blind throughout the study, a double-dummy approach was applied using placebo injections such that all study participants received the same number of injections at each corresponding visit.

Special precautions were taken to ensure study blinding; study sites had blinded and unblinded personnel. Bimekizumab and placebo injections were administered at the investigational sites by unblinded, dedicated study personnel according to the site-specific blinding plan. Unblinded study personnel were responsible for recording the administration information on source documents, and administration of IMP as sc injections. The following individuals could, as necessary, have had access to the randomisation code as indicated:

• Members of the DMC who participated in unblinded sessions were given information about the IMP allocation for those study participants for whom data were provided.

• The unblinded, independent CRO staff supporting preparation of the data outputs for the DMC reviews.

The unblinded study site personnel were not involved in the study in any way other than assuring the IMP was taken from the correct kit and prepared according to the IMP handling manual and administering the IMP to the study participants.

Statistical methods

Primary efficacy endpoint

The primary analysis of the primary efficacy endpoint was undertaken using a logistic regression model using the randomised set (RS) as the primary population. A composite estimand approach was used with intercurrent events being handled as failures as described in Table 8.

Table 8. Estimated Details and Attributes for Primary Endpoint

		Estimands for Primary Endpoint			
Objective Clinical Category	**Statistical Category (Section)**	**Variable/ Endpoint**	**Pop**	**IES**	**PLS (Analysis)**
Primary Objective: To evaluate the efficacy of bimekizumab in study participants with moderate to severe HS					
$HiSCR_{50}$	Primary (Section 8.2.2)	$HiSCR_{50}$ response at Week 16	RS	The main intercurrent events are receipt of systemic antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16. A **composite strategy** will be used, ie, the occurrence of an intercurrent event will be handled by evaluating the corresponding participants as treatment failures (nonresponders).	The odds ratio versus placebo based on a logistic regression. Missing values will be imputed using MI – MCMC/Monotone Regression under a missing at random assumption.

The Baseline value for a study participant was defined as the latest non-missing measurement for that study participant up to and including the day of administration of first IMP, unless otherwise stated.

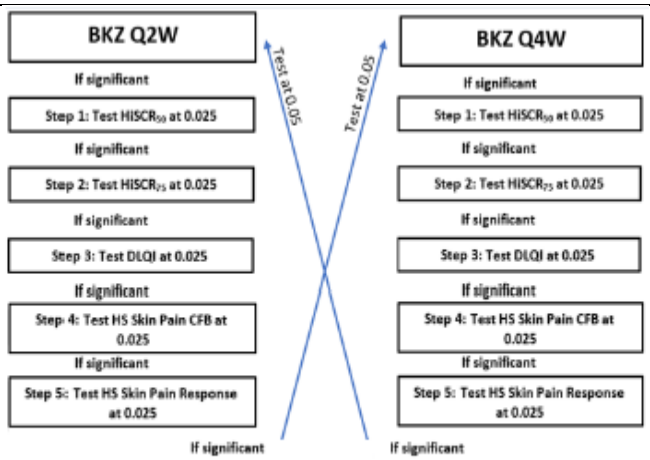
Multiplicity

To control the overall type I error rate at 0.05 for the multiple comparisons in the primary and secondary efficacy endpoints, a closed testing procedure under a parallel gatekeeping framework was applied.

Under this framework, each bimekizumab dose of 320mg Q2W and 320mg Q4W was compared with placebo in the first instance at a familywise error rate of 0.025 (α/2). Simultaneously within each dose, closed testing for the primary and secondary efficacy endpoints was performed.

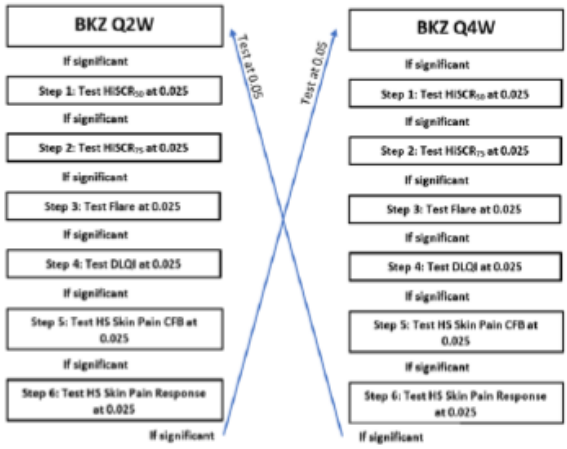
Briefly, the primary endpoint was evaluated at Step 1 at a significance level of 0.025. If Step 1 was significant at 0.025, each secondary endpoint was then tested sequentially in the order shown in the figures below, moving to the next step only if significance was achieved at 0.025. In the event that Step 6 was significant at 0.025 for a given dose, then Steps 1 to 6 were repeated for the other dose using a significance level of 0.05.

Sequence of testing HS0003



AN=abscess and inflammatory nodule; BKZ=bimekizumab; CFB=change from Baseline; DLQI=Dermatology Life Quality Index; HiSCR=Hidradenitis Suppurativa Clinical Response; HiSCR50=a ≥50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HiSCR75=a ≥75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HS=hidradenitis Suppurativa; Q2W=every 2 weeks; Q4W=every 4 weeks

Sequence of testing HS0004



AN=abscess and inflammatory nodule; BKZ=bimekizumab; CFB=change from Baseline; DLQI=Dermatology Life Quality Index; HiSCR=Hidradenitis Suppurativa Clinical Response; HiSCR50=a ≥50% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HiSCR75=a ≥75% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; HS=hidradenitis Suppurativa; Q2W=every 2 weeks; Q4W=every 4 weeks

Analysis of the primary efficacy variable:

The primary efficacy endpoint was the HiSCR50 response at Week 16 and corresponding analyses were based on the RS. The primary efficacy analysis evaluated the composite estimand in the RS. The composite estimand combined the clinically meaningful improvement from Baseline based on the HiSCR50 response and completion of study treatment through Week 16 without receiving systemic antibiotic rescue medication or discontinuing IMP due to an AE or lack of efficacy. The primary analysis was based on a logistic regression model including a fixed effect for treatment, Hurley Stage at Baseline, and Baseline antibiotic use.

Analysis of the secondary efficacy variables:

The secondary efficacy analyses were performed based on the RS.

For HiSCR75 at Week 16, logistic regression, as specified for the primary analysis, was implemented to test for superiority. The same analysis approach as outlined for the primary efficacy endpoint was applied.

Change from Baseline in DLQI Total Score at Week 16 was presented by treatment group.

The analysis model was based on an analysis of covariance with fixed effects of treatment, Hurley Stage at Baseline, and Baseline antibiotic use and Baseline value as a covariate. The least squares mean (LSM), standard error (SE), and 95% confidence interval (CI) for the LSM were presented by treatment group. For the comparison between placebo and bimekizumab: the difference between the LSM, the associated 97.5% CI for the contrasts, and the corresponding p-value were presented. If one dose regimen was

tested at the 0.05 significance level, then the CI was 95% instead of 97.5% for that dose with a corresponding Zα/2 of 1.96. Similar analyses were performed for the Change from Baseline in HSSDD worst skin pain score at Week 16, with the addition of analgesic use as a covariate. The analysis of HSSDD worst skin pain response at Week 16 was based on a logistic regression model including a fixed effect for treatment, Hurley Stage at Baseline, Baseline antibiotic use, and analgesic use. The odds ratio versus placebo, p value (from Wald test), and 97.5% CI were calculated. If one dose regimen was tested at the 0.05 significance level, then the CI was 95% instead of 97.5% for that dose. The number and percentage of participants who were pain responders at Week 16 were summarised by treatment group.

Analysis of the other efficacy variables: For continuous variables, descriptive statistics included number of study participants with available measurements (n), mean, standard deviation, median, minimum, and maximum. For electronic PRO continuous variables, descriptive statistics also included variable score, absolute and percentage changes from Baseline, Q1 and Q3, 10th, and 90th percentiles. For categorical variables, the number and percentage of study participants in each category were presented. To account for missing data, percentages were based only on those study participants with observed data for the variable being summarised. As the denominator may have been different from the number of study participants in the analysis set being considered, the denominator was displayed in the table.

Missing data methodology

The missing data methods applied in HS0003 and HS0004 were identical in principle. This methodology was also utilised for endpoints in the pooled analyses.

Different approaches were used to handle missing data including how intercurrent events (defined as receipt of systemic antibiotic rescue medication or discontinuation of study treatment due to an adverse event [AE] or lack of efficacy prior to the given visit) were to be considered. A composite strategy was implemented in which a positive clinical outcome was defined as the study participant achieving HiSCR50 at the given visit and not receiving systemic antibiotic rescue medication, and not discontinuing study treatment due to an AE or lack of efficacy on or prior to that visit.

For the primary efficacy endpoint if study participants had an intercurrent event then the efficacy variable at that timepoint and all subsequent timepoints (whether the data were observed or not) were set to 'nonresponse' as the study participant had not met the criteria for response based on the composite estimand. All remaining missing data for the endpoint were imputed using multiple imputation Markov-Chain Monte Carlo method (MI-MCMC)/monotone regression for the primary analysis.

In addition, sensitivity analyses using NRI, MI-MCMC/reference-based methods, tipping point analysis, and observed case (OC) methods were performed, to assess the impact of different methods of handling missing data. In the primary analysis for the individual study SAPs for HS0003 and HS0004 any systemic antibiotic use treated as an intercurrent event is designated as modified non-responder imputation (mNRI) (All-antibiotics [ABX]). Note: In some table titles/descriptions, this approach is also referred to as "multiple imputation (MI) using Markov-Chain Monte Carlo MCMC)/Monotone Regression."

For secondary binary efficacy endpoints, intercurrent events were handled, and missing data was imputed, using the same methods as for the primary efficacy endpoint. NRI and OC methods were performed as sensitivity analyses. For secondary continuous efficacy endpoints, MI-MCMC/monotone regression was the primary method for imputing missing data, regardless of whether the missing data were preceded by an intercurrent event.

Results

Participant flow

A total of 1014 subjects, 505 subjects in study HS0003 and 509 subjects in study HS0004, were randomised to bimekizumab Q2W/Q2W, bimekizumab Q4W/Q4W, bimekizumab Q2W/Q4W, or placebo to bimekizumab Q2W treatment arms.

Table 9. Study HS0003 and HS0004 and Pool E1 Disposition and discontinuation reasons – ITP (RS)

	HS0003			HS0004			Pool E1			
	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291	PBO N=146	BKZ 320mg Q4W N=288	BKZ 320mg Q2W N=580	All Study Participants N=1014
Disposition	n (%)									
Started ITP	72 (100)	143 (99.3)	286 (99.0)	74 (100)	142 (98.6)	290 (99.7)	146 (100)	285 (99.0)	576 (99.3)	1007 (99.3)
Completed ITP	65 (90.3)	127 (88.2)	259 (89.6)	133 (92.4)	262 (90.0)	395 (90.8)	134 (91.8)	260 (90.3)	521 (89.8)	915 (90.2)
Discontinued Initial Treatment Period	7 (9.7)	16 (11.1)	27 (9.3)	5 (6.8)	9 (6.3)	28 (9.6)	12 (8.2)	25 (8.7)	55 (9.5)	92 (9.1)
Primary reason for study discontinuation										
Adverse event	1 (1.4)	5 (3.5)	7 (2.4)	1 (1.4)	1 (0.7)	9 (3.1)	2 (1.4)	6 (2.1)	16 (2.8)	24 (2.4)
Lack of efficacy	0	0	0	0	0	1 (0.3)	0	0	1 (0.2)	1 (0.1)
Protocol violation	0	2 (1.4)	2 (0.7)	1 (1.4)	0	1 (0.3)	1 (0.7)	2 (0.7)	3 (0.5)	6 (0.6)
Lost to follow-up	1 (1.4)	3 (2.1)	2 (0.7)	1 (1.4)	0	3 (1.0)	2 (1.4)	3 (1.0)	5 (0.9)	10 (1.0)
Consent withdrawn (not due to AE)	4 (5.6)	6 (4.2)	14 (4.8)	2 (2.7)	8 (5.6)	12 (4.1)	6 (4.1)	14 (4.9)	26 (4.5)	46 (4.5)
Other	1 (1.4)	0	2 (0.7)	0	0	2 (0.7)	1 (0.7)	0	4 (0.7)	5 (0.5)

Table 10. Study HS0003 Disposition and discontinuation reasons – MTP (MS)

	PBO/BKZ 320mg Q2W N=65 n (%)	BKZ 320mg Q4W/Q4W N=125 n (%)	BKZ 320mg Q2W/Q4W N=129 n (%)	BKZ 320mg Q2W/Q2W N=129 n (%)	All Study Participants N=448 n (%)
Started MTP	65 (100)	125 (100)	129 (100)	129 (100)	448 (100)
Completed MTP	44 (67.7)	87 (69.6)	104 (80.6)	98 (76.0)	333 (74.3)
Discontinued study during MTP	21 (32.3)	38 (30.4)	25 (19.4)	31 (24.0)	115 (25.7)
Primary reason for study discontinuation					
AE	9 (13.8)	7 (5.6)	5 (3.9)	6 (4.7)	27 (6.0)
Lack of efficacy	1 (1.5)	7 (5.6)	3 (2.3)	3 (2.3)	14 (3.1)
Protocol violation	1 (1.5)	2 (1.6)	1 (0.8)	2 (1.6)	6 (1.3)
Lost to follow up	2 (3.1)	5 (4.0)	3 (2.3)	3 (2.3)	13 (2.9)
Consent withdrawn by study participant (not due to AE)	7 (10.8)	12 (9.6)	11 (8.5)	14 (10.9)	44 (9.8)
Other	1 (1.5)	5 (4.0)	2 (1.6)	3 (2.3)	11 (2.5)
Discontinued IMP during MTP	0	1 (0.8)	1 (0.8)	0	2 (0.4)

AE=adverse event; BKZ=bimekizumab; IMP=investigational medicinal product; ITP=Initial Treatment Period; MS=Maintenance Set; MTP=Maintenance Treatment Period; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: A participant was considered to have started the MTP if they received any dose of IMP in the MTP. A participant was considered to have completed the MTP if they had completed the study.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO. Placebo/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Table 11. Study HS0004 Disposition and discontinuation reasons – MTP (MS)

	PBO/BKZ 320mg Q2W N=69 n (%)	BKZ 320mg Q4W/Q4W N=133 n (%)	BKZ 320mg Q2W/Q4W N=130 n (%)	BKZ 320mg Q2W/Q2W N=131 n (%)	All Study Participants N=463 n (%)
Started MTP	69 (100)	133 (100)	130 (100)	131 (100)	463 (100)
Completed MTP	61 (88.4)	109 (82.0)	107 (82.3)	110 (84.0)	387 (83.6)
Discontinued study during MTP	8 (11.6)	24 (18.0)	23 (17.7)	21 (16.0)	76 (16.4)
Primary reason for study discontinuation					
AE	0	7 (5.3)	6 (4.6)	4 (3.1)	17 (3.7)
Lack of efficacy	0	4 (3.0)	2 (1.5)	2 (1.5)	8 (1.7)
Protocol violation	0	0	2 (1.5)	1 (0.8)	3 (0.6)
Lost to follow up	2 (2.9)	3 (2.3)	1 (0.8)	2 (1.5)	8 (1.7)
Consent withdrawn by study participant (not due to AE)	6 (8.7)	9 (6.8)	10 (7.7)	11 (8.4)	36 (7.8)
Other	0	1 (0.8)	2 (1.5)	1 (0.8)	4 (0.9)

AE=adverse event; BKZ=bimekizumab; IMP=investigational medicinal product; ITP=Initial Treatment Period; MTP=Maintenance Treatment Period; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: A participant was considered to have started the MTP if they received any dose of IMP in the MTP. A participant was considered to have completed the MTP if they had completed the study.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Recruitment

In study HS0003, the first participant enrolled on the 19 February 2020 and the last participant last Week 48 Visit was 26 October 2022. The study was conducted at 86 sites in Australia, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Spain, Switzerland, Turkey, and United States.

In study HS0004, the first participant enrolled on the 2 March 2020 and the last participant completed 28 September 2022. The study was conducted at 90 sites in Australia, Bulgaria, Canada, the Czech Republic, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Poland, Spain, the United Kingdom, and the United States.

Conduct of the study

Protocol amendments

The protocols for studies HS0003 and HS0004 were simultaneously amended on four occasions:

Protocol Amendment 1 (dated 06 December 2019 – no study participants enrolled at time of amendment)

The main reason for this non substantial amendment was to update the company name in line with the new Code of Companies and Associations recently adopted by Belgium. Other key changes included clarification of the wording of the exploratory biomarker objective.

Protocol Amendment 2 (dated 16 December 2019 - no study participants enrolled at time of amendment)

The purpose of this non substantial amendment was to update the study discontinuation/withdrawal criteria for study participants with inflammatory bowel disease (IBD).

Protocol Amendment 3 (dated 03 February 2021 – approximately 162 study participants enrolled in HS0003 and 300 in HS0004 at time of amendment)

The purpose of this substantial amendment was to update the protocol based on Regulatory Agency feedback and provide procedural clarifications.

Key changes included the following:

- Order of secondary efficacy endpoints was aligned for closed testing procedure 15 February 2023 Week 48 HS0003
- Removal of 30% cap on enrollment for the Baseline antibiotic therapy strata
- Aligned the final Independent DMC Charter and the DMC statistical analysis plan (SAP) for the planned unblinded futility analysis for the DMC
- Update and clarifications to Schedule of Activities, inclusion criteria, exclusion criteria, and severe acute respiratory syndrome. Necessary protocol revisions due to the COVID-19 pandemic
- Removal of depression as a safety topic of interest while maintaining collection of data to monitor for this potential effect
- Added lesion care section and updated wound care section
- Clarified and updated prohibited medications and associated washout periods
- Addition of specific infection-related IMP interruption criterion

Protocol Amendment 4 (dated 06/09 May 2022 for studies HS0004 and HS0003 respectively - all study participants were enrolled at the time of the amendment)

The purpose of this substantial amendment was to align with FDA recommendations to use a threshold for within-patient clinically meaningful change to define treatment success in order to establish efficacy for skin pain in Phase 3 studies of patients with moderate to severe HS.

The Sponsor conducted analyses to determine the threshold for within-patient clinically meaningful change that was applied in the final analysis for a responder definition based on the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD) worst skin pain item score using established guidelines and analytical methods. Pain response status at Week 16 using this definition was added as a secondary endpoint to the study. This change also resulted in an addition to the sample size section, including assumptions on response rates.

Protocol Amendment 5 (study HS0003 only, dated 27 September 2022 - and all 505 study participants were enrolled at the time of the amendment)

The purpose of this substantial amendment was to remove the flare (secondary) endpoint from the statistical testing procedure. The rationale for the amendment was the lack of unanimous consensus on the definition of HS flare, including the flare definition used in previous and ongoing clinical studies (outside of and independent of HS0003), the continued lack of published validation studies of a flare endpoint, and inconsistent data on the flare endpoint observed both within the bimekizumab program and in recently published data from another experimental HS treatment. Flare was included as an 'Other' endpoint in the study.

Protocol Deviations

Table 12. Important protocol deviations ITP (RS) study HS0003

	PBO N=72 n (%)	BKZ 320mg Q4W N=144 n (%)	BKZ 320mg Q2W N=289 n (%)	BKZ total N=433 n (%)	All Study Participants N=505 n (%)
Study participants with no important protocol deviations	58 (80.6)	114 (79.2)	238 (82.4)	352 (81.3)	410 (81.2)
Study participants with at least 1 important protocol deviation	14 (19.4)	30 (20.8)	51 (17.6)	81 (18.7)	95 (18.8)
Inclusion criteria deviation	1 (1.4)	0	1 (0.3)	1 (0.2)	2 (0.4)
Exclusion criteria deviation	0	1 (0.7)	3 (1.0)	4 (0.9)	4 (0.8)
Withdrawal criteria deviation	1 (1.4)	0	1 (0.3)	1 (0.2)	2 (0.4)
Prohibited concomitant medication use	13 (18.1)	24 (16.7)	40 (13.8)	64 (14.8)	77 (15.2)
Incorrect treatment or dose	0	0	0	0	0
Treatment noncompliance	0	1 (0.7)	6 (2.1)	7 (1.6)	7 (1.4)
Procedural noncompliance	0	4 (2.8)	4 (1.4)	8 (1.8)	8 (1.6)

Table 13. Important protocol deviations – MTP (MS) study HS0003

	PBO/BKZ 320mg Q2W N=65 n (%)	BKZ 320mg Q4W/Q4W N=125 n (%)	BKZ 320mg Q2W/Q4W N=129 n (%)	BKZ 320mg Q2W/Q2W N=129 n (%)	All Study Participants N=448 n (%)
Study participants with no important protocol deviations	65 (100)	123 (98.4)	127 (98.4)	125 (96.9)	440 (98.2)
Study participants with at least 1 important protocol deviation	0	2 (1.6)	2 (1.6)	4 (3.1)	8 (1.8)
Inclusion criteria deviation	0	0	0	0	0
Exclusion criteria deviation	0	0	0	0	0
Withdrawal criteria deviation	0	0	0	1 (0.8)	1 (0.2)
Prohibited concomitant medication use	0	2 (1.6)	2 (1.6)	2 (1.6)	6 (1.3)
Incorrect treatment or dose	0	0	0	0	0
Treatment noncompliance	0	0	0	1 (0.8)	1 (0.2)
Procedural noncompliance	0	0	0	0	0
Study participants excluded from the PK-PPS	0	0	0	0	0

BKZ=bimekizumab; ITP=Initial Treatment Period; MS=Maintenance Set; MTP=Maintenance Treatment Period; PBO=placebo; PK-PPS=Pharmacokinetic Per-Protocol Set; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: Important protocol deviations were deviations that may have significantly impacted the completeness, accuracy, and/or reliability of the study data or that may have significantly affected a participant's rights, safety, or well-being.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Table 14. Important protocol deviations – ITP (RS) study HS0004

Deviation category	PBO N=74 n (%)	BKZ 320mg Q4W N=144 n (%)	BKZ 320mg Q2W N=291 n (%)	BKZ Total N=435 n (%)	All Study Participants N=509 n (%)
Study participants with no important protocol deviations	65 (87.8)	120 (83.3)	242 (83.2)	362 (83.2)	427 (83.9)
Study participants with at least 1 important protocol deviation	9 (12.2)	24 (16.7)	49 (16.8)	73 (16.8)	82 (16.1)
Inclusion criteria deviation	1 (1.4)	1 (0.7)	2 (0.7)	3 (0.7)	4 (0.8)
Exclusion criteria deviation	0	1 (0.7)	1 (0.3)	2 (0.5)	2 (0.4)
Withdrawal criteria deviation	1 (1.4)	0	2 (0.7)	2 (0.5)	3 (0.6)
Prohibited concomitant medication use	5 (6.8)	19 (13.2)	38 (13.1)	57 (13.1)	62 (12.2)
Incorrect treatment or dose	1 (1.4)	0	0	0	1 (0.2)
Treatment noncompliance	1 (1.4)	1 (0.7)	1 (0.3)	2 (0.5)	3 (0.6)
Procedural noncompliance	1 (1.4)	4 (2.8)	7 (2.4)	11 (2.5)	12 (2.4)

Table 15. Important protocol deviations – MTP (RS) study HS0004

Deviation category	PBO/BKZ 320mg Q2W N=69 n (%)	BKZ 320mg Q4W/Q4W N=133 n (%)	BKZ 320mg Q2W/Q4W N=130 n (%)	BKZ 320mg Q2W/Q2W N=131 n (%)	All Study Participants N=463 n (%)
Study participants with no important protocol deviations	65 (94.2)	127 (95.5)	120 (92.3)	119 (90.8)	431 (93.1)
Study participants with at least 1 important protocol deviation	4 (5.8)	6 (4.5)	10 (7.7)	12 (9.2)	32 (6.9)
Inclusion criteria deviation	0	0	0	1 (0.8)	1 (0.2)
Exclusion criteria deviation	0	0	0	0	0
Withdrawal criteria deviation	0	0	1 (0.8)	1 (0.8)	2 (0.4)
Prohibited concomitant medication use	3 (4.3)	0	6 (4.6)	4 (3.1)	13 (2.8)
Incorrect treatment or dose	0	2 (1.5)	2 (1.5)	0	4 (0.9)
Treatment noncompliance	1 (1.4)	3 (2.3)	0	2 (1.5)	6 (1.3)
Procedural noncompliance	0	2 (1.5)	2 (1.5)	4 (3.1)	8 (1.7)
Study participants excluded from the PK-PPS	0	0	0	0	0

BKZ=bimekizumab; ITP=Initial Treatment Period; MS=Maintenance Set; MTP=Maintenance Treatment Period; PBO=placebo; PK-PPS=Pharmacokinetic Per-Protocol Set; PPS=Per-Protocol Set; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: Important protocol deviations were deviations that may have significantly impacted the completeness, accuracy, and/or reliability of the study data or that may have significantly affected a participant's rights, safety, or well-being.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Baseline data

Demographic characteristics (Pool E1)

The mean age of all study participants was 36.6 years of age, with a median range of 18 to 78 years of age. More than half of the participants were female (56.8%), the majority of study participants were White (79.7%), not of Hispanic or Latino ethnicity (93.0%), 10.8% of the participants were Black or African American, and 45.6% were current smokers. The mean body weight and mean BMI overall were 97.2kg and 33.06kg/m2, respectively.

Overall, demographic characteristics were well balanced across treatment groups in Pool E1, with some exceptions:

- The proportion of study participants <40 years of age was higher in the bimekizumab 320mg Q4W group (66.0%) compared with the bimekizumab 320mg Q2W group (61.0%).
- The proportion of males was lower in the bimekizumab 320mg Q4W (39.2%) group compared with the placebo group (48.6%). The proportion of males in the bimekizumab 320mg Q2W group was 43.8%. The proportions of females were higher in the bimekizumab 320mg Q4W (60.8%) and bimekizumab 320mg Q2W (56.2%) groups compared with the placebo group (51.4%).
- The median body weight was higher in the bimekizumab 320mg Q4W (98.0kg) group compared with the placebo group (91.9kg). The median body weight was 93.3kg in the bimekizumab 320mg Q2W group.
- The proportion of study participants in the ≥120kg weight group and the proportion of study participants with a BMI of ≥40kg/m2 was lower in the bimekizumab 320mg Q2W group (16.2% and 17.1%, respectively) compared with the placebo group (21.2% and 22.6%, respectively). The proportion of study participants in the ≥120kg weight group and the proportion of study participants with a BMI of ≥40kg/m2 in the bimekizumab 320mg Q4W group was 18.1% and 22.2%, respectively.
- The mean BMI values were comparable across treatment groups (range: 32.68kg/m2 to 33.80kg/m2).
- There was a higher proportion of participants from the geographic region of North America in the bimekizumab 320mg Q4W group (42.0%) compared with the placebo group (37.0%). The proportion of participants from North America in the bimekizumab 320mg Q2W group was 36.2%.
- There was a lower proportion of participants from the geographic region of Western Europe in the bimekizumab 320mg Q4W group (26.7%) compared with the placebo group (32.9%). The proportion of participants from Western Europe in the bimekizumab 320mg Q2W group was 29.0%.
- There was a higher proportion of participants who never smoked in the bimekizumab 320mg Q4W group (41.3%) compared with the placebo group (36.3%). The proportion of participants who never smoked in the bimekizumab 320mg Q2W group was 37.4%. There was a lower proportion of participants who currently smoked in the bimekizumab 320mg Q4W (43.8%) and bimekizumab 320mg Q2W (45.0%) groups compared with the placebo group (51.4%).

Differences between studies HS0003 and HS0004

Demographic characteristics for Pool E1 are generally similar to those reported for the individual Phase 3 studies.

Differences were observed between the individual studies for gender (63.0% female and 37.0% male in HS0003 vs 50.7% female and 49.3% male in HS0004), geographic region (North America: 46.7% in HS0003 vs 29.3% in HS0004; Central/Eastern Europe: 8.9% in HS0003 vs 42.2% in HS0004; and Western Europe: 36.0% in HS0003 and 21.8% in HS0004), and BMI ≥30kg/m2 (64.2% in HS0003 and 54.2% in HS0004).

Baseline disease characteristics

Overall, the mean duration of disease was 8.00 years (median range: 0.5 to 51.3 years), and the mean Baseline hs-CRP was 17.52mg/L. Overall, 55.7% of study participants had Baseline Hurley Stage II and 44.3% had Baseline Hurley Stage III. Antibiotic use at Baseline was low overall (8.5%). Based on the HS-PGA, 44.3% and 44.8% of participants had moderate or very severe lesions, respectively, with fewer participants classified as having severe lesions (10.7%). Overall, the mean IHS4 score was 34.2

(indicating severe disease). The mean HSSDD worst skin pain score was 5.47. The mean baseline Abscess and Inflammatory Nodule (AN) Count was 16.3. The mean DLQI Total Score was 11.4, and the mean HiSQOL Total Score was 25.2.

Baseline disease characteristics for Pool E1 are generally similar to those reported for the individual Phase 3 studies (HS0003 and HS0004).

Differences between the individual studies were observed for Hurley Stage II (50.3% in HS0003 vs 61.1% in HS0004) and duration of disease (mean years 9.01 in HS0003 vs 7 in HS0004).

Prior and Concomitant disease

Study HS0003

The majority of study participants in the ITP reported a previous or ongoing medical history condition at Baseline (87.2%). Overall, the most frequently reported conditions/diseases at Baseline were in the SOCs of Skin and subcutaneous disorders (33.9%), Metabolism and nutrition disorders (33.3%), and Infections and infestations (30.9%). The most frequently reported conditions/diseases at Baseline by PT were depression (18.0%), hypertension (18.0%), and anxiety (15.4%). The incidences of previous or ongoing medical conditions/diseases at Baseline by PT were generally similar across treatment groups.

Study HS0004

The majority of study participants in the ITP reported a previous or ongoing medical history condition at Baseline (78.9%). Most frequently reported conditions/diseases at Baseline were in the SOCs of Metabolism and nutrition disorders (32.0%), Skin and subcutaneous disorders (23.3%), and Vascular disorders (22.7%). The most frequently reported conditions/diseases at Baseline by PT were hypertension (21.5%), obesity (14.4%), and depression (10.1%). The incidences of previous or ongoing medical conditions/diseases at Baseline by PT were generally similar across treatment groups.

Prior and concomitant medications

Study HS0003

The use of prior antibiotic medications was similar across the bimekizumab 320mg Q4W (77.6%), bimekizumab 320mg Q2W (80.8%), and placebo (77.8%) groups. Overall, the most frequently reported prior antibiotic medications were those commonly used for the treatment of HS. These included the tetracycline class of antibiotics (56.7% of participants) clindamycin (22.4%; also taken as clindamycin hydrochloride [10.4%]) and rifampicin (20.8%; also taken as isoniazid/rifampicin [1.0%]).

During the ITP, the use of concomitant systemic antibiotic rescue medications (i.e., intercurrent events) was lower in the bimekizumab 320mg Q4W group (15.3%) and the bimekizumab 320mg Q2W group (17.0%) compared with the placebo group (20.8%). Overall, the most commonly reported concomitant systemic antibiotic rescue medications were amoxicillin/ amoxicillin trihydrate clavulanate potassium (3.4%) and doxycycline (2.0%;).

During the Maintenance Treatment Period, the use of concomitant systemic antibiotic rescue medications (i.e., intercurrent events) was lower in the bimekizumab 320mg Q4W/Q4W (39.2%), bimekizumab 320mg Q2W/Q4W (34.1%), and bimekizumab 320mg Q2W/Q2W (38.0%) groups compared with the placebo/bimekizumab 320mg Q2W (46.2%) groups. Overall, the most commonly reported concomitant systemic antibiotic rescue medications were amoxicillin/amoxicillin trihydrate clavulanate potassium (8.5%;]) and doxycycline (6.7%).

Study HS0004

The use of prior antibiotic medications was also similar across the bimekizumab 320mg Q4W (90.1%), bimekizumab 320mg Q2W (90.7%), and placebo (90.5%) groups. Overall, the most frequently reported prior antibiotic medications were clindamycin (36.6%), doxycycline (35.4%,), and rifampicin (27.7%).

The use of concomitant systemic antibiotic rescue medications (i.e., intercurrent events) was higher in the bimekizumab 320mg Q2W group (15.1%) compared with the placebo group (8.1%) and slightly higher compared with the bimekizumab 320mg Q4W group (12.5%) during the Initial Treatment Period in the RS. Overall, the most commonly reported concomitant systemic antibiotic rescue medications were clindamycin (2.2%) amoxicillin (2.0%; also taken as amoxicillin trihydrate clavulanate potassium [2.0%]), and doxycycline (2.0%).

The use of concomitant systemic antibiotic rescue medications (i.e., intercurrent events) was higher in the bimekizumab 320mg Q2W/Q4W (32.3%) and the bimekizumab 320mg Q2W/Q2W (28.2%) groups compared with the bimekizumab 320mg Q4W/Q4W (24.1%) and the placebo/bimekizumab 320mg Q2W (21.7%) groups during the MTP. Overall, the most commonly reported concomitant systemic antibiotic rescue medications were doxycycline (5.6%), amoxicillin (3.2%; also taken as amoxicillin trihydrate clavulanate potassium [4.8%] and amoxicillin trihydrate [0.2%]), and clindamycin (3.2%)

Numbers analysed

Efficacy analyses were performed on the RS, except for some sensitivity analyses (which used the FAS, PPS, and CFS) and some other efficacy endpoint analyses specific to the Maintenance Treatment Period (which used the MS). The analysis sets for HS0003, and HS004 are presented here.

Table 16. Study HS0003

Analysis Set	PBO N=72 n (%)	BKZ 320mg Q4W N=144 n (%)	BKZ 320mg Q2W N=289 n (%)	BKZ total N=433 n (%)	All Study Participants N=505 n (%)
RS	72 (100)	144 (100)	289 (100)	433 (100)	505 (100)
SS	72 (100)	143 (99.3)	286 (99.0)	429 (99.1)	501 (99.2)
FAS	71 (98.6)	140 (97.2)	284 (98.3)	424 (97.9)	495 (98.0)
AMS	65 (90.3)	143 (99.3)	286 (99.0)	429 (99.1)	494 (97.8)
MS	65 (90.3)	125 (86.8)	258 (89.3)	383 (88.5)	448 (88.7)
PPS	70 (97.2)	135 (93.8)	272 (94.1)	407 (94.0)	477 (94.5)
PK-PPS	64 (88.9)	140 (97.2)	286 (99.0)	426 (98.4)	490 (97.0)
CFS	69 (95.8)	140 (97.2)	283 (97.9)	423 (97.7)	492 (97.4)

AMS=Active Medication Set; BKZ=bimekizumab; CFS=COVID-19 Free Set; COVID-19=coronavirus disease 2019; FAS=Full Analysis Set; ITP=Initial Treatment Period; MS=Maintenance Set; PBO=placebo; PK-PPS=Pharmacokinetic Per-Protocol Set; PPS=Per-Protocol Set; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Note: Bimekizumab 320mg Q2W participants were pooled from BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Table 17. Study HS0004

Disposition	PBO N=74 n (%)	BKZ 320mg Q4W N=144 n (%)	BKZ 320mg Q2W N=291 n (%)	BKZ Total N=435 n (%)	All Study Participants N=509 n (%)
RS	74 (100)	144 (100)	291 (100)	435 (100)	509 (100)
SS	74 (100)	142 (98.6)	290 (99.7)	432 (99.3)	506 (99.4)
FAS	73 (98.6)	142 (98.6)	288 (99.0)	430 (98.9)	503 (98.8)
AMS	69 (93.2)	142 (98.6)	290 (99.7)	432 (99.3)	501 (98.4)
MS	69 (93.2)	133 (92.4)	261 (89.7)	394 (90.6)	463 (91.0)
PPS	72 (97.3)	141 (97.9)	287 (98.6)	428 (98.4)	500 (98.2)
PK-PPS	69 (93.2)	142 (98.6)	289 (99.3)	431 (99.1)	500 (98.2)
CFS	73 (98.6)	140 (97.2)	276 (94.8)	416 (95.6)	489 (96.1)

AMS=Active Medication Set; BKZ=bimekizumab; CFS=COVID-19 Free Set; COVID-19=coronavirus disease 2019; FAS=Full Analysis Set; ITP=Initial Treatment Period; MS=Maintenance Set; PBO=placebo; PK-PPS=Pharmacokinetic Per-Protocol Set; PPS=Per-Protocol Set; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Note: Bimekizumab 320mg Q2W participants were pooled from the BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Table 18. Number of participants in Pool E1

Study	Placebo	BKZ 320mg Q4W	BKZ 320mg Q2W
HS0003	72	144	289
HS0004	74	144	291
Total	146	288	580

BKZ=bimekizumab; CSR=clinical study report; Q2W=every 2 weeks; Q4W=every 4 weeks

Table 19. Number of participants in Pool E2

Study	BKZ 320mg Q2W/ BKZ 320mg Q2W	BKZ 320mg Q4W/ BKZ 320mg Q4W	BKZ 320mg Q2W/ BKZ 320mg Q4W	Placebo/ BKZ 320mg Q2W
HS0003	143	144	146	72
HS0004	145	144	146	74
Total	288	288	292	146

BKZ=bimekizumab; CSR=clinical study report; Q2W=every 2 weeks; Q4W=every 4 weeks

Outcomes and estimation

The primary and secondary efficacy endpoints were evaluated using a fixed-sequence, closed testing procedure, including a parallel gatekeeping framework to account for multiplicity.

Table 20. Sequential testing procedure of primary and secondary efficacy endpoints at Week 16 by randomised treatment group (RS) Study HS0003

Ordered sequential procedure	BKZ 320mg Q4W			BKZ 320mg Q2W			Observation
	Point estimate (97.5% CI)	p-value	Significant difference (Yes/No) [a]	Point estimate (97.5% CI)	p-value	Significant difference (Yes/No) [a]	
#1 $HiSCR_{50}$ [b] response at Week 16 vs PBO	2.000 (0.979, 4.089)	0.030	No	2.234 (1.159, 4.307)	0.006	Yes	Primary
#2 $HiSCR_{75}$ [c] response at Week 16 vs PBO	1.416 (0.615, 3.260)	0.350	No	2.175 (1.021, 4.635)	0.021	Yes	Secondary
#3 Change from Baseline in DLQI Total Score at Week 16 vs PBO	-2.574 (-4.472, -0.675)	0.002	No	-2.682 (-4.394, -0.970)	<0.001	Yes	Secondary
#4 Change from Baseline in Skin Pain score (as assessed by "worst skin pain" item in HSSDD) at Week 16 vs PBO	-0.551 (-1.521, 0.418)	0.201	No	-1.186 (-2.050, -0.322)	0.002	Yes	Secondary
#5 Pain response [d] status (as assessed by "worst skin pain" item in HSSDD) at Week 16 vs PBO	1.618 (0.489, 5.352)	0.367	No	2.757 (0.909, 8.364)	0.041	No	Secondary

a All tests were performed using a closed testing procedure under a parallel gatekeeping framework. Each dose of BKZ was tested simultaneously compared to PBO at a familywise error rate of 0.025.
b HiSCR50 is defined as a ≥50% reduction from Baseline in the total AN count with no increase from Baseline in abscess or draining tunnel count at Week 16.
c HiSCR75 is defined as a ≥75% reduction from Baseline in the total AN count with no increase from Baseline in abscess or draining tunnel count at Week 16.
d Skin pain response based on clinically meaningful change status at Week 16, as assessed by the "worst skin pain" item in the HSSDD, is defined as an improvement in the weekly worst skin pain score of at least 3 points· among study participants with a score of ≥3 at Baseline.

Table 21. Sequential testing procedure of primary and secondary efficacy endpoints at Week 16 by randomised treatment group (RS) Study HS0004

Ordered sequential procedure	BKZ 320mg Q4W			BKZ 320mg Q2W			Observation
	Point estimate (97.5% CI)	p-value	Significant difference (Yes/No) [a]	Point estimate (97.5% CI)	p-value	Significant difference (Yes/No) [a]	
#1 $HiSCR_{50}$ [b] response at Week 16 vs PBO	2.422 (1.221, 4.804)	0.004	Yes	2.287 (1.220, 4.291)	0.003	Yes	Primary
#2 $HiSCR_{75}$ [c] response at Week 16 vs PBO	2.722 (1.182, 6.267)	0.007	Yes	3.007 (1.374, 6.581)	0.002	Yes	Secondary
#3 Flare by Week 16 vs PBO	0.798 (0.378, 1.683)	0.497	No	1.050 (0.541, 2.041)	0.868	No	Secondary
#4 Change from Baseline in DLQI Total Score at Week 16 vs PBO	-2.393 (-3.920, -0.867)	<0.001	No	-2.309 (-3.705, -0.914)	<0.001	No	Secondary
#5 Change from Baseline in Skin Pain score (as assessed by "worst skin pain" item in HSSDD) at Week 16 vs PBO	-0.898 (-1.684, -0.113)	0.010	No	-1.265 (-1.978, -0.552)	<0.001	No	Secondary
#6 Pain response [d] status (as assessed by "worst skin pain" item in HSSDD) at Week 16 vs PBO	3.273 (0.974, 10.997)	0.028	No	3.756 (1.189, 11.867)	0.010	No	Secondary

a. All tests were performed using a closed testing procedure under a parallel gatekeeping framework. Each dose of BKZ was tested simultaneously compared to PBO at a familywise error rate of 0.025.
b. HiSCR50 is defined as a ≥50% reduction from Baseline in the total AN count with no increase from Baseline in abscess or draining tunnel count at Week 16.
c. HiSCR75 is defined as a ≥75% reduction from Baseline in the total AN count with no increase from Baseline in abscess or draining tunnel count at Week 16.
d. Skin pain response based on clinically meaningful change status at Week 16, as assessed by the "worst skin pain" item in the HSSDD, is defined as an improvement in the weekly worst skin pain score of at least 3 units points.

Primary endpoint

Table 22. HiSCR$_{50}$ response rates at Week 16 including logistic regression (MI using MCMC/Monotone Regression) (HS0003, HS0004, and Pool E1)

	HS0003			HS0004			Pool E1		
	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291	PBO N=146	BKZ 320mg Q4W N=288	BKZ 320mg Q2W N=580
Responder rate (% [95% CI])	28.7 (18.1, 39.3)	45.3 (36.8, 53.8)	47.8 (41.8, 53.7)	32.2 (21.4, 42.9)	53.8 (45.4, 62.1)	52.0 (46.1, 57.8)	30.9 (23.2, 38.5)	49.8 (43.8, 55.7)	49.9 (45.7, 54.0)
Adjusted responder rate (% [95% CI])	26.7 (15.0, 38.4)	42.1 (31.0, 53.2)	44.8 (35.8, 53.8)	30.7 (18.6, 42.7)	51.7 (40.7, 62.7)	50.3 (41.5, 59.0)	28.8 (20.4, 37.3)	47.4 (39.5, 55.3)	47.7 (41.4, 54.0)
n/Nsub (%)	24/65 (36.9)	72/124 (58.1)	151/257 (58.8)	24/70 (34.3)	80/133 (60.2)	164/265 (61.9)	48/135 (35.6)	152/257 (59.1)	315/522 (60.3)
Odds ratio vs PBO	-	2.000	2.234	-	2.422	2.287	-	2.227	2.252
95% CI for odds ratio	-	(1.071, 3.738)	(1.259, 3.966)	-	(1.331, 4.408)	(1.320, 3.965)	-	(1.447, 3.427)	(1.514, 3.349)
p-value	-	0.030	0.006	-	0.004	0.003	-	<0.001[a]	<0.001[a]
Difference vs PBO	-	15.432	18.145	-	21.037	19.610	-	18.6	18.9
95% CI for difference	-	(2.135, 28.730)	(6.313, 29.977)	-	(7.509, 34.566)	(7.501, 31.719)	-	(9.1, 28.1)	(10.4, 27.4)

BKZ=bimekizumab; CI=confidence interval; CSR=clinical study report; HiSCR=Hidradenitis Suppurativa Clinical Response; ISE=Integrated Summary of Efficacy; MCMC=Markov-Chain Monte Carlo; MI=multiple imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

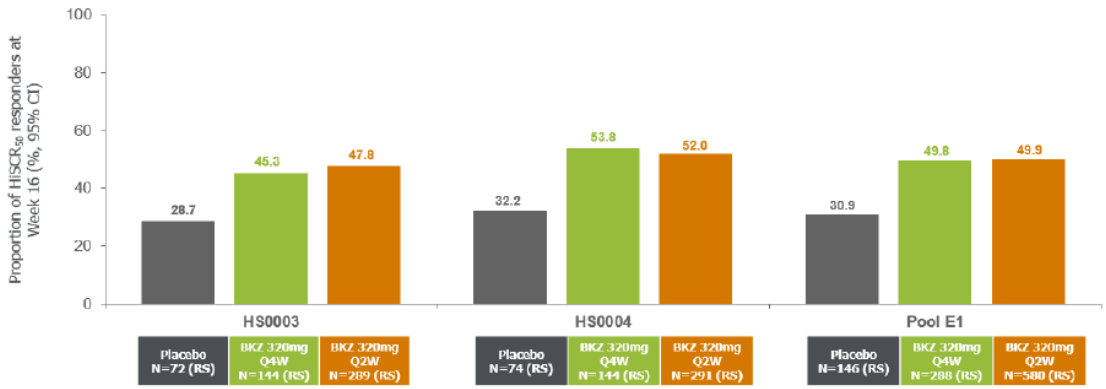
Note: A HiSCR$_{50}$ response was achieved at a given visit if the percentage change from Baseline in abscess and inflammatory nodule count was less than or equal to -50%, and there was no increase from Baseline in abscess or draining tunnel count.

Note: Intermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Lesion counts were imputed and then dichotomized to obtain the response status. Participants who experienced an intercurrent event were treated as nonresponders following the intercurrent event.

Note: In the n/Nsub (%) row, Nsub represents the number of participants with a nonmissing measurement at Week 16, and percentages were calculated accordingly (ie, where data recorded after an intercurrent event were included as recorded).

Note: Adjusted responder rate, difference in responder rates and CIs, odds ratio, corresponding CIs and p-value (from Wald test) were obtained from logistic regression with factors for treatment, Hurley Stage at Baseline, and Baseline antibiotic use.

Figure 20. HiSCR$_{50}$ response rates at Week 16 (mNRI [All-ABX]) (HS0003, HS0004, and Pool E1)



ABX=antibiotics; BKZ=bimekizumab; CI=confidence interval; CSR=clinical study report; HiSCR=Hidradenitis Suppurativa Clinical Response; ISE=Integrated Summary of Efficacy; mNRI=modified nonresponder imputation; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: A HiSCR$_{50}$ response was achieved at a given visit if the percentage change from Baseline in abscess and inflammatory nodule count was less than or equal to -50%, and there was no increase from Baseline in abscess or draining tunnel count.

Sensitivity analyses of the primary efficacy endpoint

Results of the sensitivity analyses for the HiSCR50 responder rate at Week 16 supported the primary efficacy result, except for the tipping point analyses. Tipping point analyses are designed to "tip" significant results based on stringent assumptions related to missing data.

Supportive analyses of intercurrent events due to antibiotics: Pool E1

To assess the impact of antibiotics on the primary efficacy variable, 2 additional post hoc analyses were performed to understand to what extent antibiotic use influenced efficacy.
Supportive post-hoc analysis methods for the primary analysis were performed with alternative methods for defining intercurrent events related to systemic antibiotic use (antibiotic use defined as rescue for HS and antibiotic use based on international guidelines by drug class).

Figure 21. Analysis schematic with different methods for handling systemic antibiotic use

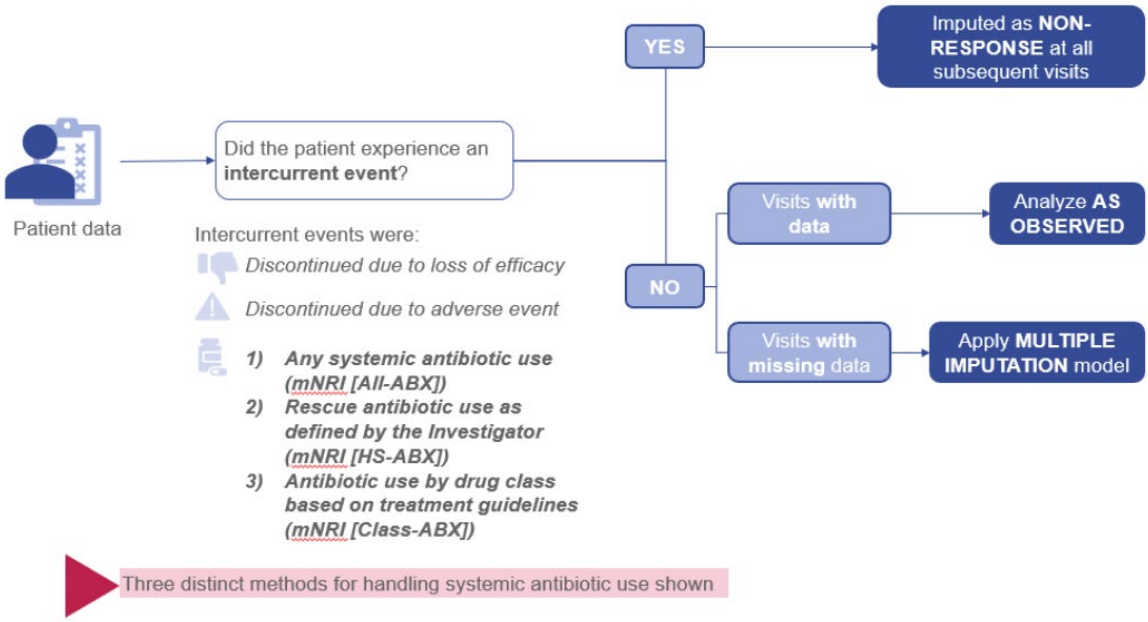


Table 23. Summary of intercurrent events during the Combined ITP and MTP (RS) Study HS0003

Intercurrent event type	PBO/BKZ 320mg Q2W N=72 n (%)	BKZ 320mg Q4W/Q4W N=144 n (%)	BKZ 320mg Q2W/Q4W N=146 n (%)	BKZ 320mg Q2W/Q2W N=143 n (%)
All intercurrent events	38 (52.8)	71 (49.3)	65 (44.5)	62 (43.4)
Discontinued due to adverse event	1 (1.4)	10 (6.9)	8 (5.5)	2 (1.4)
Discontinued due to lack of efficacy	1 (1.4)	2 (1.4)	0	0
Systemic antibiotic rescue medication use	36 (50.0)	59 (41.0)	57 (39.0)	60 (42.0)

BKZ=bimekizumab; ITP=Initial Treatment Period; MTP=Maintenance Treatment Period; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.
Note: Bimekizumab 320mg Q2W participants were pooled from BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Table 24. Summary of intercurrent events during the Combined ITP and MTP (RS) Study HS0004

Intercurrent event type	PBO/BKZ 320mg Q2W N=74 n (%)	BKZ 320mg Q4W/Q4W N=144 n (%)	BKZ 320mg Q2W/Q4W N=146 n (%)	BKZ 320mg Q2W/Q2W N=145 n (%)
All intercurrent events	18 (24.3)	51 (35.4)	63 (43.2)	56 (38.6)
Discontinued due to adverse event	1 (1.4)	4 (2.8)	7 (4.8)	7 (4.8)
Discontinued due to lack of efficacy	0	3 (2.1)	1 (0.7)	1 (0.7)
Systemic antibiotic rescue medication use	17 (23.0)	44 (30.6)	55 (37.7)	48 (33.1)

BKZ=bimekizumab; ITP=Initial Treatment Period; MTP=Maintenance Treatment Period; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

The time to an intercurrent event during the Initial Treatment Period was similar for the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups compared with the placebo group for both pivotal studies.

The time to initiation of systemic antibiotic therapy (intercurrent event) during the Initial Treatment Period was similar for the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups compared with the placebo group in for both pivotal studies.

Table 25. Systemic antibiotic use by analysis method definition during the 48-week treatment period: Pool E2

Systemic antibiotic definition	PBO/BKZ 320mg Q2W N=146	BKZ 320mg Q4W/Q4W N=288	BKZ 320mg Q2W/Q4W N=292	BKZ 320mg Q2W/Q2W N=288
All systemic antibiotic use (mNRI [All-ABX])	53 (36.3)	103 (35.8)	112 (38.4)	108 (37.5)
Rescue antibiotic use as defined by the Investigator (mNRI [HS-ABX])	21 (14.4)	38 (13.2)	33 (11.3)	28 (9.7)
Antibiotic use by drug class based on treatment guidelines (mNRI [Class-ABX])	23 (15.8)	47 (16.3)	42 (14.4)	37 (12.8)

ABX=antibiotics; BKZ=bimekizumab; HS=hidradenitis suppurativa; ISE=Integrated Summary of Efficacy; mNRI=modified non-responder imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks

Table 26. Comparison of primary and supportive analysis methods for defining intercurrent events relative to antibiotic use for HiSCR$_{50}$ at Week 16: Pool E1

	PBO			BKZ 320mg Q4W			BKZ 320mg Q2W		
	mNRI (All-ABX)	mNRI (HS-ABX)	mNRI (Class-ABX)	mNRI (All-ABX)	mNRI (HS-ABX)	mNRI (Class-ABX)	mNRI (All-ABX)	mNRI (HS-ABX)	mNRI (Class-ABX)
	N=146			N=288			N=580		
Responder rate (%, [95% CI])	30.9 (23.2, 38.5)	33.4 (25.6, 41.2)	33.9 (26.1, 41.7)	49.8 (43.8, 55.7)	56.1 (50.2, 62.0)	54.2 (48.2, 60.2)	49.9 (45.7, 54.0)	56.9 (52.8, 61.1)	55.4 (51.3, 59.6)

ABX=antibiotics; BKZ=bimekizumab; CI=confidence interval; HiSCR=Hidradenitis Suppurativa Clinical Response; HS=hidradenitis suppurativa; ISE=Integrated Summary of Efficacy; ITP=Initial Treatment Period; MI=multiple imputation; mNRI=modified non-response imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SAP=Statistical Analysis Plan

Note: A HiSCR$_{50}$ response was achieved at a given visit if the percentage change from Baseline in abscess and inflammatory nodule count was less than or equal to -50%, and there was no increase from Baseline in abscess or draining tunnel count.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Note: Bimekizumab 320mg Q2W participants were pooled from the BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Note: All-ABX=any systemic antibiotic use treated as an intercurrent event: This was the primary analysis method defined in the study SAP. It counted all antibiotic use as an intercurrent event (treatment failure) and is designated as mNRI.

Note: Class-ABX=systemic antibiotic use based on standard of care for HS (Dermatology Association, European HS Foundation, European Academy of Dermatology and Venereology, Swiss Consensus Group, Brazilian Society of Dermatology) by drug class were treated as an intercurrent event: Drug coding was used to identify antibiotics used for HS based on international guidelines, and these were treated as intercurrent events. This analysis was described in the ISAP and is designated as mNRI.

Note: HS-ABX=systemic antibiotic use for HS rescue (as defined by the Investigator) treated as an intercurrent event: The Case Report Form allowed the Investigator to mark whether an antibiotic was given as rescue medication for HS. In this analysis, only those antibiotics marked as being given as rescue for HS were treated as intercurrent events. This analysis was described in the ISAP and is designated as mNRI.

HiSCR50 at Week 16 by systemic antibiotic use in the ITP

For study participants who had systemic antibiotic use initiated for any reason during the ITP versus those who did not

The percentage of HiSCR50 responders at Week 16 among those who did not have systemic antibiotic use was higher across all treatment groups (placebo, bimekizumab 320mg Q4W, bimekizumab 320mg Q2W): 34.4%, 53.6%, and 55.9%, respectively, compared with those who used systemic antibiotics: 23.8%, 47.5%, and 46.2%, respectively. This analysis is based on a non-responder imputation (NRI).

Table 27. Analysis of HiSCR$_{50}$ responder rate at Week 16 by systemic antibiotic use during the ITP (RS [NRI]) (Pool E1)

Variable	PBO N=146 n/N (%)	BKZ 320mg Q4W N=288 n/N (%)	BKZ 320mg Q2W N=580 n/N (%)
Systemic Antibiotic use Intercurrent Event during the ITP			
No	43/125 (34.4)	133/248 (53.6)	272/487 (55.9)
Yes	5/21 (23.8)	19/40 (47.5)	43/93 (46.2)

BKZ=bimekizumab; HiSCR=Hidradenitis Suppurativa Clinical Response; ISE=Integrated Summary of Efficacy; ITP=Initial Treatment Period; NRI=nonresponder imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: A HiSCR$_{50}$ response was achieved at a given visit if the percentage change from Baseline in abscess and inflammatory nodule count was less than or equal to -50%, and there was no increase from Baseline in abscess or draining tunnel count.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Note: Bimekizumab 320mg Q2W participants were pooled from the BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Analysis of HiSCR50 responder rate at Week 16 by lesion intervention during the ITP (RS [NRI])

Study HS0003

The HiSCR50 responder rates were higher for study participants who had lesion intervention compared with those who did not in the bimekizumab 320mg Q4W group (67.3% vs 44.3%, respectively). The HiSCR50 responder rates were lower for study participants who had lesion intervention compared with those who did not in the bimekizumab 320mg Q2W group (33.7% vs 48.1%, respectively).

Study HS0004

Lesion intervention: the HiSCR50 responder rates were lower for study participants who had lesion intervention compared with those who did not in the bimekizumab 320mg Q4W group (36.5% vs 53.7%) and the bimekizumab 320mg Q2W group (32.2% vs 51.3%).

Analysis of HiSCR50 responder rate at Week 16 by Hurley stage during the ITP

Overall in the pooled analyses, 55.7% of study participants had Baseline Hurley Stage II and 44.3% had Baseline Hurley Stage III. At Week 16, study participants who had Baseline Hurley Stage II compared with Baseline Hurley Stage III had similar HiSCR50 and HiSCR75 responder rates in the bimekizumab Q4W group and higher responder rates in the bimekizumab Q2W total group. At Week 48, study participants who had Baseline Hurley Stage II compared with Baseline Hurley Stage III had higher HiSCR50 and HiSCR75 responder rates in the bimekizumab Q4W/Q4W group and similar responder rates in the bimekizumab Q2W/Q2W group.

In Study HS0003 the HiSCR50 responder rates were higher for study participants who had Hurley Stage II compared with Hurley Stage III in the bimekizumab 320mg Q2W group (53.1% vs 42.1%, respectively).

In HS0004 the HiSCR50 responder rates were higher for study participants who had Hurley Stage II compared with Hurley Stage III in the bimekizumab 320mg Q2W group (58.1% vs 42.4%, respectively).

In the E1 pooled analysis response rates in the bimekizumab 320mg Q2W group were higher in participants with Hurley Stage II at Baseline (55.6%) compared with those with Hurley Stage III at Baseline (42.4%).

Ranked secondary endpoints Study HS0003 and Study HS0004

A summary of the results of the ranked secondary endpoints for both pivotal studies and the integrated analysis is presented below.

Flare was the second ranked endpoint for study HS0004 and was downgraded to an ‘other’ endpoint for study HS0003 during protocol amendment #5.

Table 28. Summary of secondary endpoints at Week 16 for the Phase 3 studies and Pool E1 for the ITP

Endpoint	HS0003			HS0004			Pool E1		
	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291	PBO N=146	BKZ 320mg Q4W N=288	BKZ 320mg Q2W N=580
$HiSCR_{75}$ responder rate (% [95% CI])	18.4 (9.3, 27.5)	24.7 (17.3, 32.1)	33.4 (27.8, 39.1)	15.6 (7.2, 24.0)	33.7 (25.7, 41.7)	35.7 (30.1, 41.3)	16.9 (10.8, 23.1)	29.3 (23.9, 34.8)	34.6 (30.6, 38.6)
DLQI Total Score; absolute CfB; mean (SE)	-2.7 (0.9)	-5.5 (0.6)	-5.0 (0.4)	-3.2 (0.6)	-4.7 (0.5)	-4.6 (0.3)	-3.0 (0.5)	-5.1 (0.4)	-4.8 (0.3)
HSSDD worst skin pain score; absolute CfB; mean (SE)	-0.99 (0.38)	-1.56 (0.26)	-2.00 (0.17)	-0.36 (0.30)	-1.44 (0.24)	-1.83 (0.17)	-0.70 (0.23)	-1.48 (0.18)	-1.92 (0.12)
HSSDD worst skin pain response; responder rate (% [95% CI])	15.0 (3.6, 26.5)	22.1 (12.7, 31.4)	32.3 (25.1, 39.5)	10.9 (1.7, 20.1)	28.6 (19.5, 37.8)	31.8 (25.1, 38.4)	12.8 (5.4, 20.1)	25.0 (18.7, 31.4)	32.4 (27.6, 37.2)

BKZ=bimekizumab; CfB=change from Baseline; CI=confidence interval; CSR=clinical study report; DLQI=Dermatology Life Quality Index; HiSCR=Hidradenitis Suppurativa Clinical Response; HSSDD=Hidradenitis Suppurativa Symptom Daily Diary; ISE=Integrated Summary of Efficacy; ITP=Initial Treatment Period; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error

Note: A $HiSCR_{75}$ response was achieved at a given visit if the percentage change from Baseline in abscess and inflammatory nodule count was less than or equal to -75%, and there was no increase from Baseline in abscess or draining tunnel count.

Note: Worst pain score was assessed by the "worst pain" item in the HSSDD. The score was derived from the weekly average of scores, defined as the sum of the scored item over the course of the study week divided by the number of days in which the item was completed, relative to each respective visit date.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Note: BKZ 320mg Q2W participants were pooled from BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Table 29. $HiSCR_{75}$ at Week 16 (study HS0003, study HS0004, Pool E1)

	HS0003			HS0004			Pool E1		
	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291	PBO N=146	BKZ 320mg Q4W N=288	BKZ 320mg Q2W N=580
Responder rate (% [95% CI])	18.4 (9.3, 27.5)	24.7 (17.3, 32.1)	33.4 (27.8, 39.1)	15.6 (7.2, 24.0)	33.7 (25.7, 41.7)	35.7 (30.1, 41.3)	16.9 (10.8, 23.1)	29.3 (23.9, 34.8)	34.6 (30.6, 38.6)
Adjusted responder rate (% [95% CI])	20.3 (9.4, 31.2)	26.5 (16.7, 36.4)	35.7 (27.0, 44.4)	16.3 (6.8, 25.7)	34.6 (24.2, 44.9)	36.8 (28.4, 45.2)	18.2 (11.0, 25.3)	31.2 (23.8, 38.5)	36.4 (30.4, 42.5)
n/Nsub (%)	13/65 (20.0)	42/124 (33.9)	107/257 (41.6)	12/70 (17.1)	51/133 (38.3)	112/265 (42.3)	25/135 (18.5)	93/257 (36.2)	219/522 (42.0)
Odds ratio vs PBO	-	1.416	2.175	-	2.722	3.007	-	2.039	2.584
95% CI for odds ratio	-	(0.683, 2.936)	(1.123, 4.215)	-	(1.313, 5.644)	(1.516, 5.964)	-	(1.220, 3.408)	(1.608, 4.150)
p-value	-	0.350	0.021	-	0.007	0.002	-	0.007[a]	<0.001[a]
Difference vs PBO	-	6.217	15.352	-	18.299	20.574	-	13.0	18.3
95% CI for difference	-	[-6.437, 18.871]	[3.710, 26.995]	-	[6.181, 30.417]	[9.888, 31.260]	-	[4.2, 21.8]	[10.4, 26.1]

a Denotes nominal p-value for Pool E1.

Note: BKZ 320mg Q2W participants were pooled from the BKZ 320mg Q2W/Q2W and BKZ 320mg Q2W/Q4W groups.

Flare by Week 16 (only an endpoint in Study HS0004)

The flare rate at any time during the ITP was similar in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups compared with the placebo group (23.6% and 28.8% vs 28.0%; p=0.497 and p=0.868, respectively).

Table 30. Analysis of flare by Week 16 (RS [MI using MCMC/monotone regression]) (HS0004)

Variable	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291
At any time across ITP			
Flare rate (%, [95% CI])	28.0 (17.6, 38.4)	23.6 (16.5, 30.7)	28.8 (23.5, 34.1)
Adjusted flare rate (%, [95% CI])	26.4 (14.7, 38.1)	22.3 (13.4, 31.1)	27.4 (19.5, 35.2)
n/Nsub (%)	15/73 (20.5)	18/142 (12.7)	42/288 (14.6)
Odds ratio vs PBO	-	0.798	1.050
97.5% CI for odds ratio	-	(0.378, 1.683)	(0.541, 2.041)
95% CI for odds ratio	-	(0.415, 1.533)	(0.588, 1.877)
p-value	-	0.497	0.868
Difference vs PBO	-	-4.152	0.960
95% CI for difference	-	[-16.350, 8.047]	[-10.370, 12.289]

Table 31. Absolute change from Baseline in DLQI Total Score at Week 16 (Study HS0003, Study HS0004, Pool E1)

	HS0003			HS0004			Pool E1		
Variable	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291	PBO N=146	BKZ 320mg Q4W N=288	BKZ 320mg Q2W N=580
Descriptive statistics, n	64	124	250	68	131	264	132	255	514
Mean (SD)	-2.67 (6.15)	-5.51 (6.47)	-5.01 (6.05)	-3.07 (5.03)	-4.14 (5.35)	-4.49 (5.64)	-2.88 (5.59)	-4.80 (5.95)	-4.74 (5.84)
Median	-2.00	-5.00	-4.00	-3.00	-3.00	-3.00	-2.00	-4.00	-4.00
Q1, Q3	-6.00, 1.00	-8.50, -2.00	-8.00, -1.00	-6.50, 0.00	-7.00, 0.00	-8.00, 0.00	-6.00, 0.00	-8.00, -1.00	-8.00, -1.00
Min, max	-20.0, 18.0	-28.0, 10.0	-26.0, 11.0	-17.0, 9.0	-22.0, 9.0	-25.0, 10.0	-20.0, 18.0	-28.0, 10.0	-26.0, 11.0
ANCOVA results									
LS mean (SE)	-2.532 (0.783)	-5.106 (0.603)	-5.214 (0.472)	-2.382 (0.640)	-4.776 (0.529)	-4.692 (0.405)	-2.476 (0.502)	-4.945 (0.393)	-4.955 (0.314)
95% CI for LS mean	[-4.069, -0.996]	[-6.287, -3.924]	[-6.139, -4.289]	[-3.636, -1.128]	[-5.813, -3.738]	[-5.486, -3.897]	[-3.461, -1.491]	[-5.715, -4.175]	[-5.570, -4.340]
Difference [a] vs PBO	-	-2.574	-2.682	-	-2.393	-2.309	-	-2.469	-2.480
95% CI for difference	-	[-4.233, -0.914]	[-4.179, -1.186]	-	[-3.729, -1.058]	[-3.530, -1.089]	-	[-3.531, -1.407]	[-3.441, -1.518]
p-value	-	0.002	<0.001	-	<0.001	<0.001	-	<0.001[b]	<0.001[b]

a The differences presented were 'BKZ minus PBO'. Negative values indicate an improvement in symptoms.
b Denotes nominal p-value for Pool E1.

Absolute change from Baseline in HSSDD worst skin pain at Week 16 (Study HS0003, Study HS0004, Pool E1 [All-ABX])

Table 32. Analysis of change from Baseline in HSSDD worst skin pain score at Week 16 (RS [MI using MCMC/monotone regression]) HS0003, HS0004 and Pool E1

Variable	HS0003			HS0004			Pool E1		
	PBO N=72	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=289	PBO N=74	BKZ 320mg Q4W N=144	BKZ 320mg Q2W N=291	PBO N=146	BKZ 320mg Q4W N=288	BKZ 320mg Q2W N=580
Descriptive statistics, n	33	72	174	52	94	192	85	166	366
Mean (SD)	-1.09 (2.02)	-1.68 (2.29)	-1.91 (2.59)	-0.44 (2.14)	-1.65 (2.60)	-1.90 (2.43)	-0.69 (2.11)	-1.67 (2.46)	-1.90 (2.50)
Median	-0.47	-1.79	-1.73	-0.24	-1.68	-1.86	-0.43	-1.71	-1.77
Q1, Q3	-2.20, 0.43	-3.23, 0.00	-3.42, -0.14	-1.57, 0.63	-3.57, -0.14	-3.47, 0.00	-2.00, 0.57	-3.50, 0.00	-3.43, 0.00
Min, max	-6.9, 2.3	-7.1, 4.8	-7.8, 5.6	-7.7, 3.9	-7.2, 6.0	-9.3, 3.3	-7.7, 3.9	-7.2, 6.0	-9.3, 5.6
ANCOVA results									
LS mean (SE)	-0.971 (0.392)	-1.523 (0.297)	-2.157 (0.225)	-0.299 (0.334)	-1.197 (0.272)	-1.564 (0.228)	-0.702 (0.254)	-1.339 (0.204)	-1.882 (0.156)
95% CI for LS mean	[-1.742, -0.200]	[-2.106, -0.939]	[-2.598, -1.716]	[-0.953, 0.355]	[-1.731, -0.664]	[-2.012, -1.116]	[-1.202, -0.203]	[-1.740, -0.939]	[-2.187, 1.577]
Difference [a] vs PBO	-	-0.551	-1.186	-	-0.898	-1.265	-	-0.637	-1.179
95% CI for difference	-	[-1.398, 0.296]	[-1.941, -0.431]	-	[-1.585, -0.211]	[-1.888, -0.641]	-	[-1.184, -0.089]	[-1.673, -0.686]
p-value	-	0.201	0.002	-	0.010	<0.001	-	0.023[b]	<0.001[b]

[a]The differences presented are 'BKZ minus PBO.' Negative values indicate an improvement in symptoms.
[b] The p-values for the BKZ 320mg Q4W and Q2W doses compared with PBO are considered nominal because the testing procedure stopped at the flare endpoint.

Table 33. HSSDD worst skin pain responder rate based on threshold for clinically meaningful within-patient change (at least a 3-point reduction) at Week 16 among study participants with a score of ≥3 at Baseline (MI using MCMC/monotone regression)

	HS0003			HS0004			Pool E1		
	PBO N=72 Nresp=46	BKZ 320mg Q4W N=144 Nresp=103	BKZ 320mg Q2W N=289 Nresp=190	PBO N=74 Nresp=49	BKZ 320mg Q4W N=144 Nresp=108	BKZ 320mg Q2W N=291 Nresp=209	PBO N=146 Nresp=95	BKZ 320mg Q4W N=288 Nresp=211	BKZ 320mg Q2W N=580 Nresp=399
Responder rate (% [95% CI])	15.0 (3.6, 26.5)	22.1 (12.7, 31.4)	32.3 (25.1, 39.5)	10.9 (1.7, 20.1)	28.6 (19.5, 37.8)	31.8 (25.1, 38.4)	12.8 (5.4, 20.1)	25.0 (18.7, 31.4)	32.4 (27.6, 37.2)
Adjusted responder rate (% [95% CI])	16.7 (3.6, 29.8)	24.4 (12.3, 36.5)	35.4 (24.1, 46.6)	10.2 (0.7, 19.7)	27.0 (14.7, 39.3)	29.8 (18.9, 40.7)	13.2 (5.2, 21.3)	25.6 (17.0, 34.1)	33.0 (25.2, 40.8)
n/Nsub (%)	4/26 (15.4)	21/66 (31.8)	55/138 (39.9)	4/42 (9.5)	28/78 (35.9)	62/163 (38.0)	8/68 (11.8)	49/144 (34.0)	117/301 (38.9)
Odds ratio vs PBO	-	1.618	2.757	-	3.273	3.756	-	2.268	3.258
95% CI for odds ratio	-	(0.569, 4.606)	(1.045, 7.276)	-	(1.134, 9.445)	(1.373, 10.271)	-	(1.064, 4.837)	(1.624, 6.536)
p-value	-	0.367	0.041	-	0.028	0.010	-	0.034[a]	<0.001[a]
Difference vs PBO	-	7.678	18.658	-	16.793	19.568	-	12.4	19.8
95% CI for difference	-	[-8.359, 23.715]	[3.323, 33.994]	-	[3.362, 30.224]	[7.495, 31.640]	-	[1.9, 22.9]	[10.3, 29.3]

[a] Denotes nominal p-value for Pool E1.

Exploratory analysis

Long-term efficacy data for the bimekizumab 320mg Q2W and bimekizumab 320mg Q4W treatment arms from Baseline through Week 48

Efficacy results up to Week 48 for the subgroup of subjects who were randomised to either the Bimekizumab Q2W or Q4W dose regimens and had completed 48 weeks of treatment at the time of the primary endpoint analysis data cut-off date are based on observed data. Pool E2 was used to evaluate the long-term efficacy data for the bimekizumab 320mg Q2W and bimekizumab 320mg Q4W treatment arms from Baseline through Week 48. This pool was also used to investigate the effect of reducing the dosing regimen from bimekizumab 320mg Q2W to Q4W, as well as to evaluate the onset and maintenance of treatment effect for participants originally randomised to placebo who switched to bimekizumab 320mg Q2W for Week 16 to 48.

Responder rates over time: HiSCR50, HiSCR75, and HiSCR90

Study HS0003

The HiSCR50 responder rates increased rapidly over time through Week 12 and was higher from Week 4 to Week 16 in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W total groups compared with the placebo group. The HiSCR50 and HiSCR90 responder rates over time through Week 16 were similar for the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups.

Figure 22. Line plots of $HiSCR_{50}$, $HiSCR_{75}$, and $HiSCR_{90}$ responder rates over time by treatment group (RS [MI using MCMC/monotone regression – mNRI (all-ABX)])

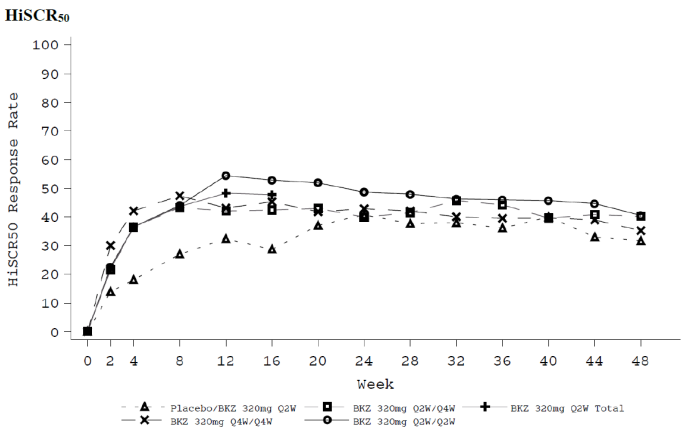


Figure 23. Line plots of HiSCR$_{50}$ responder rates over time by treatment group (RS [mNRI (HS-ABX)], OC) (HS0003)

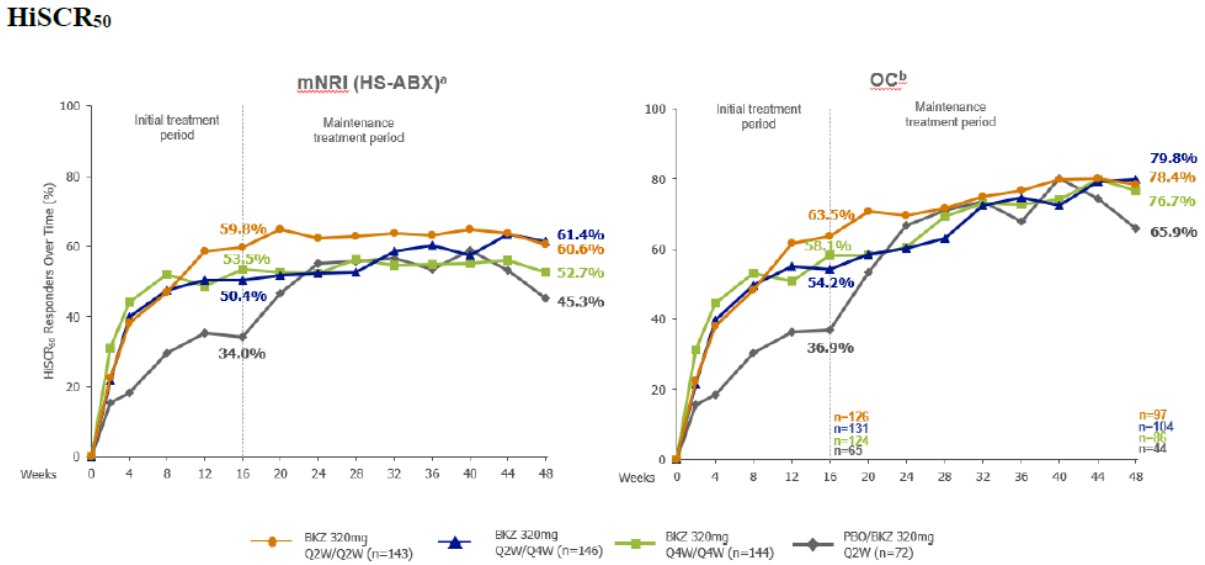


Figure 24. Line plots, HiSCR$_{75}$, responder rates over time by treatment group (RS [MI using MCMC/monotone regression – mNRI (all-ABX)])

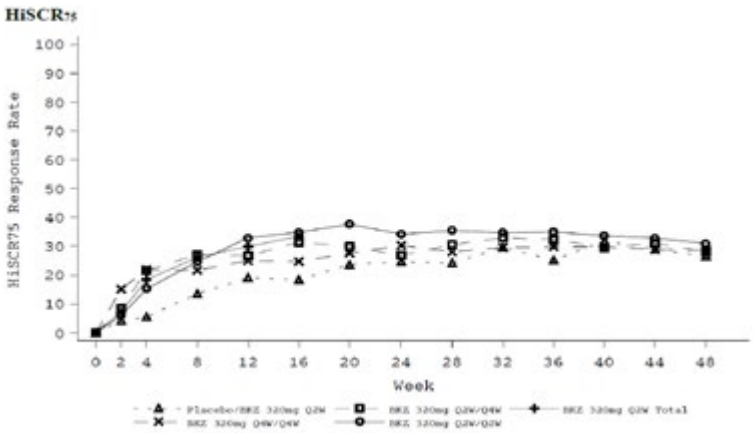


Figure 25. Line plots of HiSCR$_{75}$ responder rates over time by treatment group (RS [mNRI (HS-ABX)], OC) (HS0003)

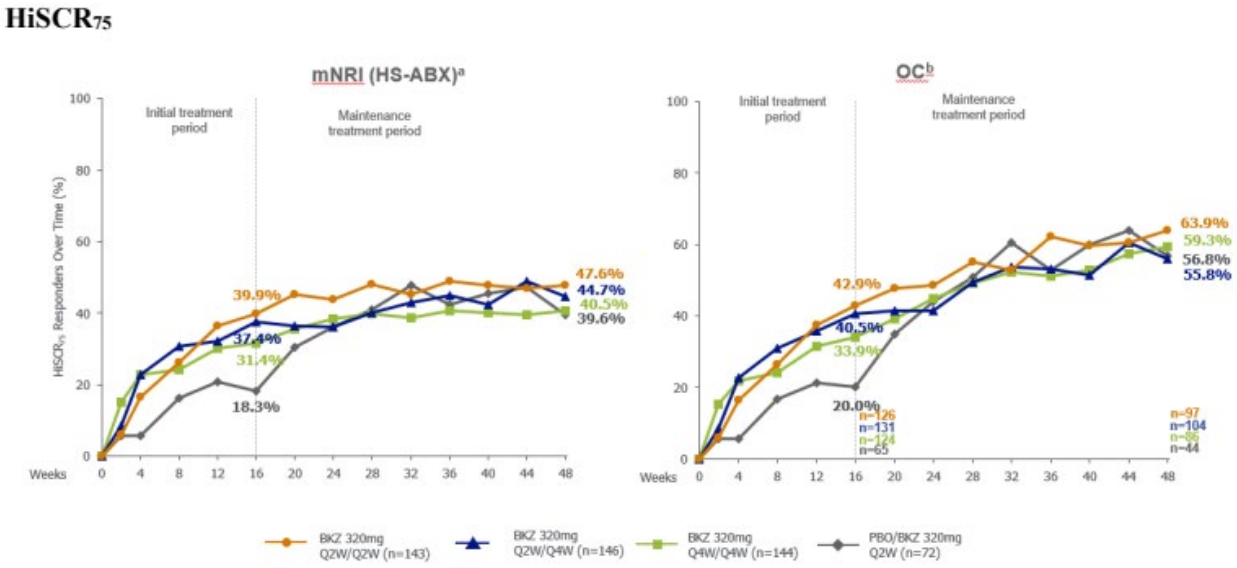
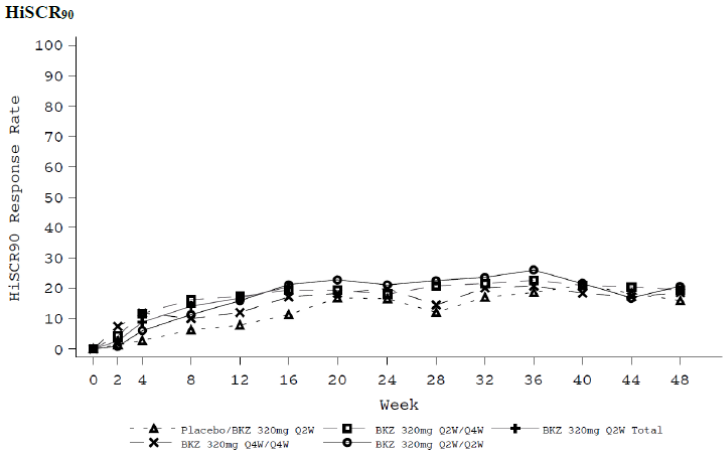
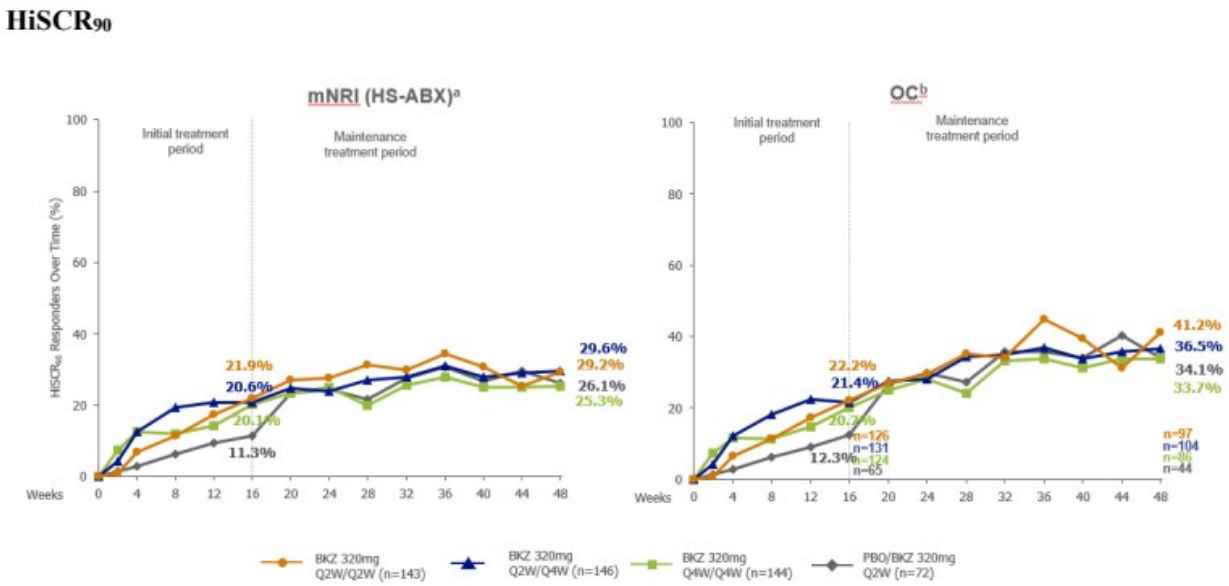


Figure 26. Line plots of HiSCR$_{90}$ responder rates over time by treatment group (RS [MI using MCMC/monotone regression – mNRI (all-ABX)]) (HS0003)





Study HS0004

The HiSCR50 over time through Week 16 were similar for the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups.

Figure 27. Line plots of HiSCR$_{50}$, HiSCR$_{75}$, and HiSCR$_{90}$ responder rates over time by treatment group (RS [MI using MCMC/monotone regression – mNRI (all-ABX)]])

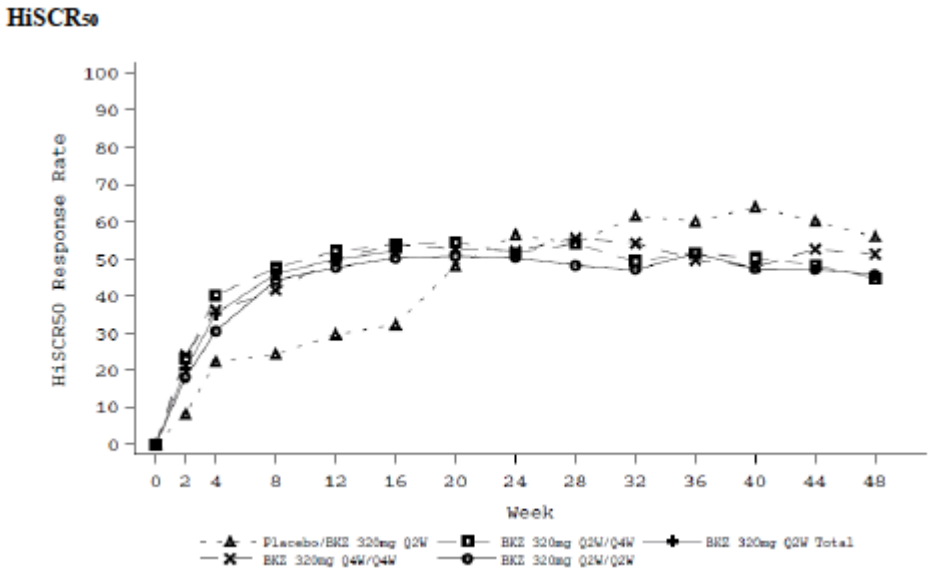


Figure 28. Line plots of HiSCR$_{50}$, HiSCR$_{75}$, HiSCR$_{90}$ responder rates over time by treatment group (RS [mNRI (HS-ABX)], OC) (HS0004)

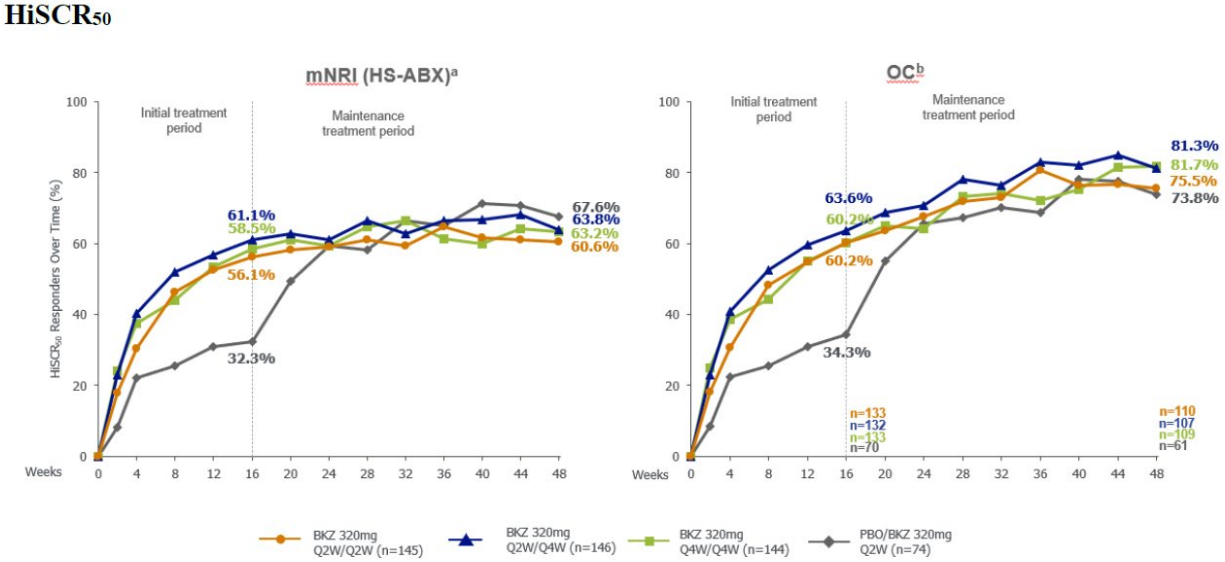
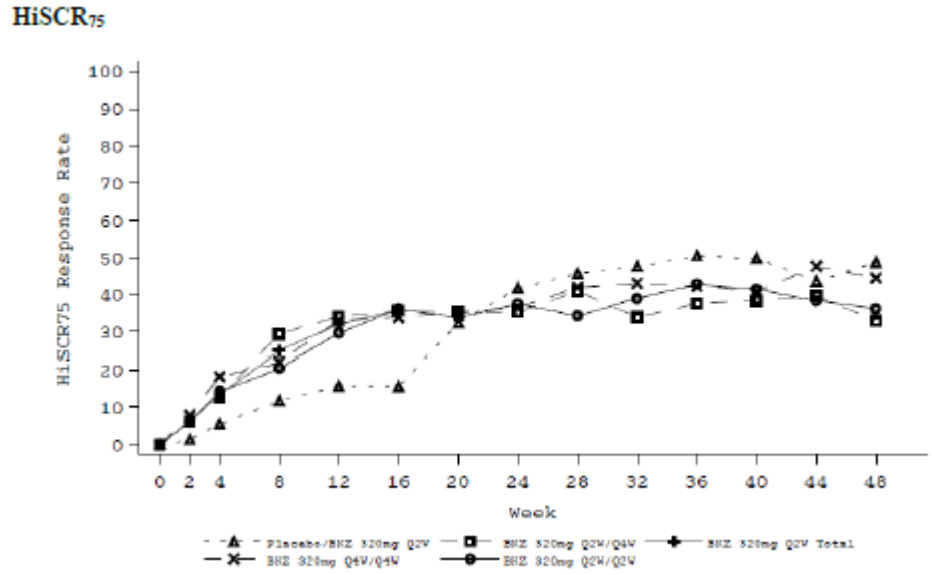
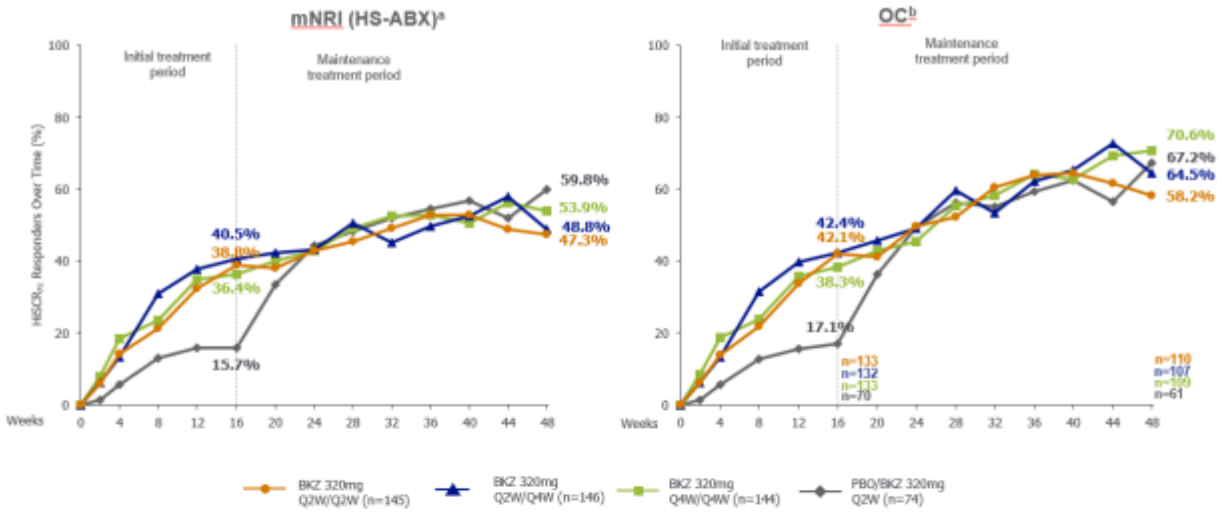


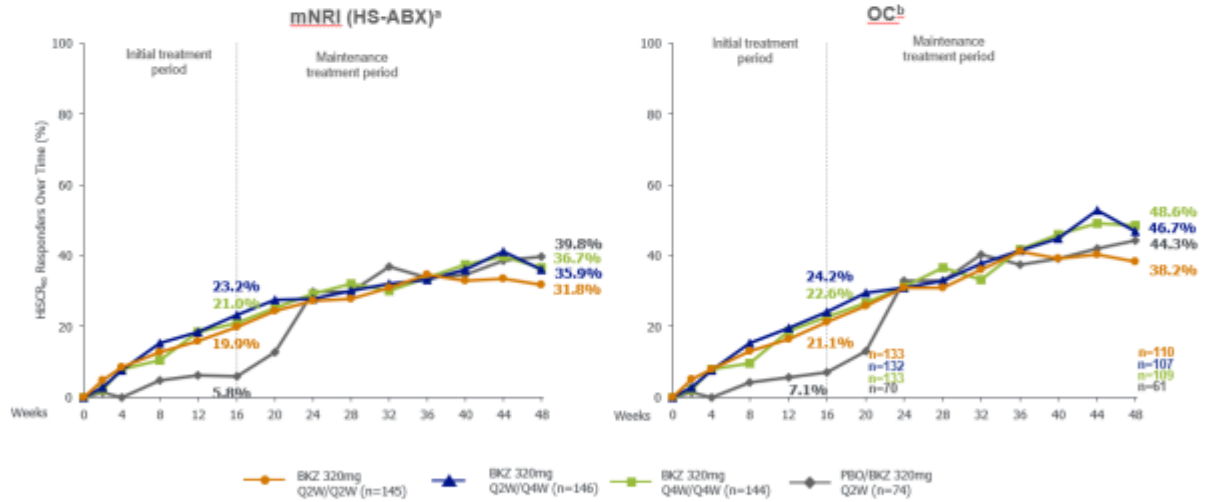
Figure 29. Line plot of HiSCR$_{75}$ responder rates overtime by treatment group (RS [MI using MCMC/monotone regression – mNRI (all-ABX)]])



HiSCR75



HiSCR90

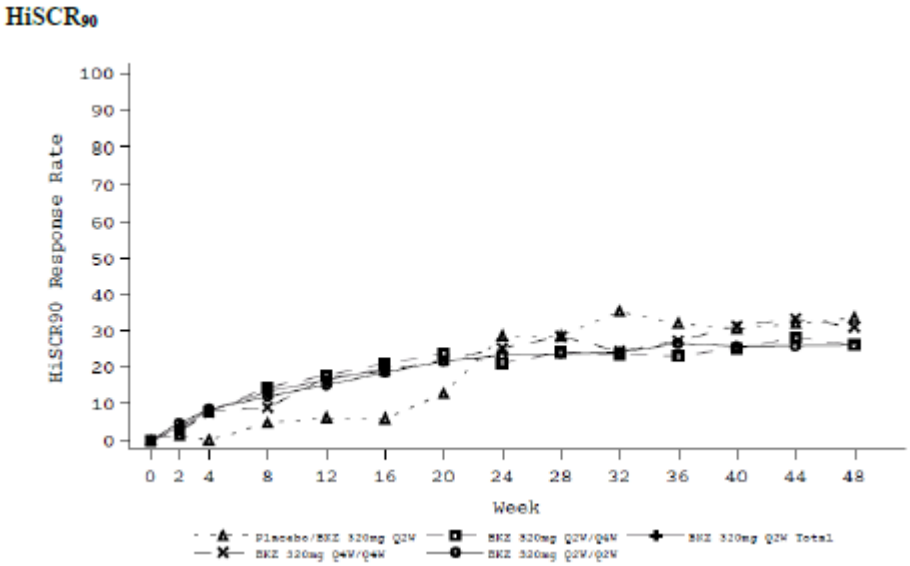


AB=abscess; ABX=antibiotics; AE=adverse event; AN=abscess and inflammatory nodule; BKZ=bimekizumab; DT=draining tunnels; HiSCR=Hidradenitis Suppurativa Clinical Response; HS= hidradenitis suppurativa; ISE=Integrated Summary of Efficacy; ITP=Initial Treatment Period; mNRI=modified non-responder imputation; OC=observed case; PBO=placebo; PI=Principal Investigator; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

[a] mNRI (HS-ABX): Patients who take systemic antibiotics as rescue medication for HS as defined by the PI or who discontinue due to AE or lack of efficacy are treated as non-responders at all subsequent visits. Other missing data were imputed via multiple imputation

[b] Observed case (OC): All available data after an intercurrent event were summarized as recorded in the database, and all missing data were left missing.

Figure 30. Line plot of HiSCR$_{90}$, responder rates overtime by treatment group (RS [MI using MCMC/monotone regression – mNRI (all-ABX)]])

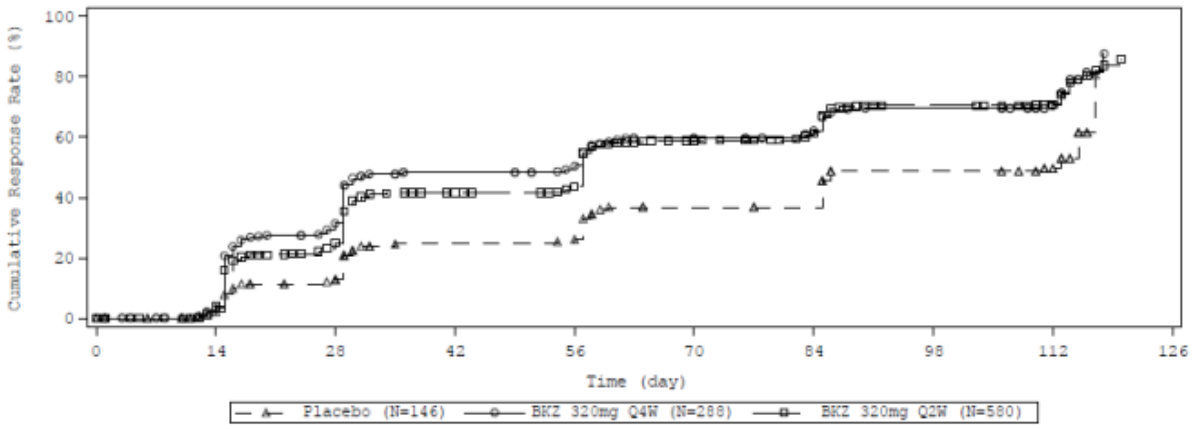


Time to response of HiSCR50, HiSCR75, HiSCR90

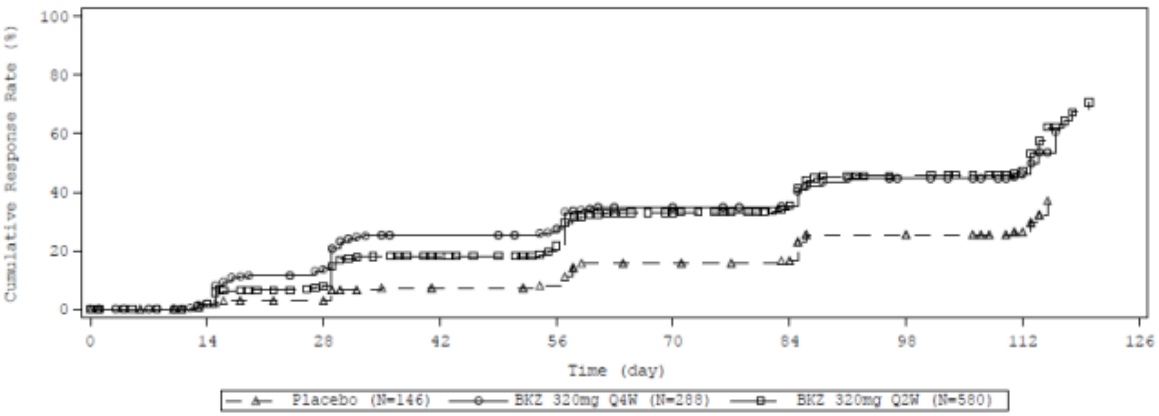
In Pool E1, study participants in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups achieved HiSCR50, HiSCR75, and HiSCR90 more rapidly than study participants in the placebo group during the ITP, with no dose response observed. The median time to HiSCR50 response was 56 days, 57 days, and 113 days for the bimekizumab 320mg Q4W, bimekizumab 320mg Q2W, and placebo groups, respectively (nominal p<0.001 for bimekizumab 320mg Q4W vs placebo; nominal p<0.001 for bimekizumab 320mg Q2W vs placebo). The median time to HiSCR75 response was 114 days, 113 days, and not calculated (NC) for the bimekizumab 320mg Q4W, bimekizumab 320mg Q2W, and placebo groups, respectively (nominal p<0.001 for bimekizumab 320mg Q4W vs placebo; nominal p<0.001 for bimekizumab 320mg Q2W vs placebo). The median time to HiSCR90 response was NC, 120 days, and NC for the bimekizumab 320mg Q4W, bimekizumab 320mg Q2W, and placebo groups, respectively (nominal p<0.001 for bimekizumab 320mg Q4W vs placebo; nominal p<0.001 for bimekizumab 320mg Q2W vs placebo). All nominal p-values are based on a log-rank test stratified by Baseline Hurley Stage and Baseline antibiotic use.

Figure 31. Kaplan-Meier plots for time to $HiSCR_{50}$, $HiSCR_{75}$, and $HiSCR_{90}$– ITP: Pool E1

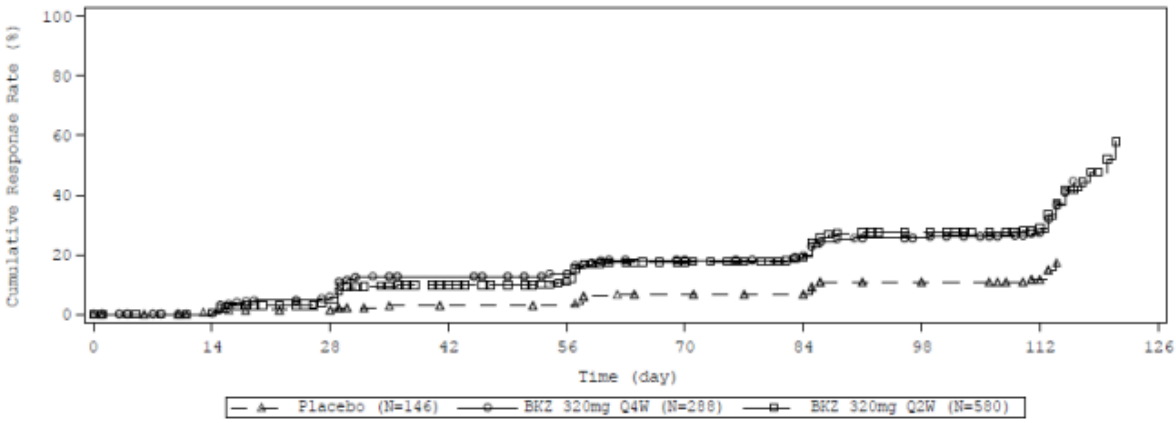
$HiSCR_{50}$



$HiSCR_{75}$



$HiSCR_{90}$



Combined Initial and Maintenance Treatment Period

In pool E2, the median time to HiSCR50 response was 56 days, 57 days, 57 days, and 113 days for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and placebo/bimekizumab 320mg Q2W groups, respectively. The median time to HiSCR75 response was 114 days, 113 days, 113 days, and 169 days for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and placebo/bimekizumab 320mg Q2W groups, respectively. The median time to HiSCR90 response was 225 days, 197 days, 197 days, and 233 days for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and placebo/bimekizumab 320mg Q2W groups, respectively.

Time to loss of response of HiSCR25, HiSCR50, HiSCR75, HiSCR90, and HiSCR100 in Week 16 responders – Up to Week 48

In Pool E2, the median time to loss of HiSCR50 response among those who had a HiSCR50 response at Week 16 was 170 days, 160 days, 224 days, and 225 days for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and the placebo/bimekizumab 320mg Q2W groups, respectively. The median time to loss of HiSCR75 response among those who had a HiSCR75 response at Week 16 was 126 days, 141 days, 189 days, and 175 days for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and the placebo/bimekizumab 320mg Q2W groups, respectively. The median time to loss of HiSCR90 response among those who had a HiSCR90 response at Week 16 was 85 days, 68 days, 64 days, and NC for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and the placebo/bimekizumab 320mg Q2W group.

Lesion and AN counts

Absolute and percentage change from Baseline in total lesion counts over time by lesion type overall (MI using MCMC monotone regression): Pool E2

Overall, lesion count distributions at Baseline were similar across treatment groups. Greater percentage reductions from Baseline in mean relevant lesion counts (i.e., those comprising the HiSCR: abscesses, IN, combined AN, and DT) were observed in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W total groups compared with the placebo group. Onset of effect was rapid, beginning at Week 2 and increasing consistently through Week 16. Reductions in AB and DT in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups were similar through Week 16. Reductions in IN were greater in the bimekizumab 320mg Q2W group compared with the bimekizumab 320mg Q4W through Week 16.

Table 34. Improvements in AB, IN, AN, and DT counts in the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, bimekizumab 320mg Q2W/Q2W, and placebo/bimekizumab 320mg Q2W groups through Week 48 (E2 pooled analysis)

Treatment group	Visit	Statistic	Lesion type			
			AB	IN	AN	DT
PBO/BKZ 320mg Q2W N=146	Baseline	Mean (SE)	2.7 (0.4)	11.8 (0.7)	14.4 (0.8)	3.4 (0.3)
	Week 4	Mean CfB (SE)	-0.3 (0.2)	-2.4 (0.4)	-2.7 (0.4)	-0.1 (0.2)
		Mean % CfB (SE)	-9.4 (9.3)	-19.2 (4.4)	-20.6 (3.4)	-11.3 (6.1)
	Week 16	Mean CfB (SE)	-0.4 (0.2)	-3.9 (0.6)	-4.2 (0.7)	-0.4 (0.2)
		Mean % CfB (SE)	-15.5 (12.6)	-25.4 (7.0)	-28.1 (5.1)	-17.6 (7.3)
	Week 32	Mean CfB (SE)	-1.6 (0.3)	-7.9 (0.6)	-9.5 (0.7)	-1.7 (0.3)
		Mean % CfB (SE)	-62.2 (9.1)	-58.7 (9.7)	-64.9 (4.9)	-52.2 (7.7)
	Week 48	Mean CfB (SE)	-2.1 (0.4)	-8.9 (0.7)	-10.9 (0.8)	-1.9 (0.3)
		Mean % CfB (SE)	-74.0 (6.8)	-71.5 (4.3)	-72.7 (4.1)	-54.2 (8.3)
BKZ 320mg Q4W/Q4W N=288	Baseline	Mean (SE)	4.0 (0.4)	13.7 (1.1)	17.7 (1.2)	3.3 (0.2)
	Week 4	Mean CfB (SE)	-1.7 (0.2)	-4.9 (0.6)	-6.6 (0.6)	-0.9 (0.1)
		Mean % CfB (SE)	-48.8 (5.4)	-33.7 (4.7)	-39.8 (3.3)	-28.9 (4.2)
	Week 16	Mean CfB (SE)	-2.1 (0.3)	-6.3 (0.9)	-8.4 (1.0)	-1.3 (0.2)
		Mean % CfB (SE)	-61.1 (6.7)	-32.0 (7.7)	-42.0 (5.3)	-44.4 (5.3)
	Week 32	Mean CfB (SE)	-2.5 (0.3)	-7.9 (1.1)	-10.4 (1.2)	-1.7 (0.2)
		Mean % CfB (SE)	-68.0 (5.8)	-44.0 (7.6)	-52.2 (5.5)	-51.7 (5.6)
	Week 48	Mean CfB (SE)	-2.9 (0.3)	-8.6 (1.2)	-11.4 (1.3)	-1.8 (0.2)
		Mean % CfB (SE)	-73.6 (5.2)	-48.3 (8.6)	-56.6 (6.2)	-51.3 (6.4)
BKZ 320mg Q2W/Q4W N=292	Baseline	Mean (SE)	3.6 (0.4)	13.6 (0.8)	17.2 (1.0)	3.8 (0.3)
	Week 4	Mean CfB (SE)	-1.3 (0.2)	-4.6 (0.4)	-6.0 (0.5)	-1.2 (0.1)
		Mean % CfB (SE)	-44.3 (4.6)	-35.8 (3.0)	-37.2 (2.9)	-33.9 (4.0)
	Week 12	Mean CfB (SE)	-1.9 (0.2)	-6.2 (0.5)	-8.1 (0.6)	-1.4 (0.2)
		Mean % CfB (SE)	-59.7 (5.6)	-45.8 (4.0)	-47.2 (3.8)	-37.0 (5.4)
	Week 16	Mean CfB (SE)	-2.0 (0.3)	-6.9 (0.5)	-8.9 (0.7)	-1.5 (0.2)
		Mean % CfB (SE)	-63.8 (5.5)	-51.3 (3.9)	-52.5 (3.7)	-41.0 (5.8)
	Week 32	Mean CfB (SE)	-2.4 (0.3)	-9.1 (0.6)	-11.5 (0.8)	-2.0 (0.2)
		Mean % CfB (SE)	-67.1 (5.4)	-62.2 (3.7)	-63.6 (3.5)	-50.6 (5.4)
	Week 48	Mean CfB (SE)	-2.5 (0.3)	-9.8 (0.7)	-12.4 (0.8)	-2.0 (0.2)
		Mean % CfB (SE)	-73.0 (4.9)	-66.8 (4.0)	-68.5 (3.6)	-46.5 (6.5)
BKZ 320mg Q2W/Q2W N=288	Baseline	Mean (SE)	3.4 (0.3)	11.4 (0.6)	14.7 (0.7)	3.8 (0.3)
	Week 4	Mean CfB (SE)	-1.4 (0.2)	-3.5 (0.4)	-4.9 (0.4)	-0.9 (0.1)
		Mean % CfB (SE)	-51.7 (3.9)	-26.9 (5.3)	-33.7 (3.4)	-22.0 (4.2)
	Week 12	Mean CfB (SE)	-1.9 (0.2)	-5.1 (0.4)	-7.1 (0.5)	-1.5 (0.2)
		Mean % CfB (SE)	-66.5 (4.4)	-46.1 (4.0)	-51.5 (3.8)	-35.3 (5.1)
	Week 16	Mean CfB (SE)	-2.0 (0.2)	-5.5 (0.5)	-7.5 (0.5)	-1.7 (0.2)
		Mean % CfB (SE)	-69.3 (4.5)	-46.1 (4.6)	-51.5 (4.2)	-42.9 (5.6)
	Week 32	Mean CfB (SE)	-2.3 (0.2)	-7.4 (0.5)	-9.7 (0.6)	-2.0 (0.2)
		Mean % CfB (SE)	-68.6 (5.5)	-58.4 (4.8)	-63.0 (4.2)	-44.9 (6.5)
	Week 48	Mean CfB (SE)	-2.5 (0.3)	-8.3 (0.6)	-10.9 (0.7)	-2.1 (0.2)
		Mean % CfB (SE)	-72.6 (5.5)	-62.9 (4.5)	-66.0 (4.1)	-46.0 (7.0)

BKZ 320mg Q2W Total N=580	Baseline	Mean (SE)	3.5 (0.2)	12.5 (0.5)	16.0 (0.6)	3.8 (0.2)
	Week 4	Mean CfB (SE)	-1.4 (0.1)	-4.1 (0.3)	-5.4 (0.3)	-1.0 (0.1)
		Mean % CfB (SE)	-48.2 (3.0)	-31.5 (3.0)	-35.6 (2.2)	-27.9 (2.9)
	Week 12	Mean CfB (SE)	-1.9 (0.2)	-5.7 (0.3)	-7.6 (0.4)	-1.5 (0.1)
		Mean % CfB (SE)	-63.4 (3.4)	-46.4 (2.8)	-49.7 (2.8)	-36.8 (3.7)
	Week 16	Mean CfB (SE)	-2.0 (0.2)	-6.2 (0.3)	-8.2 (0.4)	-1.6 (0.1)
		Mean % CfB (SE)	-66.5 (3.5)	-49.1 (2.9)	-52.2 (2.8)	-42.5 (4.0)

AB=abscess; AN=abscess and inflammatory nodule; BKZ=bimekizumab; CfB=change from baseline; DT=draining tunnels; IN=inflammatory nodules; ISE=Integrated Summary of Efficacy; MCMC=Markov-Chain Monte Carlo; MI=multiple imputation; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error

Note: Intermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Participants who experienced an intercurrent event were treated as missing following the intercurrent event and imputed using the MI method for missing data.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the ITP for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Change from Baseline in IHS4

IHS4 was a pre-defined exploratory variable with 35 mean Baseline scores ranging from 30.6 to 36.0, representing severe disease. Overall, the mean reductions from Baseline in IHS4 scores were substantially greater in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W total groups compared with the placebo group beginning at Week 2 and consistently greater at each visit through Week 16 to week 48, with no dose response observed.

Table 35. Absolute change from Baseline in IHS4 by visit (MI-using MCMC monotone regression): Pool E2

Visit	Statistic	PBO/BKZ 320mg Q2W N=146	BKZ 320mg Q4W/Q4W N=288	BKZ 320mg Q2W/Q4W N=292	BKZ 320mg Q2W/Q2W N=288	BKZ Q2W total N=580
Baseline	Mean (SE)	30.6 (1.8)	35.0 (2.0)	36.0 (2.0)	33.4 (1.5)	34.7 (1.2)
Week 2	Mean CfB (SE)	-1.8 (0.8)	-8.4 (0.9)	-7.6 (0.8)	-7.2 (0.8)	-7.4 (0.5)
Week 4	Mean CfB (SE)	-3.5 (0.9)	-11.9 (1.0)	-12.0 (0.9)	-10.0 (0.9)	-11.0 (0.7)
Week 12	Mean CfB (SE)	-7.0 (1.3)	-13.7 (1.5)	-15.6 (1.3)	-14.9 (1.2)	-15.4 (0.9)
Week 16	Mean CfB (SE)	-6.2 (1.5)	-15.8 (1.5)	-16.8 (1.4)	-16.3 (1.3)	-16.6 (0.9)
Week 20	Mean CfB (SE)	-12.5 (1.5)	-16.9 (1.6)	-18.6 (1.5)	-17.3 (1.3)	NA
Week 32	Mean CfB (SE)	-17.9 (1.7)	-19.9 (1.8)	-21.9 (1.5)	-20.0 (1.4)	NA
Week 48	Mean CfB (SE)	-20.7 (1.9)	-21.5 (1.9)	-22.8 (1.6)	-21.8 (1.5)	NA

BKZ=bimekizumab; CfB=change from baseline; IHS4=International Hidradenitis Suppurativa Severity Scoring System; ISE=Integrated Summary of Efficacy; MCMC=Markov-Chain Monte Carlo; MI=multiple imputation; NA=not applicable; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SE=standard error

Note: Intermittent missing data were imputed using MI with MCMC method followed by monotone regression for monotone missing data. Participants who experienced an intercurrent event ware treated as missing following the intercurrent event and imputed using the MI method for missing data.

Note: Participants were randomized at Baseline to 1 of 4 treatment sequences, with treatment switched after the Initial Treatment Period for the PBO/BKZ 320mg Q2W and BKZ 320mg Q2W/Q4W groups, starting at Week 16. Participants were summarized according to randomized treatment as allocated at Baseline.

Absolute change from Baseline in other HS symptoms

The results for change from Baseline in HSSDD mell or odour score, drainage or oozing score, and itch score by visit during the ITP.

Table 36. Analysis of change from Baseline in other HS symptoms assessed by HSSDD – ITP: Pool E1

	Smell or odor score [a]			Worst itch score [b]			Drainage or oozing score [c]		
Visit	PBO N=146 Mean (SE)	BKZ 320mg Q4W N=288 Mean (SE)	BKZ 320mg Q2W N=580 Mean (SE)	PBO N=146 Mean (SE)	BKZ 320mg Q4W N=288 Mean (SE)	BKZ 320mg Q2W N=580 Mean (SE)	PBO N=146 Mean (SE)	BKZ 320mg Q4W N=288 Mean (SE)	BKZ 320mg Q2W N=580 Mean (SE)
BL	4.29 (0.26)	4.53 (0.17)	4.29 (0.13)	4.81 (0.21)	4.75 (0.17)	4.55 (0.12)	4.47 (0.25)	4.59 (0.17)	4.50 (0.13)
Week 2	-0.15 (0.11)	-0.62 (0.10)	-0.58 (0.06)	-0.24 (0.12)	-0.49 (0.10)	-0.39 (0.07)	-0.16 (0.12)	-0.86 (0.11)	-0.79 (0.07)
Week 4	-0.28 (0.13)	-0.81 (0.10)	-0.72 (0.08)	-0.39 (0.17)	-0.75 (0.12)	-0.68 (0.08)	-0.23 (0.15)	-1.07 (0.11)	-1.01 (0.08)
Week 12	-0.31 (0.18)	-0.98 (0.15)	-1.20 (0.10)	-0.62 (0.21)	-0.99 (0.16)	-1.09 (0.12)	-0.36 (0.20)	-1.28 (0.15)	-1.49 (0.11)
Week 16	-0.50 (0.22)	-1.19 (0.15)	-1.34 (0.11)	-0.82 (0.22)	-1.05 (0.16)	-1.29 (0.12)	-0.73 (0.23)	-1.49 (0.15)	-1.64 (0.11)

Disease Flare Rate

In Pool E1 (MI-using MCMC monotone regression [All-ABX]) the flare rate at any time during the Initial Treatment Period was higher in the placebo group (37.8%) compared with the bimekizumab 320mg Q4W (29.8%), and bimekizumab 320mg Q2W total (28.7%) groups. During the Combined Initial and Maintenance Treatment Period (Pool E2), the flare rate at any time was similar across treatment groups (range: 42.1% to 49.6%).

Skin pain response defined as at least a 30% reduction and 1-point reduction from Baseline in HS Skin Pain score assessed by the HSSQ among study participants with a score of ≥3 at Baseline

Table 37. Analysis of the HSSQ skin pain response rate by visit – MTP (MI using MCMC/monotone regression): Pool E2

Response	PBO/BKZ 320mg Q2W N=146 Nresp=127	BKZ 320mg Q4W/Q4W N=288 Nresp=254	BKZ 320mg Q2W/Q4W N=292 Nresp=260	BKZ 320mg Q2W/Q2W N=288 Nresp=252
At any time in MTP				
Responder rate (% [95% CI])	74.5 (66.8, 82.2)	75.4 (69.9, 80.8)	70.3 (64.6, 76.0)	75.0 (69.5, 80.5)
n/Nsub (%)	103/116 (88.8)	208/230 (90.4)	208/238 (87.4)	207/232 (89.2)
Week 16				
Responder rate (% [95% CI])	29.1 (20.9, 37.3)	42.5 (36.3, 48.8)	47.0 (40.8, 53.3)	55.1 (48.8, 61.5)
n/Nsub (%)	37/116 (31.9)	115/225 (51.1)	132/236 (55.9)	143/225 (63.6)
Week 18				
Responder rate (% [95% CI])	49.3 (40.2, 58.4)	50.3 (43.9, 56.8)	47.9 (41.6, 54.2)	49.8 (43.4, 56.1)
n/Nsub (%)	61/108 (56.5)	132/216 (61.1)	134/225 (59.6)	127/218 (58.3)
Week 32				
Responder rate (% [95% CI])	53.9 (44.9, 62.8)	47.4 (40.9, 54.0)	43.0 (36.7, 49.4)	43.0 (36.6, 49.4)
n/Nsub (%)	74/102 (72.5)	136/192 (70.8)	132/202 (65.3)	130/197 (66.0)
Week 48				
Responder rate (% [95% CI])	42.2 (32.9, 51.4)	42.5 (35.8, 49.2)	37.3 (31.1, 43.5)	43.3 (36.9, 49.7)
n/Nsub (%)	60/88 (68.2)	127/172 (73.8)	122/189 (64.6)	134/177 (75.7)

HS-PGA

In the pooled analysis, at week 16, 36.9% of participants in the PBO/BKZ arm had a severe/very severe disease compared with 20.5% of Q4W treated group and 21.2% of Q2W total group.

At Week 48, greater proportions of study participants in the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, and bimekizumab 320mg Q2W/Q2W groups had shifted to less severe categories, with no dose response observed. In participants who switched from placebo to bimekizumab 320mg Q2W, shifts similar to the other active treatments were observed at Week 48. In participants who switched from placebo to bimekizumab 320mg Q2W 9.6% had severe/very severe disease at week 48 compared with 7.7% of Q4W/Q4W treated group and 8.2% of the Q2W/Q4W and 8.6% of the Q2W/Q2W total group.

Health-related quality of life

Absolute change from Baseline in DLQI Total Score

In Pool E1, the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W total groups all had greater improvements (indicated by decreases from Baseline) in DLQI Total Score compared with the placebo

group up to Week 16 (placebo, bimekizumab 320mg Q4W, bimekizumab 320mg Q2W groups mean [SE]: -3.0 [0.5], -5.1 [0.4], and -4.8 [0.3], respectively).

At Week 48, in the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, and bimekizumab 320mg Q2W/Q2W groups (mean [SE]: -6.5 [0.4], -5.2 [0.4], and -5.5 [0.4], respectively). In study participants who switched from placebo to bimekizumab 320mg Q2W at Week 16, improvements in DLQI Total Score were observed as soon as Week 20 (mean [SE]: -5.7 [0.6]) and were also similar to those in the other active treatment groups by Week 20 and maintained through Week 48 (mean [SE]: -6.7 [0.6]).

Change from Baseline in HiSQOL total score by visit (MI-using MCMC monotone regression): Pool E2

Improvements in HiSQOLTotal Score were observed as early as Week 4 in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W total groups (mean change from Baseline [SE]: -8.3 [0.7] and -7.7 [0.4], respectively) through Week 48 (mean CfB [SE] of -13.8 [0.9], and -13.3 [0.9], respectively). Similar improvements were observed for HiSQOL subscale scores (symptoms, psychosocial, and activities and adaptations)

Visit	Statistic	PBO/BKZ 320mg Q2W N=146	BKZ 320mg Q4W/Q4W N=288	BKZ 320mg Q2W/Q4W N=292	BKZ 320mg Q2W/Q2W N=288	BKZ Q2W total N=580
Baseline	Mean (SE)	26.5 (1.2)	25.8 (0.8)	24.4 (0.8)	24.8 (0.8)	24.6 (0.5)
Week 4	Mean CfB (SE)	-3.9 (0.8)	-8.3 (0.7)	-7.7 (0.6)	-7.8 (0.7)	-7.7 (0.4)
Week 16	Mean CfB (SE)	-5.6 (1.0)	-11.0 (0.9)	-10.7 (0.7)	-11.6 (0.7)	-11.2 (0.5)
Week 32	Mean CfB (SE)	-12.9 (1.4)	-12.3 (0.9)	-11.2 (0.8)	-12.4 (0.9)	-
Week 48	Mean CfB (SE)	-14.2 (1.3)	-13.8 (0.9)	-12.8 (0.8)	-13.3 (0.9)	-

Ancillary analyses

Subgroup analyses for HiSCR50 response at Week 16

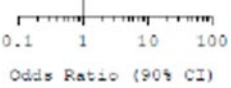
Subgroup analyses of HiSCR50 at Week 16 in the individual Phase 3 studies were performed for HS0003 and HS0004.

Pooled analysis (E1) data are presented here. The subgroup analyses were performed using the primary analysis method (mNRI [All-ABX]), NRI, and OC. The Week 16 subgroup analysis results presented in the following sections are based on the primary analysis method of mNRI (All-ABX). As specified in the integrated statistical analysis plan (ISAP), subgroup by treatment interactions with p-values <0.10 have been subject to further evaluation.

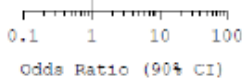
Figure 32. Treatment BKZ 320mg Q4W

Treatment: BKZ 320mg Q4W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	← Favoring Placebo	Favoring→ BKZ	Interaction p-value
Age							
<40 yrs	190	91	2.089 (1.338, 3.261)	52.0%/34.2%			
>=40 yrs	98	55	2.548 (1.352, 4.802)	44.3%/23.8%			0.697
Gender							
Female	175	75	1.770 (1.092, 2.866)	47.9%/34.2%			
Male	113	71	2.926 (1.680, 5.095)	50.7%/26.0%			0.287
Disease Duration (years)							
<median [5.30]	155	62	2.580 (1.510, 4.408)	53.8%/31.1%			
>=median [5.30]	133	84	1.921 (1.161, 3.178)	43.6%/28.7%			0.575
Geographic Region							
North America	121	54	2.530 (1.398, 4.578)	51.9%/29.9%			
Western Europe	77	48	2.347 (1.205, 4.574)	47.5%/27.9%			
Central/Eastern Europe	74	33	1.406 (0.685, 2.885)	46.9%/38.6%			
Asia/Australia	16	11	3.560 (0.756, 16.757)	43.6%/17.9%			0.601

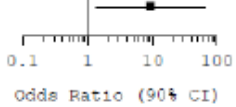


Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	← Favoring Placebo	Favoring BKZ →	Interaction p-value
Weight (kg)							
<= 100kg	153	89	2.116 (1.325, 3.381)	49.8%/32.0%			
> 100kg	134	57	2.354 (1.309, 4.233)	48.3%/28.5%			0.809
Weight (kg)							
<70	24	11	1.374 (0.379, 4.979)	49.5%/41.6%			
70 - <95	105	68	1.890 (1.097, 3.255)	48.4%/33.1%			
95 - <120	106	36	2.768 (1.326, 5.780)	47.0%/24.3%			
>=120	52	31	3.328 (1.432, 7.737)	55.1%/27.0%			0.484
BMI (kg/m2)							
<25	35	26	2.503 (0.989, 6.332)	62.7%/40.3%			
25 - <30	69	41	1.604 (0.809, 3.179)	44.6%/33.4%			
>=30	183	79	2.707 (1.633, 4.490)	48.0%/25.5%			0.642



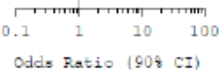
Treatment: BKZ 320mg Q4W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	← Favoring Placebo	Favoring BKZ →	Interaction p-value
BMI (kg/m2)							
<25	35	26	2.503 (0.989, 6.332)	62.7%/40.3%			
25 - <30	69	41	1.604 (0.809, 3.179)	44.6%/33.4%			
30 - <35	66	23	4.458 (1.628, 12.208)	49.4%/18.0%			
35 - <40	53	23	1.116 (0.448, 2.782)	34.1%/31.6%			
>=40	64	33	3.911 (1.729, 8.847)	58.8%/26.8%			0.477
Race							
Black or African American	34	13	NC (NC, NC)	NC/NC			
White	224	119	NC (NC, NC)	NC/NC			
Asian	10	8	NC (NC, NC)	NC/NC			
All Other Races	19	5	NC (NC, NC)	NC/NC			
Missing	1	1	NC (NC, NC)	NC/NC			NC
Systemic Antibiotic Therapy at Randomization							
No	270	135	2.077 (1.433, 3.009)	49.6%/32.2%			
Yes	18	11	9.274 (1.334, 64.475)	45.7%/8.3%			NC



Treatment: BKZ 320mg Q4W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	← Favoring Placebo	Favoring BKZ →	Interaction p-value
Systemic Antibiotic use Intercurrent Event during the Initial Treatment Period							
No	248	125	2.512 (1.712, 3.687)	57.2%/34.8%			
Yes	40	21	3.358 (1.221, 9.236)	50.3%/23.2%			0.676
Prior Biologic Therapy for any Indication							
No	241	117	2.105 (1.413, 3.136)	49.5%/31.8%			
Yes	47	29	2.931 (1.210, 7.099)	51.0%/26.2%			0.618
Prior Biologic Therapy for HS							
No	241	117	2.105 (1.413, 3.136)	49.5%/31.8%			
Yes	47	29	2.931 (1.210, 7.099)	51.0%/26.2%			0.618
Hurley Stage at Baseline							
II	160	79	2.398 (1.463, 3.930)	49.7%/29.2%			
III	128	67	2.053 (1.213, 3.478)	49.5%/32.3%			0.727



Treatment: BKZ 320mg Q4W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	← Favoring Placebo	Favoring BKZ →	Interaction p-value
AN Baseline Count							
<20	212	112	2.087 (1.379, 3.160)	46.4%/29.3%			
>=20	76	34	2.606 (1.223, 5.552)	55.7%/32.6%			0.693
Analgesic Users for the Initial Treatment Period							
No	231	109	2.071 (1.377, 3.116)	50.7%/33.2%			
Yes	57	37	2.750 (1.232, 6.138)	43.8%/22.1%			0.605
Antibody Positivity							
Negative	198			47.9%/NA			
Positive	62			51.5%/NA			
Missing	28			53.0%/NA			
Smoking Status							
Never	119	53	3.404 (1.886, 6.142)	60.9%/31.4%			
Former	42	17	2.973 (0.908, 9.736)	42.2%/19.9%			
Current	126	75	1.527 (0.907, 2.572)	40.7%/31.0%			0.245

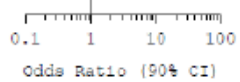
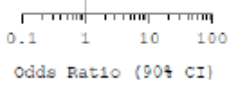


Figure 33. Treatment BKZ 320 Q2W

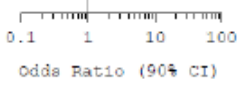
Treatment: BKZ 320mg Q2W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
Age					
<40 yrs	354	91	1.906 (1.260, 2.882)	49.7%/34.2%	
>=40 yrs	226	55	3.122 (1.757, 5.545)	49.4%/23.8%	0.276
Gender					
Female	326	75	1.872 (1.193, 2.937)	49.3%/34.2%	
Male	254	71	2.724 (1.650, 4.494)	48.9%/26.0%	0.343
Disease Duration (years)					
<median [5.30]	290	62	2.437 (1.479, 4.017)	52.4%/31.1%	
>=median [5.30]	290	84	2.099 (1.335, 3.300)	45.8%/28.7%	0.786
Geographic Region					
North America	210	54	1.755 (1.002, 3.075)	42.8%/29.9%	
Western Europe	168	48	2.218 (1.218, 4.039)	46.1%/27.9%	
Central/Eastern Europe	153	33	2.596 (1.338, 5.038)	61.9%/38.6%	
Asia/Australia	49	11	4.395 (1.074, 17.978)	48.8%/17.9%	0.575



Treatment: BKZ 320mg Q2W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
Weight (kg)					
<= 100kg	360	89	2.337 (1.537, 3.552)	52.3%/32.0%	
> 100kg	217	57	1.999 (1.148, 3.480)	44.2%/28.5%	0.769
Weight (kg)					
<70	68	11	1.657 (0.548, 5.016)	54.1%/41.6%	
70 - <95	231	60	2.118 (1.301, 3.447)	51.2%/33.1%	
95 - <120	184	36	2.942 (1.455, 5.948)	48.6%/24.3%	
>=120	94	31	1.978 (0.899, 4.351)	42.2%/27.0%	0.941
BMI (kg/m2)					
<25	96	26	1.853 (0.870, 3.950)	55.5%/40.3%	
25 - <30	143	41	2.339 (1.264, 4.329)	54.0%/33.4%	
>=30	338	79	2.436 (1.512, 3.922)	45.4%/25.5%	0.763

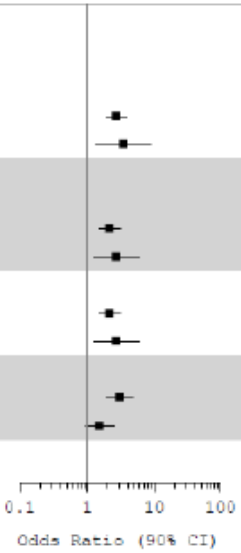


Treatment: BKZ 320mg Q2W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
BMI (kg/m2)					
<25	96	26	1.853 (0.870, 3.950)	55.5%/40.3%	
25 - <30	143	41	2.339 (1.264, 4.329)	54.0%/33.4%	
30 - <35	138	23	4.246 (1.624, 11.098)	48.2%/18.0%	
35 - <40	101	23	1.689 (0.736, 3.876)	43.9%/31.6%	
>=40	99	33	1.998 (0.926, 4.312)	42.2%/26.8%	0.879
Race					
Black or African American	63	13	NC (NC, NC)	NC/NC	
White	465	119	NC (NC, NC)	NC/NC	
Asian	24	8	NC (NC, NC)	NC/NC	
All Other Races	25	5	NC (NC, NC)	NC/NC	
Missing	3	1	NC (NC, NC)	NC/NC	NC
Systemic Antibiotic Therapy at Randomization					
No	523	135	2.065 (1.466, 2.910)	49.5%/32.2%	
Yes	57	11	10.654 (1.762, 64.434)	49.1%/8.3%	NC

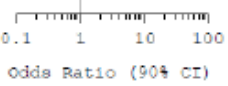
Treatment: BKZ 320mg Q2W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
Systemic Antibiotic use Intercurrent Event during the Initial Treatment Period					
No	487	125	2.684 (1.888, 3.816)	58.9%/34.8%	
Yes	93	21	3.484 (1.373, 8.841)	51.3%/23.2%	0.768
Prior Biologic Therapy for any Indication					
No	463	117	2.164 (1.497, 3.128)	50.2%/31.8%	
Yes	117	29	2.689 (1.218, 5.936)	48.9%/26.2%	0.710
Prior Biologic Therapy for HS					
No	463	117	2.164 (1.497, 3.128)	50.2%/31.8%	
Yes	117	29	2.689 (1.218, 5.936)	48.9%/26.2%	0.710
Hurley Stage at Baseline					
II	326	79	3.038 (1.919, 4.809)	55.6%/29.2%	
III	254	67	1.542 (0.949, 2.505)	42.4%/32.3%	0.098



Treatment: BKZ 320mg Q2W

Subgroup	BKZ N	PBO N	OR (90% CI)	Response BKZ/PBO	← Favoring Placebo	Favoring BKZ →	Interaction p-value
AN Baseline Count							
<20	438	112	2.404 (1.645, 3.514)	49.8%/29.3%			
>=20	142	34	1.764 (0.876, 3.551)	45.9%/32.6%			0.546
Analgesic Users for the Initial Treatment Period							
No	450	109	2.277 (1.560, 3.322)	53.0%/33.2%			
Yes	130	37	2.050 (0.987, 4.257)	36.7%/22.1%			0.832
Antibody Positivity							
Negative	384			52.8%/NA			
Positive	134			44.1%/NA			
Missing	62			38.6%/NA			
Smoking Status							
Never	217	53	2.507 (1.450, 4.333)	53.4%/31.4%			
Former	92	17	4.052 (1.337, 12.281)	49.9%/19.9%			
Current	261	75	1.957 (1.225, 3.126)	46.8%/31.0%			0.457



Impact of Immunogenicity on Efficacy

Overall, 44.4% to 47.0% of study participants in the bimekizumab treatment groups had developed ADAb at ≥1 visit by Week 16, and approximately 60% had developed ADAb at ≥1 visit by Week 48. The majority of the ADAb positivity developed after bimekizumab treatment initiation: by Week 48, between 54.0% and 58.2% of study participants in the bimekizumab treatment groups had a treatment-emergent ADAb-positive result.

Most titre values were close to the assay limit (titre of 100, which is the Minimum Required Dilution) and there was no tendency for increasing or very high titer levels over time.

At Week 16, the overall incidence of NAb-positive study participants was 24.9% for the bimekizumab 320mg Q4W group and 21.4% for the bimekizumab 320mg Q2W group, representing 53.0% and 48.0% of ADAb-positive study participants in these groups, respectively.

Across the dosing regimens tested, the overall incidence of NAb positivity for study participants dosed with bimekizumab for 48 weeks ranged from 31.2% to 38.2%, representing between 55.3% and 63.2% of ADAb-positive study participants.

Impact of ADAb and NAb on efficacy during ITP and MTP

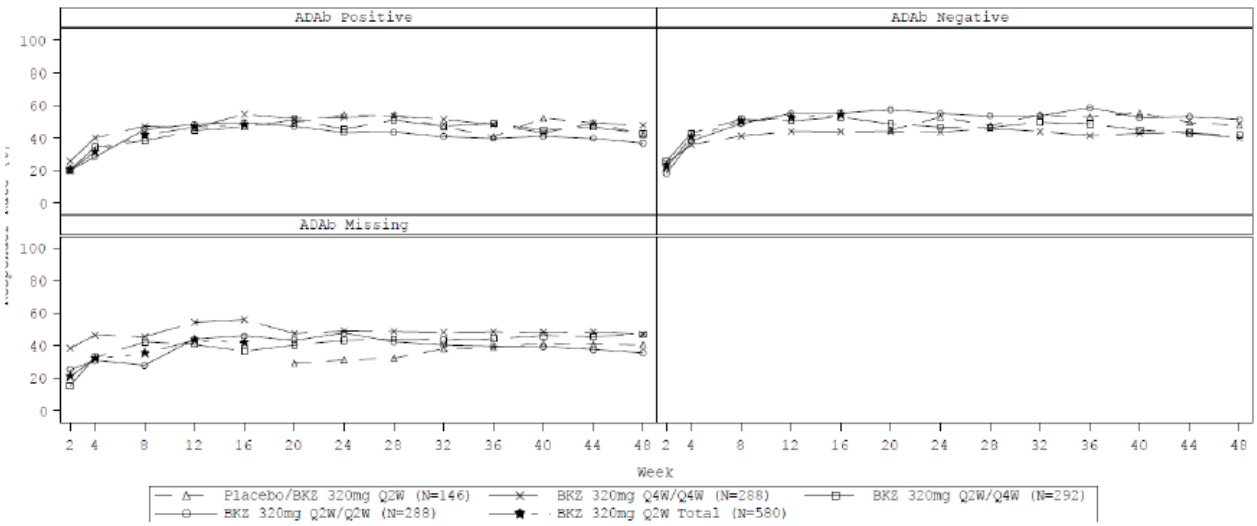
Impact of ADAb on efficacy up to Week 48 (Pool E2)

in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups, respectively response rates were higher for ADAb-negative participants receiving bimekizumab 320mg Q2W compared with ADAb-positive participants, while no trends were observed for the bimekizumab Q4W treatment arm. Similar trends were observed at Week 48.

Table 38. HiSCR$_{50/75}$ responder rates by ADAb status at selected visits up to Week 48 (efficacy subgroup status) (MI using MCMC/monotone regression) (Pool E2)

Endpoint Visit	ADAb status	PBO/BKZ 320mg Q2W N=146 RR% (90% CI)	BKZ 320mg Q4W/Q4W N=288 RR% (90% CI)	BKZ 320mg Q2W/Q4W N=292 RR% (90% CI)	BKZ 320mg Q2W/Q2W N=288 RR% (90% CI)	BKZ 320mg Q2W Total N=580 RR% (90% CI)
HiSCR$_{50}$						
Week 16	ADAb Positive	NA	54.5 (46.6, 62.4)	46.6 (38.7, 54.6)	49.3 (41.2, 57.5)	48.1 (42.4, 53.7)
	ADAb Negative	NA	43.9 (36.8, 51.0)	52.7 (45.7, 59.6)	55.1 (48.1, 62.2)	53.9 (48.9, 58.9)
Week 36	ADAb Positive	40.8 (24.7, 57.0)	48.2 (40.2, 56.3)	48.9 (40.8, 56.9)	39.7 (31.6, 47.7)	NA
	ADAb Negative	52.9 (44.3, 61.4)	41.4 (34.2, 48.5)	48.6 (41.5, 55.7)	58.6 (51.4, 65.7)	NA
Week 48	ADAb Positive	42.0 (25.6, 58.5)	47.9 (39.7, 56.0)	42.6 (34.6, 50.6)	36.7 (28.8, 44.7)	NA
	ADAb Negative	47.8 (39.1, 56.4)	39.8 (32.6, 46.9)	41.6 (34.5, 48.7)	51.3 (44.1, 58.5)	NA
HiSCR$_{75}$						
Week 16	ADAb Positive	NA	34.1 (26.6, 41.6)	29.0 (21.8, 36.2)	28.8 (21.4, 36.2)	29.0 (23.8, 34.2)
	ADAb Negative	NA	25.0 (18.8, 31.3)	40.4 (33.6, 47.3)	42.3 (35.3, 49.3)	41.3 (36.5, 46.2)
Week 36	ADAb Positive	37.0 (21.1, 52.8)	41.2 (33.1, 49.2)	34.5 (26.8, 42.1)	30.8 (23.2, 38.4)	NA
	ADAb Negative	40.5 (32.1, 48.8)	31.5 (24.7, 38.2)	38.4 (31.4, 45.4)	47.3 (40.1, 54.6)	NA
Week 48	ADAb Positive	37.3 (21.4, 53.3)	40.6 (32.6, 48.7)	31.1 (23.6, 38.6)	27.6 (20.3, 35.0)	NA
	ADAb Negative	42.2 (33.7, 50.7)	32.5 (25.6, 39.4)	30.6 (23.9, 37.2)	40.6 (33.4, 47.7)	NA

Figure 34. Plot of HiSCR$_{50}$ responder rates by visit and ADAb status up to Week 48 (efficacy subgroup status) (MI using MCMC/monotone regression) (Pool E2)



Impact of NAb on efficacy up to Week 48 (Pool E2)

At Week 16, response rates for NAb-negative participants receiving bimekizumab 320mg Q2W were higher compared with NAb-positive participants, while no trends were observed for the bimekizumab Q4W treatment arm. No trends were observed at Week 48.

Table 39. HiSCR$_{50/75}$ responder rates by NAb status at selected visits up to Week 48 (MI usingMCMC/monotone regression) (Pool E2)

Endpoint Visit	NAb status	PBO/BKZ 320mg Q2W N=146 RR% (90% CI)	BKZ 320mg Q4W/Q4W N=288 RR% (90% CI)	BKZ 320mg Q2W/Q4W N=292 RR% (90% CI)	BKZ 320mg Q2W/Q2W N=288 RR% (90% CI)	BKZ 320mg Q2W Total N=580 RR% (90% CI)
HiSCR$_{50}$						
Week 16	ADAb Negative	NA	44.2 (34.8, 53.7)	52.4 (NC, NC)	53.0 (44.1, 61.9)	52.8 (46.4, 59.2)
	NAb Positive	NA	54.3 (46.4, 62.3)	44.7 (36.8, 52.6)	53.2 (44.5, 62.0)	48.5 (42.6, 54.4)
	ADAb Positive/NAb Negative	NA	46.7 (36.2, 57.3)	56.2 (45.8, 66.5)	50.0 (40.0, 59.9)	53.0 (45.8, 60.2)
Week 36	ADAb Negative	53.5 (42.7, 64.2)	42.9 (33.5, 52.3)	49.1 (39.9, 58.3)	59.3 (50.5, 68.1)	NA
	NAb Positive	60.7 (NC, NC)	45.8 (37.7, 53.9)	46.4 (38.4, 54.5)	43.9 (35.0, 52.9)	NA
	ADAb Positive/NAb Negative	37.6 (24.4, 50.8)	45.9 (35.3, 56.5)	53.1 (42.3, 63.9)	45.2 (35.2, 55.3)	NA
Week 48	ADAb Negative	46.2 (35.4, 57.1)	39.2 (29.8, 48.5)	41.5 (32.4, 50.5)	50.5 (41.5, 59.5)	NA
	NAb Positive	52.8 (36.8, 68.8)	45.5 (37.3, 53.7)	42.5 (34.4, 50.6)	42.7 (33.8, 51.5)	NA
	ADAb Positive/NAb Negative	42.8 (29.2, 56.3)	46.4 (35.6, 57.1)	43.7 (32.7, 54.6)	39.1 (29.2, 49.0)	NA
HiSCR$_{75}$						
Week 16	ADAb Negative	NA	24.2 (16.1, 32.4)	42.7 (NC, NC)	38.8 (NC, NC)	40.7 (NC, NC)
	NAb Positive	NA	32.5 (25.0, 40.0)	29.6 (22.3, 36.9)	32.6 (24.3, 40.9)	31.0 (25.5, 36.5)
	ADAb Positive/NAb Negative	NA	30.0 (20.3, 39.7)	37.0 (26.9, 47.1)	36.5 (27.0, 46.1)	36.9 (29.9, 43.8)
Week 36	ADAb Negative	37.7 (27.3, 48.1)	31.0 (22.2, 39.8)	40.1 (31.1, 49.1)	48.5 (39.6, 57.5)	NA
	NAb Positive	57.1 (NC, NC)	38.4 (30.5, 46.4)	32.9 (25.2, 40.5)	31.2 (22.8, 39.7)	NA
	ADAb Positive/NAb Negative	31.2 (18.6, 43.8)	37.9 (27.5, 48.4)	36.9 (26.3, 47.4)	39.3 (29.4, 49.2)	NA
Week 48	ADAb Negative	41.0 (30.2, 51.7)	31.1 (22.3, 39.9)	31.5 (22.9, 40.0)	40.9 (32.1, 49.8)	NA
	NAb Positive	51.8 (35.9, 67.7)	38.3 (30.2, 46.3)	30.1 (22.6, 37.5)	30.5 (22.1, 38.8)	NA
	ADAb Positive/NAb Negative	34.6 (21.6, 47.7)	40.5 (29.8, 51.1)	31.5 (21.1, 41.8)	31.7 (22.1, 41.2)	NA

Summary of main studies

The following Table 40 and Table 41 summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 40. Summary of efficacy for study HS0003

Title: A Phase 3, randomised, rouble-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe Hidradenitis Suppurativa (HS)		
Study identifier	HS0003 Eudra CT Number: 2019-002550-23 NCT04242446	
Design	HS0003 is a Phase 3, randomised, double-blind, placebo-controlled, multicenter, pivotal study evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS. Study participants meeting the inclusion criteria who do not meet any exclusion criteria completed a Screening Period of 14 days to up to 5 weeks; a double-blind, 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period; and a 20-week Safety Follow-up (SFU) Period following the final injection of investigational medicinal product (IMP) if study participants do not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment.	
	Duration of initial treatment phase: Duration of maintenance phase:	16 weeks 32 weeks

	Duration of Safety Follow up (SFU):		SFU Visit was planned 20 weeks after the final dose of IMP (for study participants not enrolling in open-label study HS0005)
Hypothesis	Superiority to placebo		
Treatments groups	Placebo (PBO)/BKZ 320mg every 2 weeks (Q2W)		Placebo administered Q2W until Week 16 and bimekizumab Q2W from Week 16 thereafter (up to 48 weeks) 72 randomised
	Bimekizumab (BKZ) 320mg every 4 weeks (Q4W)		Bimekizumab 320mg administered Q4W throughout the study (48 weeks) 144 randomised
	BKZ 320mg Q2W/Q4W		Bimekizumab 320mg administered Q2W until Week 16 and bimekizumab Q4W from Week 16 thereafter (up to 48 weeks) 146 randomised
	BKZ 320mg Q2W		Bimekizumab 320mg administered Q2W throughout the study (48 weeks) 143 randomised
Endpoints and definitions	Primary endpoint	$HiSCR_{50}$ at Week 16	Proportion of participants who achieved a $HiSCR_{50}$ response at Week 16 (superiority vs placebo)
	Major Secondary endpoints	$HiSCR_{75}$ at Week 16	Proportion of participants who achieved a $HiSCR_{75}$ response at Week 16 (superiority vs placebo)
		DLQI at Week 16	Absolute change from Baseline (cfb) in DLQI Total Score at Week 16
		HSSDD worst skin pain at Week 16	Absolute change from Baseline in Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HSSDD
		Skin pain response at Week 16	Proportion of participants who achieve pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16, among participants who have a Baseline score at or above the threshold value
Database lock	Interim analysis clinical cutoff once all study participants completed Week 48: 14-November-2022		

Results and Analysis

Analysis description	**Primary Analysis (Pre-specified analysis)**			
Analysis population and time point description	Intent to treat (Randomised Set) Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	72	144	289
	$HiSCR_{50}$ Week 16 %	28.7%	45.3%	47.8%
Effect estimate per comparison	Primary endpoint	Comparison groups	Bimekizumab vs. placebo	
		p-value for odds ratio (BKZ 320mg Q4W)	p=0.030	
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.006*	
	*Indicates statistical significance			
Notes	Description of the predefined primary analysis (Any systemic antibiotic use treated as an intercurrent event): This was the primary analysis method			

	defined in the individual study statistical analysis plan for HS0003 study. It treated all systemic antibiotic use as an intercurrent event (treatment failure). Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event (treatment failure). All other missing data were imputed using multiple imputation. Important findings: HS0003 met its primary endpoint ($HiSCR_{50}$ at Week 16), demonstrating clinically meaningful and statistically significant efficacy for the bimekizumab 320mg every 2 weeks (Q2W) dose compared with placebo. Observed response rates between the Q2W and Q4W doses were similar for the primary endpoint, although Q4W was not statistically significant (statistical significance threshold = 0.025).			
Analysis description	**Supportive analysis of the primary endpoint**			
Analysis population and time point description	Intent to treat (Randomised Set) Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	72	144	289
	$HiSCR_{50}$ Week 16 %	34.0%	53.5%	55.2%
Effect estimate per comparison	Primary endpoint	Comparison groups	Bimekizumab vs. placebo	
		Nominal p-value for odds ratio (BKZ 320mg Q4W)	Nominal p=0.007	
		Nominal p-value for odds ratio (BKZ 320mg Q2W)	Nominal p<0.001	
Notes	Description of the supportive analysis (Systemic antibiotic use defined as rescue for HS treated as an intercurrent event): The Case Report Form allowed the Investigator to mark whether an antibiotic was given as rescue medication for HS. In this analysis, only those antibiotics marked as being given as rescue for HS were treated as intercurrent events. Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event (treatment failure). All other missing data were imputed using multiple imputation. This analysis better reflects real world use of antibiotics for HS, and imputed treatment failure only for those systemic antibiotics intended as HS rescue medication (rather than for all systemic antibiotics as in the primary analysis). Important findings: This supportive analysis confirmed the results of the Week 16 primary analysis			
Analysis description	**Secondary analysis (Pre-specified analysis)**			
Analysis population and time point description	Intent to treat Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	72[+]	144[+]	289[+]
	$HiSCR_{75}$ at Week 16 %	18.4%	24.7%	33.4%
	DLQI Total Score at Week 16 Mean cfb	-2.7	-5.5	-5.0
	HSSDD Worst Skin Pain at Week 16 Mean cfb	-0.99	-1.56	-2.00
	HSSDD worst skin pain response at Week 16 %	15.0%	22.1%	32.3%
	[+]For the pain response endpoint, only participants with a Baseline score at or			

	above the clinically meaningful threshold value are included in the analysis. The number of participants for this analysis are as follows: PBO=46, BKZ Q4W = 103, Q2W = 190		
Effect estimate per comparison	$HiSCR_{75}$	Comparison groups	Bimekizumab vs. placebo
		p-value for odds ratio (BKZ 320mg Q4W)	p=0.350
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.021*
	DLQI Total Score Mean cfb	p-value for difference in cfb (BKZ 320mg Q4W)	p=0.002
		p-value for difference in cfb (BKZ 320mg Q2W)	p<0.001*
	HSSDD worst skin pain Mean cfb	p-value for difference in cfb (BKZ 320mg Q4W)	p=0.201
		p-value for difference in cfb (BKZ 320mg Q2W)	p=0.002*
	HSSDD worst skin pain response at Week 16 %	p-value for odds ratio (BKZ 320mg Q4W)	p=0.367
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.041
	*Indicates statistical significance		
Notes	Description of the predefined primary analysis (Any systemic antibiotic use treated as an intercurrent event): This was the primary analysis method defined in the individual study statistical analysis plan for HS0003 study. It treated all systemic antibiotic use as an intercurrent event. Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event. For binary (response) endpoints, intercurrent events rendered participants as non-responders. For continuous endpoints, participants were set to missing and subjected to multiple imputation. All other missing data were imputed using multiple imputation. Important findings: The Q2W dose also met the ranked secondary endpoints of $HiSCR_{75}$, DLQI Total Score change from baseline [cfb], and HSSDD worst skin pain score CfB. Q2W did not meet statistical significance for the worst skin pain response. However, the cumulative distribution function curves for change from Baseline in Hidradenitis Suppurativa Symptom Daily Diary (HSSDD) worst skin pain score at Week 16 for the Q2W and Q4W dose regimens were clearly separated from the placebo curve at Week 16, providing evidence of the higher response observed versus placebo regardless of the threshold considered to define response. As Q4W was not statistically significant (statistical significance threshold = 0.025) for the primary endpoint, subsequent endpoints were not evaluated for statistical significance based on the pre-specified testing procedure.		
Analysis description	**Supportive analysis of the secondary endpoints**		
Analysis population and time point description	Intent to treat Week 16		
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	72+	144+	289+
	$HiSCR_{75}$ at Week 16 %	18.3%	31.4%	38.7%
	HSSDD Worst Skin Pain response at Week 16 Mean cfb	16.1	25.3	36.7
	+For the pain response endpoint, only participants with a Baseline score at or above the clinically meaningful threshold value are included in the analysis. The number of participants for this analysis are as follows: PBO=46, BKZ Q4W = 103, BKZ Q2W = 190			

Effect estimate per comparison	$HiSCR_{75}$	Comparison groups	Bimekizumab vs. placebo
		Nominal p-value for odds ratio (BKZ 320mg Q4W)	Nominal p=0.042
		Nominal p-value for odds ratio (BKZ 320mg Q2W)	Nominal p<0.001
	HSSDD Worst Skin Pain response	Nominal p-value for odds ratio (BKZ 320mg Q4W)	Nominal p=0.230
		Nominal p-value for odds ratio (BKZ 320mg Q2W)	Nominal p=0.005
Notes	Description of the supportive analysis (Systemic antibiotic use defined as rescue for HS treated as an intercurrent event): The Case Report Form allowed the Investigator to mark whether an antibiotic was given as rescue medication for HS. In this analysis, only those antibiotics marked as being given as rescue for HS were treated as intercurrent events. Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event. Intercurrent events rendered participants as non-responders. All other missing data were imputed using multiple imputation. This analysis better reflects real world use of antibiotics for HS, and imputed treatment failure only for those systemic antibiotics intended as HS rescue medication (rather than for all systemic antibiotics as in the primary analysis). Important findings: This supportive analysis confirmed the results of the Week 16 secondary analysis.		

Table 41. Summary of efficacy for study HS0004

Title: A Phase 3, randomised, double-blind, placebo-controlled, multicenter study evaluating the efficacy and safety of bimekizumab in study participants with moderate tosSevere Hidradenitis Suppurativa (HS)		
Study identifier	HS0004 Eudra CT Number: 2019-002551-42 NCT04242498	
Design	HS0004 is a Phase 3, randomised, double-blind, placebo-controlled, multicenter, pivotal study evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS. Study participants meeting the inclusion criteria who do not meet any exclusion criteria will complete a Screening Period of 14 days to up to 5 weeks; a double-blind, 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period; and a 20-week Safety Follow-up (SFU) Period following the final injection of investigational medicinal product (IMP) if study participants do not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment.	
	Duration of initial treatment phase: Duration of maintenance phase: Duration of Safety Follow up (SFU):	16 weeks 32 weeks SFU Visit was planned 20 weeks after the final dose of IMP (for study participants not enrolling in open-label study HS0005)
Hypothesis	Superiority to placebo	
Treatments groups	Placebo (PBO)/BKZ 320mg every 2 weeks (Q2W)	Placebo administered Q2W until Week 16 and bimekizumab Q2W from Week 16 thereafter (up to 48 weeks) 74 randomised
	Bimekizumab (BKZ) 320mg every 4 weeks (Q4W)	Bimekizumab 320mg administered Q4W throughout the study (48 weeks) 144 randomised
	BKZ 320mg Q2W/Q4W	Bimekizumab 320mg administered Q2W until Week 16 and bimekizumab Q4W from Week 16 thereafter (up to 48 weeks)

			146 randomised
	BKZ 320mg Q2W		Bimekizumab 320mg administered Q2W throughout the study (48 weeks) 145 randomised
Endpoints and definitions	Primary endpoint	$HiSCR_{50}$ at Week 16	Proportion of participants who achieved a $HiSCR_{50}$ response at Week 16 (superiority vs placebo)
	Major Secondary endpoints	$HiSCR_{75}$ at Week 16	Proportion of participants who achieved a $HiSCR_{75}$ response at Week 16 (superiority vs placebo)
		Flare by Week 16	Proportion of participants who achieve a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline (flares) for at least one visit by Week 16
		DLQI at Week 16	Absolute change from Baseline (CFB) in DLQI Total Score at Week 16
		HSSDD worst skin pain at Week 16	Absolute change from Baseline in Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HSSDD
		Skin pain response at Week 16	Proportion of participants who achieve pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16, among participants who have a Baseline score at or above the threshold value
Database lock	13 October 2022		

Results and Analysis

Analysis description	**Primary Analysis (Pre-specified analysis)**			
Analysis population and time point description	Intent to treat (Randomised Set) Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	74	144	291
	$HiSCR_{50}$ Week 16 %	32.2%	53.8%	52.0%
Effect estimate per comparison	Primary endpoint	Comparison groups	Bimekizumab vs. placebo	
		p-value for odds ratio (BKZ 320mg Q4W)	p=0.004*	
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.003*	
	*Indicates statistical significance			
Notes	Description of the predefined primary analysis (Any systemic antibiotic use treated as an intercurrent event): This was the primary analysis method defined in the individual study statistical analysis plan for HS0004 study. It treated all systemic antibiotic use as an intercurrent event (treatment failure). Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event (treatment failure). All other missing data were imputed using multiple imputation. Important findings: HS0004 met its primary endpoint ($HiSCR_{50}$ at Week 16), demonstrating clinically meaningful and statistically significant efficacy of both bimekizumab 320mg Q4W and 320mg Q2W initial treatment at Week 16 compared with placebo. No dose response was observed.			
Analysis description	**Supportive analysis of the primary endpoint**			
Analysis population	Intent to treat (Randomised Set)			

and time point description	Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	74	144	291
	$HiSCR_{50}$ Week 16 %	32.3%	58.5%	58.7%
Effect estimate per comparison	Primary endpoint	Comparison groups	Bimekizumab vs. placebo	
		Nominal p-value for odds ratio (BKZ 320mg Q4W)	Nominal p<0.001	
		Nominal p-value for odds ratio (BKZ 320mg Q2W)	Nominal p<0.001	
Notes	<u>Description of the supportive analysis (Systemic antibiotic use defined as rescue for HS treated as an intercurrent event):</u> The Case Report Form allowed the Investigator to mark whether an antibiotic was given as rescue medication for HS. In this analysis, only those antibiotics marked as being given as rescue for HS were treated as intercurrent events. Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event (treatment failure). All other missing data were imputed using multiple imputation. This analysis better reflects real world use of antibiotics for HS, and imputed treatment failure only for those systemic antibiotics intended as HS rescue medication (rather than for all systemic antibiotics as in the primary analysis). <u>Important findings:</u> This supportive analysis confirmed the results of the Week 16 primary analysis			
Analysis description	**Secondary analysis (Pre-specified analysis)**			
Analysis population and time point description	Intent to treat Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	74[+]	144[+]	291[+]
	$HiSCR_{75}$ at Week 16%	15.6%	33.7%	35.7%
	Flare by Week 16 %	28.0%	23.6%	28.8%
	DLQI Total Score at Week 16 Mean cfb	-3.2	-4.7	-4.6
	HSSDD Worst Skin Pain at Week 16 Mean cfb	-0.36	-1.44	-1.83
	HSSDD worst skin pain response at Week 16 %	10.9%	28.6%	31.8%
	[+]For the pain response endpoint, only participants with a Baseline score at or above the clinically meaningful threshold value are included in the analysis. The number of participants for this analysis are as follows: PBO=49, BKZ Q4W = 108, BKZ Q2W = 209			
Effect estimate per comparison	$HiSCR_{75}$	Comparison groups	Bimekizumab vs. placebo	
		p-value for odds ratio (BKZ 320mg Q4W)	p=0.007[*]	
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.002[*]	
	Flare	p-value for odds ratio (BKZ 320mg Q4W)	p=0.497	
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.868	

	DLQI Total Score Mean cfb	p-value for difference in cfb (BKZ 320mg Q4W)	p<0.001
		p-value for difference in cfb (BKZ 320mg Q2W)	p<0.001
	HSSDD Worst Skin Pain Mean cfb	p-value for difference in cfb (BKZ 320mg Q4W)	p=0.010
		p-value for difference in cfb (BKZ 320mg Q2W)	p<0.001
	HSSDD worst skin pain response	p-value for odds ratio (BKZ 320mg Q4W)	p=0.028
		p-value for odds ratio (BKZ 320mg Q2W)	p=0.010
	*Indicates statistical significance		
Notes	Description of the predefined primary analysis (Any systemic antibiotic use treated as an intercurrent event): This was the primary analysis method defined in the individual study statistical analysis plan for HS0004 study. It treated all systemic antibiotic use as an intercurrent event. Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event. For binary (response) endpoints, intercurrent events rendered participants as non-responders. For continuous endpoints, participants were set to missing and subjected to multiple imputation. All other missing data were imputed using multiple imputation. Important findings: HS0004 also met the ranked secondary endpoint of $HiSCR_{75}$ for both BKZ Q2W and BKZ Q4W. The testing procedure stopped at the third ranked endpoint (flare) for not achieving statistical significance for both doses versus placebo. While not statistically significant, clinically meaningful changes were observed for the remainder of the ranked secondary endpoints.		
Analysis description	**Supportive analysis of the secondary endpoints**		
Analysis population and time point description	Intent to treat Week 16		

Descriptive statistics and estimate variability				
	Treatment group	PBO	BKZ 320mg Q4W	BKZ 320mg Q2W
	Number of participants	74+	144+	291+
	$HiSCR_{75}$ at Week 16 %	15.7%	36.4%	39.7%
	HSSDD worst skin pain response at Week 16 Mean cfb	11.1%	32.9%	36.7%
	+For the pain response endpoint, only participants with a Baseline score at or above the clinically meaningful threshold value are included in the analysis. The number of participants for this analysis are as follows: PBO=49, BKZ Q4W = 108, BKZ Q2W = 209			

Effect estimate per comparison	$HiSCR_{75}$	Comparison groups	Bimekizumab vs. placebo
		Nominal p-value for odds ratio (BKZ 320mg Q4W)	Nominal p<0.001
		Nominal p-value for odds ratio (BKZ 320mg Q2W)	Nominal p<0.001
	HSSDD Worst Skin Pain response	Nominal p-value for odds ratio (BKZ 320mg Q4W)	Nominal p=0.004
		Nominal p-value for odds ratio (BKZ 320mg Q2W)	Nominal p<0.001
Notes	Description of the supportive analysis (Systemic antibiotic use defined as rescue for HS treated as an intercurrent event): The Case Report Form allowed the Investigator to mark whether an antibiotic was given as rescue medication for HS. In this analysis, only those antibiotics marked as being given as rescue for HS were treated as intercurrent events. Withdrawal of treatment due to an adverse event or lack of efficacy were also treated as in intercurrent event. Intercurrent events rendered participants as non-responders. All other missing data were imputed using multiple imputation. This analysis better reflects real world use of antibiotics for HS, and imputed treatment failure only for those systemic antibiotics intended as HS rescue medication (rather than for all systemic antibiotics as in the primary analysis). Important findings: This supportive analysis confirmed the results of the Week 16 secondary analysis.		

Supportive study

HS0005 is an open-label, parallel group, multicentre study evaluating the long-term treatment of bimekizumab in study participants with moderate to severe HS who have completed the feeder studies, HS0003 or HS0004, through Week 48. At the Week 48 Visit in the feeder studies, eligible study participants continuing into HS0005 completed the final study visit assessments from the feeder study, completed Week 0 assessments for HS0005, and then received their first open-label dose of bimekizumab in HS0005. The MAH provided a snapshot (data cut-off date: 27 September 2023) of HS0005 efficacy data available for 654/658 study participants enrolled in the study. Secondary efficacy endpoints evaluated include lesion (HiSCR50 and HiSCR75), symptom (Hidradenitis Suppurativa Symptom Questionnaire [HSSQ] skin pain), and quality of life- (Dermatology Life Quality Index [DLQI] Total Score) measures. Upon CHMP's request, the MAH agreed to submit the final results for assessment, once available.

2.4.3. Discussion on clinical efficacy

The clinical development program of bimekizumab (BKZ) in study participants with moderate to severe Hidradenitis Suppurativa (HS) consists of 1 completed Phase 2 study (HS0001), 2 completed Phase 3 studies (HS0003 and HS0004), and 1 ongoing OLE study (HS0005 with study participants entering from HS0003 and HS0004).

Dose selection

The dose regimen of bimekizumab evaluated in the Phase 3 program for HS was selected on the basis of the PK and exposure response outcomes of study HS0001 and the perceived greater inflammatory burden and need for a more intensive treatment regimen for HS than that seen for other autoinflammatory skin disorders. In study HS0001, a loading dose of 640 mg was given at baseline, followed by 320 mg Q2W up to week 10. Although the PK data from study HS0001 showed lower exposures for bimekizumab in HS compared to subjects with PSO, HiSCR50 response rates >50% were achieved from week 4 with a loading dose of 640 mg, followed by 320 mg Q2W.

The highest dose used in other bimekizumab indications (PSO dose regimen of 320mg Q4W) was chosen as a comparator arm in the initial treatment period (ITP) and the maintenance treatment period (MTP) for the phase 3 studies to determine the optimal monthly BKZ dose required to achieve and sustain efficacy over long-term (maintenance) treatment. The decision to omit a loading dose for the phase 3 program has been adequately justified on the basis of PK and exposure/response data from the 46 patients enrolled in HS0001, prior CHMP feedback regarding loading doses in other BKZ indications, and the dose regimens (no loading doses) for the PSO, PsA, and axSpA indications. Overall, the choice of dosing regimen for the phase 3 HS studies has been adequately justified and is accepted by the CHMP.

Design and conduct of clinical studies

Study design

The two completed Phase 3 studies, were multi-centre, randomised, double-blind, placebo-controlled, 2-period studies of identical design with the aim to determine the clinical efficacy and safety of bimekizumab compared to placebo in subjects with moderate to severe HS. No active comparator arm was included in the phase 3 development. Although not considered a barrier to approval, as discussed in the CHMP SA comparison with other licensed treatment options (e.g. adalimumab) would have been of clinical interest.

Study subjects were randomly assigned in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 4 treatment sequences (Q2W/Q2W, Q4W/Q4W, Q2W/Q4W, placebo/Q2W in each study (HS0003 and HS0004). In order to maintain the blind, a double-dummy approach was applied using placebo injections such that all study participants received the same number of injections at each corresponding visit. Both studies included a 30-day screening period, an initial 16-week double-blind treatment period (ITP), and a subsequent 32-week double-blind treatment period (MTP), plus a 20-week safety follow-up (SFU) (from last IMP injection) for any study participant who discontinued from the study prior to Week 48, or who did not continue in the OLE study HS0005.

The study design was adequate to evaluate time to response and maintenance of effect, on treatment, up to 48 weeks. In further support of long-term maintenance of treatment effect, study HS0005 is currently ongoing. The impact of reducing dosing from Q2W to Q4W was assessed but the impact of treatment withdrawal or treatment pause as well as the HS rebound pattern, although recommended to be assessed at the time of CHMP SA, was not evaluated and could have provided useful information on treatment approaches for responders over the longer term. Further evaluation of durability of treatment effect including the impact of treatment breaks and maintenance of effect over longer term period would provide important information regarding the effects of stopping treatment and on the sustainability of clinical response to bimekizumab. The CHMP recommends the MAH to conduct a randomised withdrawal study to evaluate the durability of effect upon withdrawal or treatment pause.

Overall, the study design of the pivotal studies is similar to that used for other agents recently approved for treatment of HS and is generally considered adequate to meet the primary objective of the studies.

The inclusion and exclusion criteria were identical for both studies. Subjects with moderate to severe HS (based on Hurley Stage II or III criteria) who had an inadequate response to antibiotic treatment were entered in the studies. This could include participants who were intolerant of, or who had a contraindication to or who experienced disease recurrence after one or more systemic antibiotics. Limits for a definition of inadequate antibiotic response were removed for the two pivotal studies (a 3-month period was required in HS0001). Although no antibiotic is licensed specifically for use in HS, antibiotics specified in the treatment guidelines were specified in the protocol.

Patients with a draining fistula count greater than 20 at baseline were excluded. Due to the complexity of assessing draining fistulas, especially when there are multiple fistulas in the same anatomical region,

allowing an unlimited number of draining fistulas reduces the accuracy and assessment of the draining fistula count. Overall, and taking into account that this approach was accepted for the HS studies of adalimumab and secukinumab; the MAH's rational for limiting draining fistulas to 20 is accepted by the CHMP.

Endpoints

The MAH has included an extensive range of efficacy outcomes to evaluate the impact of BKZ on inflammatory lesions and skin tunnels, associated symptoms (e.g., pain, draining, odour) and QOL.

HiSCR50 at week 16, the primary endpoint for both studies (HS0003 and HS0004), is a dynamic lesion-based outcome measure assessed by the clinician. Although extent of inflammation can be estimated, there is no direct assessment of severity with this score. This endpoint is however supported by good quality validation studies. This primary endpoint was agreed in the CHMP SA for this procedure and was previously used as the primary efficacy outcome in the clinical development programs for adalimumab and secukinumab in HS.

A more stringent HiSCR measure (HiSCR75) was chosen as the first ranked secondary endpoint for both studies to further explore depth of response. The other ranked secondary endpoints include HSSDD pain score analysis, the Dermatology Life Quality Index (DLQI) and assessment of flare (the ranked secondary endpoint 'Flare' by Week 16 which was a secondary endpoint for HS0004 was downgraded to an 'Other' endpoint in HS0003, this is further discussed below). These lesion-, symptom- and HRQoL-based measures are clinically relevant and inform on the impact of bimekizumab on clinically relevant signs and symptoms of HS.

Other endpoints including a number of additional lesion-, symptom- (pain, drainage, odour, itch) and HRQoL-based measures reported by the patient, further explore the time to response, depth of response and durability of response across the 48-week treatment period. A number of these endpoints are well validated and have been extensively used in clinical trials for HS, however a number of the symptom-based (HSSDD and HSSQ used to evaluate pain), and HRQoL-based (HiSQOL) endpoints are novel endpoints that have not been extensively used in clinical trials. However, all of the endpoints are clinically meaningful and are acceptable.

In line with the recommendation of the CHMP SA, to provide a deeper analysis of response, HISCR90 has been included as 'other efficacy variables'. An additional recommendation to upgrade long-term response, i.e., the primary endpoint after 1 year was not implemented as the week 48 data for the primary and key secondary endpoints were not in the statistical testing procedure for key secondary endpoints due to lack of placebo control. However, analyses for these data comparing regimens at week 48 were included in HS0003 and HS0004 protocols as other endpoints. This is accepted by the CHMP.

Overall, the selected endpoints support evaluation of the impact of bimekizumab on physical signs of disease activity, the extent of skin involvement including frequency and severity of inflammatory lesions and the presence of secondary lesions, including skin tunnels.

Sample size and statistical methods

The sample size justification is adequate for both pivotal phase 3 studies. The statistical methods are considered acceptable to the CHMP.

Conduct of the studies

The protocol for both studies was amended on 4 occasions with an additional amendment (#5) to the protocol for study HS0003. Three of these amendments (#3,#4 and #5) were considered to be substantial amendments.

In protocol Amendment #3 which was implemented a year after both studies had commenced, a 30% cap on enrollment for the Baseline antibiotic therapy strata was removed, a lesion care section was added and updated wound care section and prohibited medications and associated washout periods was included and specific infection-related IMP interruption criterion was added. These changes had no clinically relevant impact on the evaluation of the primary and secondary endpoints.

Protocol Amendment # 4 updated the protocol with FDA recommendations to use a threshold for within-patient clinically meaningful change to define treatment success in order to establish efficacy for skin pain in the Phase 3 studies of patients with moderate to severe HS. Pain response status at Week 16 using this definition was added as a secondary endpoint to the study. This change also resulted in an addition to the sample size section, including assumptions on response rates.

Protocol amendment #5 downgraded the ranked secondary endpoint 'Flare' by Week 16 which was a secondary endpoint for HS0004 to an 'Other' endpoint in HS0003. The downgrading of the endpoint was recommended by CHMP during the SA procedure. This was only applied to HS0003 as the amendment was implemented after the DLP for HS0004.

Disposition Demographics and Baseline characteristics

A total of 1014 study participants with moderate to severe HS were randomised to receive either bimekizumab or placebo in the Phase 3 studies HS0003 and HS0004.

Completion rates were high in HS0003 and HS0004. A large majority progressed to the MTP for both pivotal studies. Of the study subjects who started studies HS0003 and HS0004, 65.9% and 76.0% completed the study, respectively. As discussed by the MAH, this is a higher discontinuation rate than that seen for other indications approved for bimekizumab but is similar to discontinuation rates for other similar treatments for HS. Most of the discontinuations in both the ITP and MTP were attributed to adverse events and consent being withdrawn by the study participant. Upon CHMP's request, the MAH has clarified that no additional information is available for treatment discontinuations reported as being due to consent being withdrawn in studies HS0003 and HS0004. Site surveys provide some further insight into the reasons behind participants withdrawing consent. High participant burden of every 2-week (Q2W) clinic visits and injections for 48 weeks were the primary drivers for withdrawal of consent which was exacerbated by post-Covid opening up of workplaces. A post hoc analysis of HiSCR50 at last assessed visit by withdrawal reason was conducted by the MAH. The percentage of responders among the participants withdrawing consent (51.4%) was higher than among participants who withdrew due to lack of efficacy (31.8%) and similar to the percentage of responders among those who withdrew due to a protocol deviation (46.2%) or due to an adverse event (53.4%). The CHMP agreed with the MAH that there is no trend suggesting an association between a participant's decision to withdraw consent and lack of efficacy.

Across both studies (E1 pooled analysis) the mean age of all study participants was 36.6 years and more than half of the participants were female (56.8%). The majority of study participants were White (79.7%). Only 10.8% of subjects were Black even though there are reports of a higher prevalence of HS in the black population and black patients are more likely to present with Hurley stage II and III disease HS. Black patients are underrepresented in this development program however there is no evidence that efficacy of bimekizumab in HS is impacted by race. The mean body weight and mean BMI overall were 97.2 kg and 33.06 kg/m2, respectively.

The baseline disease characterised in terms of Hurley score, IHS4 score, HSSDD and DLQI across HS003, HS004 and Pool E1 were indicative of subjects who were severely affected by their HS. No subjects with Hurley stage I disease were recruited and only 2 subjects were classified as having mild disease in the HS PGA.

Factors indicating HS severity differed between studies. More participants in study HS0003 compared to HS0004 had Stage III disease (Stage II 50.3% and Stage III 49.7% in HS0003 vs 61.1% and 38.9% in HS0004). There was a trend towards higher indices of disease activity in HS0003 compared to HS0004, i.e. mean IHS4 scores (35.2 vs 33.2,) mean DLQI 12 vs 10.8, Mean Baseline hs-CRP (19.89 vs 15.1) respectively. Overall, the demographic, disease characteristics, comorbid diseases profiles of the participants reflect the complexity of a moderate to severe HS population. The CHMP agreed that these study participant characteristics were appropriate for evaluating the efficacy of bimekizumab treatment in the target patient population of moderate to severe HS.

Antibiotic use

Inadequate response to antibiotic therapy was a requirement for inclusion in the study. Prior antibiotic medication use was similar across the bimekizumab 320mg Q4W, bimekizumab 320mg Q2W, and placebo groups in both studies but was higher overall in the HS0004 study compared to HS0003 study. Over 90% of participants had a history of prior antibiotic in HS0004 whereas overall 78.7% of participants in study HS0003 reported prior antibiotic use despite a higher proportion of subjects with more severe disease in study HS0003.

Antibiotic use at baseline was permitted if participants were on a stable dose of prespecified antibiotics and remained on that dose. Overall <10% of subjects in studies HS0003 and HS004 and across the pooled E1 population were being treated with antibiotics at baseline.

Use of rescue antibiotic (AB) treatment was permitted, reflecting the clinical practice in many countries and concern regarding the potential for subjects on placebo for up to 16 weeks to develop painful distressing flares. 15-20% of participants in the ITP population of study HS0003 and 8%-15% of the population in HS0004 used ABs as rescue medication. Use of rescue antibiotics was noticeably lower in the placebo arm for study HS0004 vs HS0003 (8% vs 20%). Rescue antibiotics were used less frequently in the treatment arms in the MTP for HS0004 compared to HS0003. Differences in disease severity and clinical practice across regions could have contributed to these differences. However, no clinically meaningful impact on the primary endpoint at Week 16 in the placebo-controlled treatment period was observed.

Overall, the baseline characteristics and prior medication history of the treatment groups were representative of a population with moderate to severe HS who had previously been treated with antibiotic and in some cases biological treatment and failed to respond to antibiotic treatment or were intolerant or contraindicated from using antibiotics.

To address the potential impact of concomitant antibiotic use on the interpretation of the primary endpoint the primary analysis method (mNRI [All-ABX]) imputed treatment failure for all data following use of systemic antibiotics regardless of the reason for the antibiotic. The MAH justifies this approach based on the results from the adalimumab Phase 3 program, where markedly better results were observed in the study which included concomitant systemic AB treatment. Additional post hoc analyses, where rescue ABs (mNRI [HS-ABX] analyses) and systemic AB use (drug classes selected based on international guidelines) (mNRI [Class-ABX] analyses) were also undertaken to evaluate the impact of systemic antibiotic use as rescue medication on the primary outcome measure.

Other forms of rescue therapy such as abscess draining or triamcinolone injection were also treated as intercurrent events if more than 2 interventions were necessary in a four-week window. This was based on feedback from global HS experts, that participants who required regular interventions during the trial were not being adequately controlled on treatment. These treatments can also be part of the routine treatment of HS, possibly with regional differences and could also have affected the interpretation of the results thus the approach taken is agreed. Overall, the approach taken by the MAH to understand the

extent of intercurrent events and their effect on components of the composite variable HiSCR50 is endorsed.

Efficacy data and additional analyses

Efficacy outcomes

At Week 16, statistically significant results for the primary endpoint of HiSCR50 at Week 16 were achieved in both studies for the bimekizumab 320mg Q2W dose vs placebo, and only in study HS0004 for bimekizumab 320 mg Q4W. In study HS0003, bimekizumab 320 mg Q4W vs placebo was associated with a p-value of 0.030, but since the statistical threshold for significance was set at 0.025, this result was qualified as non-statistically significant. Consequently, 320 mg Q2W bimekizumab is the recommended posology for initiation of treatment in HS patients, since the primary endpoint results observed for this dosing was statistically significant and considered clinically relevant in both studies.

Numerically greater treatment effect compared to placebo was observed in study HS0004 compared to HS0003 (HS0004 Q2W v PLB: 19.6 (P=0.003), Q4W v PLB: 21.04 (P=0.004); HS0003 Q2W v PLB: 18.15 (p=0.006) Q4Wv PLB 15.43 (p=0.03), respectively). The pivotal trials have inconsistent results for the Q2W and Q4W regimens in terms of the treatment difference vs. placebo. As previously discussed, participants in study HS0003 appear to have had more severe/active disease at baseline which could suggest that participants with more severe disease respond less well to bimekizumab. The MAH acknowledged that study participants with more severe HS disease are harder to treat compared with those with less severe disease. However, the totality of the data assessing the primary endpoint of HiSCR50 response and secondary endpoint of HiSCR75 response demonstrate that bimekizumab has a clinically relevant response versus placebo for important subgroups defining both less severe disease (although still moderate HS) and more severe disease. There was no consistent dose effect evident across the Q4W and Q2W dose regimens in the phase 3 studies in either the ITP or MTP although the studies were not designed to compare the Q2W and Q4W regimens. In the pooled E1 analysis, the magnitude of the treatment effect for the bimekizumab 320mg Q4W and Q2W regimens vs. placebo was comparable, approximately 18.6 ($p<0.001$) and 18.9 ($p<0.001$) percentage points, respectively.

The observed treatment effect compared to placebo in this distressing chronic, recurrent condition, with few treatment options is considered to be clinically relevant.

The primary efficacy result is supported by the results of the sensitivity analyses for the HiSCR50 responder rate at Week 16 except for the very conservative tipping point analyses.

The methodology for handling intercurrent events is considered to be robust.

The primary analysis method (mNRI [All-ABX]) imputing treatment failure for all data following use of systemic antibiotics is quite stringent. The MAH justifies this approach on the hypothesis that study participants taking concomitant systemic antibiotics will have increased efficacy. This was based on the results from the adalimumab Phase 3 program, where markedly better results were observed in the study which included concomitant systemic the treatment. More tailored post-hoc analyses (based on the pooled dataset), where use of investigator identified rescue ABs and particular AB drug classes used to treat HS were treated as intercurrent events, had more favourable outcomes for both Q2W and Q4W dosing regimens over the ITP and MTP.

The post-hoc analyses performed by the MAH to assess the impact of HS disease-related systemic antibiotic use on outcome assessments in HS studies using mRNI are acknowledged. This supportive post-hoc analysis was considered to be of clinical relevance by the CHMP; therefore, the inclusion of these data in SmPC section 5.1 were accepted.

The supportive ranked secondary endpoints for study HS0003 (HISCR75, Change from baseline in DLQI, Change from baseline in Skin Pain as assessed by worst skin pain item in HSSDD), all assessed at week 16, were met, with statistically significant differences compared to placebo for subjects treated with the bimekizumab 320 Q2W dose but not Q4W.

For study HS0004, the ranked secondary endpoints included an additional endpoint 'Flare by week 16' as the second ranked secondary endpoint. The more stringent HISCR75 endpoint was met for both bimekizumab Q4W (p=0.007) and Q2W(P=0.002) treatment arms but not for the endpoint ' Flare by week 16' defined as at least a 25% increase in AN count with an absolute increase of ≥2 AN. All of the ranked secondary outcomes in study HS0004 were numerically in favour of bimekizumab.

The majority of subjects reported pain and it is perceived as the most troublesome symptom of HS. Mean baseline HSSDD score was 5 on the 11-point numeric scale which suggests that pain was, on average, moderate in severity. As discussed above, HSSDD has not been widely used in clinical trials for HS. HSSDD worst skin pain responder rates for HS0004 were comparable to the results from HS0003. The proportion of subjects compared to placebo achieving a 3-point change on the (11-point numeric rating scale) Skin Pain score based on an assessment of the 'worst pain' item in the HSSDD which is considered to be clinically meaningful difference was higher in the Q2W (19.8%) and Q4W (12.4%) treated populations compared to placebo.

In both studies, the HiSCR50, HiSCR75, and HiSCR90 responder rates increased from Week 4 to Week 16 in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W total groups compared with the placebo group. The HiSCR50, HiSCR75, and HiSCR90 responder rates (RS [MI using MCMC/monotone regression]) were generally maintained from Week 16 through Week 48 although response rates plateau from week 12 and appear to decrease slightly in HS0003 and HS0004 for the Q2W/Q4W treatment arms.

There was no clear separation in terms of a dose effect between the treatment groups over the maintenance treatment period in either study. At week 48 in the pivotal studies HS0003 and HS0004 the primary analysis ([mNRI] All-antibiotics [ABX]) suggests that the treatment effect is starting to diminish. Post hoc analysis using a methodology whereby only antibiotics used as rescue medication and specified in HS guidance were included as intercurrent events (mNRI HS-ABX) suggests durability of effect is maintained. This less stringent approach is more aligned with clinical practice. Durability of effect of bimekizumab will be further evaluated once the final CSR for HS0005 is available and submitted for assessment, which will provide data on up to 110 weeks of treatment.

Treatment of existing lesions and reduction in formation of new inflammatory lesions, skin tunnels, and scarring is a key outcome for treatment of HS. Outcomes generally align with the HiSCR50 scores. Lesion counts improved across all treatment arms up to week 48. A treatment effect compared to placebo was evident by week 2 and increased up to week 16, thereafter the magnitude of improvements in AB, IN, AN, and DT counts were less pronounced. A treatment effect in favour of initial treatment with Q2W over Q4W was only evident for inflammatory nodule counts. Overall relative and absolute change of the three components of HiSCR (inflammatory nodule count, abscess count, draining fistula count) support the outcomes of the primary analysis.

Individual HS symptoms (e.g., smell or odour, drainage or oozing) were assessed by the 'smell or odor' item, the 'itch at its worst' item and the 'amount of drainage or oozing' item in the HSSDD. In the pooled E1 analysis, there was a 20-30% reduction in symptom scores in the treatment arms and an 11-17% reduction in the placebo arms which suggests a relatively modest change in symptoms due to treatment with bimekizumab. A treatment effect was evident from week 4. At week 16 mean change from baseline was slightly higher in the Q2W treatment arm.

Skin pain response over 48 weeks was only evaluated using the HSSQ. Reductions in score were observed early in treatment and similar to HiSCR50 endpoint were maintained or improved through 48

weeks of treatment in the bimekizumab-treated groups. No dose response was observed for these outcomes.

Improvements in QoL outcomes measured by DLQI Total Score and change from Baseline in HiSQOL Total Score were observed in the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, and bimekizumab 320mg Q2W/Q2W groups through Week 48. HS can have a profound psychosocial impact on many patients. Improvements in HRQoL-based measures (DLQI and HiSQOL) total scores and in domains/subscales assessing psychological/psychosocial outcomes were observed from week 4 with improvements maintained up to week 48.

Sub-group analyses (ITP E1 analysis) based on a number of demographic, disease-related and regional factors characteristics consistently demonstrated effects favouring bimekizumab over placebo. In general, the HiSCR50 response rates for subgroup analyses were comparable for Q2W and Q4W treatment groups. A treatment by subgroup interaction was only seen for participants with Hurley Stage III (interaction p-value of <0.10) in the bimekizumab Q2W arm.

Response rates in the bimekizumab 320mg Q2W group were higher in participants with Hurley Stage II at Baseline compared with those with Hurley Stage III at Baseline whereas response rates were comparable (Hurley Stage II 49.7 % vs Hurley Stage III 49.5%) in the bimekizumab 320mg Q4W group. Response rates were higher in participants in both treatment groups (BKZ Q4W and Q2W) with a disease duration median of <5.30 years compared with those with a disease duration median of ≥5.30 years respectively. No difference of note was seen with prior biologic therapy for HS.

Response rates were lower in subjects in both treatment groups who required analgesic use in the ITP. Response rates in the bimekizumab 320 Q4W and Q2W group were higher in non-smokers compared with former or current smokers.

Response rates also varied by weight/BMI. There was a trend towards lower efficacy in subjects with higher BMI however this trend was not consistent across weight/BMI categories. A number of these subgroups had limited sample sizes which complicates interpretations of these findings. This is reflected in the wide confidence intervals seen for the OR for some of these subgroups. There were no findings that clearly suggested a requirement for changes to the warnings, posology or recommendations for use for Bimzelx.

Overall, it is agreed that efficacy has been adequately demonstrated in subgroups referenced in section 5.1 of the SmPC. A treatment by subgroup interaction was seen for participants with Hurley Stage III (interaction p-value of <0.10) in the bimekizumab Q2W arm.

In terms of proposed posology, the MAH is proposing a Q2W dosing regimen for the initial treatment phase followed by a Q4W regimen after 16 weeks. Although a positive treatment effect was noted for both bimekizumab 320mg Q2W and 320mg Q4W doses in the initial treatment phase of both pivotal trials, this was more consistent for the Q2W regimen across the HISCR50 primary endpoint and key ranked HiSCR75 secondary endpoints and change from baseline in inflammatory nodule count.

Over longer-term treatment, there is generally very little difference between the Q2W and Q4W regimens across lesion-, symptom-, and HRQoL-based outcome measures from Week 16 to 48 Week. There was no clear evidence of a drop off in effect following a change in dosing from Q2W to Q4W however the treatment effect in this arm does appear to reduce more towards the end of the MTP. The MAH's proposal to use Q2W treatment regimen up to week 16 followed by Q4W dose as the maintenance dose is endorsed by the CHMP.

The MAH initially proposed an indication for use specifying the treatment of adults with moderate to severe HS. However, the population included in the pivotal trials supports efficacy in subjects with moderate to severe active disease who require a second line treatment, i.e. who have had insufficient

response or intolerance to oral antibiotics. Upon CHMP's request and in line with the studied population, the MAH agreed and revised the indication wording to reflect the second line use of bimekizumab in patients with active disease, and aligned the wording with similar recently approved wording for indications for treatment of moderate to severe HS (i.e. adalimumab and secukinumab). In addition, the MAH agreed to update the indication to mention "active" in it, as a qualifier for disease state.

Impact of Immunogenicity on Efficacy

Overall, an increase in ADAb and Nab rates was observed over the 48-week treatment period. Response rates fluctuated by ADAb and NAb status and treatment regimen across the treatment timepoints. No clear pattern is discernible. Nevertheless, clinically relevant response rates were observed with bimekizumab for both HiSCR50 and HiSCR75 regardless of ADAb or Nab status.

2.4.4. Conclusions on the clinical efficacy

Efficacy of bimekizumab in treatment of HS has been supported by the outcomes of 2 well-designed placebo-controlled studies. The primary endpoint, HiSCR50 at week 16, was met in both studies for the Q2W dose and in one study for Q4W dose. Consequently, 320 mg Q2W bimekizumab is the recommended posology for initiation of treatment in HS patients, since the primary endpoint results observed for this dosing was statistically significant and considered clinically relevant in both studies. The outcomes of the ranked secondary endpoints, including HiSCR75, DLQI and HS skin pain response (HSSDD) more consistently favoured the Q2W dose regimen. Subjects with moderate disease responded more favourably than subjects with more severe disease. However, the totality of the data assessing the primary endpoint of HiSCR50 response and secondary endpoint of HiSCR75 response demonstrate that bimekizumab has a clinically relevant response versus placebo for important subgroups defining both less severe disease (although still moderate HS) and more severe disease.

There was no clear difference between the studied Q2W and Q4W maintenance regimens. The MAH's recommendation of a Q4W maintenance regimen for HS is endorsed. The further evaluation of durability of this treatment response over longer term will be further studied in the ongoing extension study HS0005. The MAH committed to submit these results for assessment once they become available.

The effect upon withdrawal or treatment pause in HS patients responding to treatment with bimekizumab will be evaluated post-approval as part of an adequately designed clinical trial (with a randomised withdrawal design). The CHMP recommends the MAH to submit these results for assessment once they become available.

The CHMP concluded that the efficacy data available supports the following indication:

Bimzelx is indicated for the treatment of active moderate to severe hidradenitis suppurativa (acne inversa) in adults with an inadequate response to conventional systemic HS therapy (see section 5.1).

2.5. Clinical safety

Introduction

The HS program included 2 pivotal Phase 3 double-blind studies in HS (HS0003 and HS0004), one Phase 2 study (HS0001) and an Open-label Extension (OLE) study (HS0005).

The safety evaluation mainly utilised 2 pools:

- Pool S1 consists of adult study participants treated with bimekizumab 320mg Q4W, bimekizumab 320mg Q2W, or placebo in the Phase 3 double-blind studies (HS0003 and HS0004) during the Initial Treatment Period (ITP) up to Week 16. This pool summarises the safety of bimekizumab compared to placebo through Week 16 in the HS population.
- Pool S3 consists of study participants who received at least 1 dose of bimekizumab in the Phase 2 study HS0001, or at least 1 full or partial dose in the Phase 3 studies HS0003, HS0004, and HS0005.

Two additional pools were analysed for completion:

- Pool S2 summarised the safety of bimekizumab over continuous dosing for participants originally randomised to bimekizumab Q2W who switched to bimekizumab Q4W, and for bimekizumab Q2W and bimekizumab Q4W perpetual groups.
- Pool S4 summarised the safety of bimekizumab compared to placebo through Week 16 across the bimekizumab development program for Phase 3 placebo-controlled studies in HS, PSO, PsA and axSpA; this pooling is being used to refine the MAH's position regarding bimekizumab adverse reactions.

Patient exposure

Pool S1

In Pool S1, the median study medication duration during the ITP was 112.0 days for all treatment groups. Based on the 2:2:2:1 randomisation scheme in the ITPs of HS0003 and HS0004, the total time at risk was highest in the bimekizumab total group (262.3 participant-years), higher in the bimekizumab 320mg Q2W group (175.4 participant-years) compared with the bimekizumab 320mg Q4W group (86.9 participant-years) and lowest in the placebo group (44.6 participant-years).

Table 42. Study medication duration and participant-years of time at risk during the ITP (Pool S1)

	Placebo N=146	BKZ 320mg Q4W N=285	BKZ 320mg Q2W N=576	BKZ Total N=861
Study medication duration (days), n	146	285	576	861
Mean (SD)	107.7 (17.86)	107.3 (15.93)	106.9 (17.96)	107.0 (17.31)
Median	112.0	112.0	112.0	112.0
Min, max	14, 132	28, 126	14, 144	14, 144
Total study medication duration (participant-years)	43.0	83.7	168.6	252.3
Total time at risk (participant-years)	44.6	86.9	175.4	262.3

BKZ=bimekizumab; ISS=Integrated Summary of Safety; ITP=Initial Treatment Period; max=maximum; Min=minimum; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation
Note: Total study medication duration was a subset of total time at risk excluding nontreated periods.

Pool S2

In Pool S2, the median study medication duration during the combined Initial and Maintenance Treatment Periods was 336.0 days, 335.0 days, and 336.0 days for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, and bimekizumab 320mg Q2W/Q2W groups, respectively. The total time at risk was 239.5, 245.8, and 242.1 participant-years for the bimekizumab 320mg Q4W/Q4W, bimekizumab 320mg Q2W/Q4W, and bimekizumab 320mg Q2W/Q2W groups, respectively.

Table 43. Study medication duration and participant-years of time at risk during the combined ITP and MTP (Pool S2)

	BKZ 320mg Q4W/Q4W N=285	BKZ 320mg Q2W/Q4W N=291	BKZ 320mg Q2W/Q2W N=285	BKZ Total[a] N=995
Study medication duration (days), n	285	291	285	995
Mean (SD)	283.6 (90.95)	283.9 (95.94)	287.9 (90.39)	273.9 (92.57)
Median	336.0	335.0	336.0	335.0
Min, max	1, 376	1, 427	8, 386	1, 427
Cumulative duration of exposure				
>0 months	285 (100)	291 (100)	285 (100)	995 (100)
≥4 months	258 (90.5)	259 (89.0)	257 (90.2)	893 (89.7)
≥8 months	213 (74.7)	229 (78.7)	223 (78.2)	667 (67.0)
Total study medication duration (participant-years)	221.3	226.2	224.6	746.1
Total time at risk (participant-years)	239.5	245.8	242.1	809.5

BKZ=bimekizumab; ISS=Integrated Summary of Safety; ITP=Initial Treatment Period; max=maximum; Min=minimum; MTP=Maintenance Treatment Period; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation
Note: Total study medication duration was a subset of total time at risk excluding nontreated periods.
[a] Exposure for the BKZ total group also includes BKZ exposure during the MTP for study participants in the PBO/BKZ 320mg Q2W group.

Pool S3

In Pool S3, the median study medication durations during the combined Initial, Maintenance, and OLE Treatment Periods were 239.0, 287.0, and 475.0 days for the Phase 3 bimekizumab 320mg Q4W, Phase 3 bimekizumab 320mg Q2W, and Phase 3 bimekizumab total groups, respectively. As of the clinical cut-off date, study medication exposures of at least 12 months were achieved by 137, 279, and 630 study participants in the Phase 3 bimekizumab 320mg Q4W, Phase 3 bimekizumab 320mg Q2W, and Phase 3 bimekizumab total groups, respectively. The total time at risk was 544.1, 729.4, and 1271.8 participant-years for the Phase 3 bimekizumab 320mg Q4W, Phase 3 bimekizumab 320mg Q2W, and Phase 3 bimekizumab total groups, respectively. An overview of study medication duration and participant-years of time at risk during the combined Initial, Maintenance, and OLE Treatment Periods is presented for the Phase 3 groups in Pool S3 in Table 44. For Pool S3, in Table 44, the MAH has only included data for the Phase 3 groups as this treatment group only contains an additional 46 study participants from the Phase 2 study HS0001.

Table 44. Study medication duration and participant-years of time at risk during the combined Initial, Maintenance, and OLE Treatment Periods (Pool S3)

	Phase 3 BKZ 320mg Q4W N=650	Phase 3 BKZ 320mg Q2W N=823	Phase 3 BKZ Total N=995
Study medication duration (days), n	650	823	995
Mean (SD)	287.1 (163.66)	306.4 (193.57)	442.3 (223.57)
Median	239.0	287.0	475.0
Min, max	1, 815	1, 827	1, 856
Cumulative duration of exposure			
>0 months	650 (100)	823 (100)	995 (100)
≥4 months	566 (87.1)	608 (73.9)	893 (89.7)
≥8 months	324 (49.8)	463 (56.3)	765 (76.9)
≥12 months	137 (21.1)	279 (33.9)	630 (63.3)
≥16 months	78 (12.0)	161 (19.6)	478 (48.0)
≥20 months	44 (6.8)	72 (8.7)	284 (28.5)
≥24 months	15 (2.3)	23 (2.8)	113 (11.4)
Total study medication duration (participant-years)	511.0	690.3	1204.8
Total time at risk (participant-years)	544.1	729.4	1271.8

BKZ=bimekizumab; =Integrated Summary of Safety; max=maximum; Min=minimum; OLE=Open-Label Extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation

Note: Total study medication duration was a subset of total time at risk excluding nontreated periods.

Subject disposition

Pool S1

Study discontinuation rates during the ITP in Pool S1 were low and similar for the bimekizumab total group (9.3%) compared with the placebo group (8.2%).

Pool S2

Pool S2, during the combined Initial and Maintenance Treatment Periods of the studies (i.e., HS0003 or HS0004), the discontinuation rate in the bimekizumab total group was 27.6%. The discontinuation rate was slightly higher in the bimekizumab 320mg Q4W/Q4W group (31.2%) compared with the bimekizumab 320mg Q2W/Q2W group (27.0%). The discontinuation rate in the bimekizumab 320mg Q2W/Q4W group (27.5%) was similar to that of the bimekizumab 320mg Q2W/Q2W group.

Pool S3

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, 57.7% of study participants in the Phase 3 bimekizumab total group were ongoing as of the clinical cut-off date. Study participants in the ongoing study HS0003 and the completed study HS0004 were considered 'completers' in Pool S3 if they had completed the feeder studies without enrolment in the OLE study HS0005. The low number of completers in the Phase 3 bimekizumab total group (6.7%) is due to the majority of study participants from HS0003 and HS0004 continued in the ongoing extension study HS0005.

In the Phase 3 bimekizumab total group in Pool S3, the rate of study discontinuation was 35.6%, which is consistent with recent studies in a moderate to severe HS population. The most common primary reason for discontinuation was consent withdrawn (15.8%), followed by AE (8.5%).

Adverse drug reactions (ADRs)

ADRs that are proposed for labelling were identified by the MAH by performing a medical review of data from pool S4 as follows:

• TEAEs from Pool S4 with a reported incidence ≥1% higher in the bimekizumab total group compared with the placebo group at the PT level.

• TEAEs in the bimekizumab total group from Pool S4 which do not meet the threshold of ≥1% over placebo at the PT level, but at the HLT level show a ≥1% higher incidence over placebo (considering synonyms and related group terms).

• TEAEs in the bimekizumab total group from Pool S1 which are >1% higher than placebo at the PT level that are biologically plausible based on mechanism of action and upon medical review are considered causally related, i.e., ADRs to bimekizumab.

In addition, all events from the exhaustive safety Pool S3 were reviewed for medically important events typical of a drug-induced adverse reaction.

TEAEs >1% higher in bimekizumab group vs placebo:

Table 45. TEAEs with an incidence in the bimekizumab total group of ≥1% higher than the placebo group by PT during the ITP overall (Pool S4)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=965 n (%)	BKZ Total N=2578 n (%)
Gastrointestinal disorders	22 (2.3)	96 (3.7)
Diarrhoea	22 (2.3)	96 (3.7)
Infections and infestations	47 (4.9)	353 (13.7)
Nasopharyngitis	38 (3.9)	166 (6.4)
Oral candidiasis	0	127 (4.9)
Pharyngitis	7 (0.7)	44 (1.7)
Folliculitis	2 (0.2)	38 (1.5)
Nervous system disorders	24 (2.5)	114 (4.4)
Headache	24 (2.5)	114 (4.4)
Respiratory, thoracic and mediastinal disorders	5 (0.5)	39 (1.5)
Oropharyngeal pain	5 (0.5)	39 (1.5)
Skin and subcutaneous tissue disorders	18 (1.9)	101 (3.9)
Hidradenitis	15 (1.6)	69 (2.7)
Pruritus	4 (0.4)	35 (1.4)

The most frequently reported ADRs were upper respiratory tract infections (most frequently nasopharyngitis) and oral candidiasis.

3 new ADRS with >1% difference were observed:

-Diarrhoea (Pool S4: 3.7% in the bimekizumab total group vs 2.3% in the placebo group)

The imbalance noted in Pool S4 between the bimekizumab total and placebo groups for the PT of diarrhoea was mainly driven by the indications of HS and axSpA (6.2% vs 4.8% and 2.9% vs 1.3% in the bimekizumab total group compared with the placebo group for HS and axSpA, respectively). In PSO and PsA, the incidences were similar between the bimekizumab total and placebo groups (2.1% vs 2.4% for PSO and 0.6% vs 0.5% for PsA, respectively). Diarrhoea was not considered a new ADR to bimekizumab as it is more likely related to underlying manifestations of axSpA (including gastrointestinal inflammatory diseases) or to gastroenteritis, which is already considered an ADR. Similarly, in people with HS, gastrointestinal inflammation is a common comorbidity, as demonstrated by the equally high incidence of diarrhoea in the placebo group. Gastroenteritis, which includes vomiting and diarrhoea is already listed as an ADR in SmPC section 4.8.

-Hidradenitis (Pool S4: 2.7% in the bimekizumab total group vs 1.6 % in the placebo group)

The imbalance noted in Pool S4 between the bimekizumab total and placebo groups for the PT of hidradenitis was driven by the HS indication only, as no cases were reported during the placebo-

controlled period in the PSO, PsA, or axSpA indications. While a lower incidence of hidradenitis was noted in the HS indication in the bimekizumab total group (8.0%) compared with the placebo group (10.3%) in Pool S1, the incidence was higher in the bimekizumab total group (2.7%) compared with the placebo group (1.6%) in Pool S4. The incidence rates calculated for Pool S4 are not adjusted for study or indication. Due to the different randomisation ratios across the studies pooled in Pool S4 and the different baseline risk of hidradenitis TEAEs across the indications pooled in Pool S4, the baseline risk of hidradenitis TEAEs is disproportionate between the placebo and bimekizumab treatment groups (HS contributes 15.1% of study participants in the placebo treatment group and 33.4% of study participants in the bimekizumab total treatment group).

-Pruritus (Pool S4: 1.4% in the bimekizumab total group vs 0.4% in the placebo group)

The imbalance noted in Pool S4 between the bimekizumab total and placebo groups, was mainly driven by the indications of HS and PsA (2.2% vs 0.7% and 1.0% vs 0% in the bimekizumab total group compared with the placebo group for HS and PsA, respectively). In PSO and axSpA, the incidences were similar between both groups (1.0% vs 1.2% and 0.6% vs 0.4% in the bimekizumab total group compared with the placebo group for PSO and axSpA, respectively). As discussed in the PsA application, pruritus was not considered a new ADR to bimekizumab as several events of pruritus were found to be associated with dermatitis or eczema, both of which are already considered ADRs for bimekizumab. A few events were also reported as pruritus of the eye (suggestive of conjunctivitis, which is also an ADR), and a few events were reported as pruritus at the place of PSO lesions. Further, no specific pattern was observed regarding the case characteristics (such as the time to onset or anatomical location of the itch), and overall, the MAH considered that there was insufficient evidence to consider pruritus as an ADR.

In HS, no specific pattern was observed regarding the case characteristics, and several events of pruritus were found to be associated with other events already labelled as ADRs (dermatitis or eczema, conjunctivitis Pruritus could also be associated with reported comorbidities, such as the underlying HS lesions, diabetes mellitus, and/or concurrent hypercholesteremia or concomitant use of drugs that have pruritus labelled as an ADR (e.g., metformin and antidepressants).

A medical review was also performed in Pool S4 for additional TEAEs which were reported at a ≥1% higher incidence over placebo at the HLT level (considering synonyms and related group terms). No new HLTs or group terms were subsequently identified that were required to be added as new ADRs to bimekizumab.

TEAEs identified for medical review as possible ADRs:

Table 46. TEAEs with an incidence in the bimekizumab total group of ⩾1% higher than the placebo group during the ITP (Pool S1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=146 n (%)	BKZ 320mg Q4W N=285 n (%)	BKZ 320mg Q2W N=576 n (%)	BKZ Total N=861 n (%)
Gastrointestinal disorders	7 (4.8)	18 (6.3)	43 (7.5)	61 (7.1)
Diarrhoea	7 (4.8)	17 (6.0)	36 (6.3)	53 (6.2)
Constipation	0	1 (0.4)	10 (1.7)	11 (1.3)
General disorders and administration site conditions	3 (2.1)	17 (6.0)	42 (7.3)	59 (6.9)
Pyrexia	2 (1.4)	8 (2.8)	19 (3.3)	27 (3.1)
Injection site pain	1 (0.7)	8 (2.8)	9 (1.6)	17 (2.0)
Injection site reaction	0	1 (0.4)	14 (2.4)	15 (1.7)
Infections and infestations	5 (3.4)	47 (16.5)	110 (19.1)	157 (18.2)
Oral candidiasis	0	7 (2.5)	41 (7.1)	48 (5.6)
Nasopharyngitis	3 (2.1)	10 (3.5)	23 (4.0)	33 (3.8)
Corona virus infection	2 (1.4)	5 (1.8)	20 (3.5)	25 (2.9)
Folliculitis	0	8 (2.8)	16 (2.8)	24 (2.8)
Vulvovaginal candidiasis	0	11 (3.9)	6 (1.0)	17 (2.0)
Vulvovaginal mycotic infection	0	5 (1.8)	10 (1.7)	15 (1.7)
Tinea pedis	0	2 (0.7)	7 (1.2)	9 (1.0)
Tonsillitis	0	4 (1.4)	5 (0.9)	9 (1.0)
Skin and subcutaneous tissue disorders	1 (0.7)	20 (7.0)	49 (8.5)	69 (8.0)
Pruritus	1 (0.7)	6 (2.1)	13 (2.3)	19 (2.2)
Seborrhoeic dermatitis	0	7 (2.5)	11 (1.9)	18 (2.1)
Dermatitis contact	0	4 (1.4)	12 (2.1)	16 (1.9)
Acne	0	3 (1.1)	9 (1.6)	12 (1.4)
Urticaria	0	1 (0.4)	8 (1.4)	9 (1.0)

TEAEs from Pool S1 not added as ADRs based on medical review: Diarrhoea is discussed above in the AR (also see discussion on clinical safety).

- Constipation (1.3% in the bimekizumab total group vs 0% in the placebo group)

In Pool S1, the incidence of constipation was 1.3% in the bimekizumab total group (EAIR: 4.2/100 participant-years), while no study participants reported constipation in the placebo group. There was no increased risk over time; the EAIR for constipation was lower in the Phase 3 bimekizumab total group in Pool S3 (1.8/100 participant-years) compared with the bimekizumab total group in Pool S1 (4.2/100 participant-years). Most study participants were white females with a BMI of >30kg/m2. In most study participants, constipation was mild in intensity (no events were severe), not considered drug related (as assessed by the Investigator), resolved, and did not require dose interruption. The majority of study participants who experienced constipation had significant confounding factors including medical history of

constipation, underlying perianal disease (pilonidal cysts, anal fissure or fistulae), other gastrointestinal disease, hypothyroidism, or concomitant use of medications that are labelled for constipation such as opiates, other analgesics and polypharmacy. The PT of constipation is therefore not considered a new ADR to bimekizumab by the MAH.

- Corona virus infection (2.9% in the bimekizumab total group vs 1.4% in the placebo group)

While the development program of PSO was conducted prior to the COVID-19 pandemic, the axSpA and PsA pivotal studies were largely conducted during the pandemic, and pooled across these studies the incidence of corona virus infection PTs was similar for the bimekizumab total group (0.7%) compared with the placebo group (1.5%) (axSpA application). Overall, across the different development programs there is no evidence of an increased risk for COVID-19 infections while being treated with bimekizumab, nor is there evidence of an increased risk for a severe outcome when having a COVID-19 infection. The PT of corona virus infection is therefore not considered a new ADR to bimekizumab by the MAH.

- Pyrexia (3.1% in the bimekizumab total group vs 1.4% in the placebo group)

Among the 27 bimekizumab-treated study participants with pyrexia TEAEs in Pool S1, no events were serious, severe, or led to study discontinuation. In 8 of these 27 study participants, the event was reported as being due to COVID vaccine, for which pyrexia is a known ADR. There was no mention of possible etiology for the remaining events. An association with the COVID vaccine was also seen in several bimekizumab treated study participants in Pool S3 (13 out of 54 study participants with pyrexia). No evidence of an imbalance vs placebo was observed in the other indications for bimekizumab. The PT of pyrexia is therefore not considered a new ADR to bimekizumab by the MAH.

- Urticaria (1.0% in the bimekizumab total group vs 0% in the placebo group)

Among the 9 bimekizumab-treated study participants with urticaria TEAEs in Pool S1, no events were serious, severe, or led to study discontinuation. All events were resolved or resolving, and the majority of events (7 out of 9) were not considered drug related (as assessed by the Investigator). In 4 of these 9 study participants, urticaria was associated with known allergic reactions (seasonal allergy/allergic rhinitis, or latex allergy). In another study participant, time to onset of urticaria was more suggestive of this event being associated with concurrent use of phenoxymethylpenicillin to treat otitis media, and another study participant was later diagnosed with urticaria cholinergic related to stress. No alternative explanations were mentioned for the 3 remaining cases, although they resolved within a few days (11 to 17 days) and did not recur during the treatment period. In comparison to Pool S1, no increase in the EAIR of urticaria was seen with longer bimekizumab exposure in Pool S3 (EAIRs of 3.4/100 participant-years in the bimekizumab total group in Pool S1 and 1.6/100 participant-years in the Phase 3 bimekizumab total group in Pool S3). Of the 20 study participants with urticaria in Pool S3, 8 study participants had a known history of allergic reactions (food, seasonal, latex or iodine) and 4 other study participants had alternative causes identified (drug [phenoxymethylpenicillin and Bactrim], stress, or food). No urticaria event led to study discontinuation. Considering the low EAIR in the Phase 3 bimekizumab total group in Pool S3 and no evidence of an imbalance vs placebo in the other indications for bimekizumab (urticaria occurred in 0.5% of study participants in the bimekizumab total group compared with 0% of study participants in the placebo group in Pool S4), the PT of urticaria is therefore not considered a new ADR to bimekizumab by the MAH.

<u>TEAEs proposed to be added as ADRs based on medical review:</u>

Following medical review of TEAEs reported with a placebo-controlled imbalance in Pool S1, the following PTs are proposed to be added as ADRs to bimekizumab:

• Vulvovaginal candidiasis (2.0% in the bimekizumab total group vs 0% in the placebo group).

• Vulvovaginal mycotic infection (1.7% in the bimekizumab total group vs 0% in the placebo group).

Of the 17 bimekizumab-treated study participants with vulvovaginal candidiasis TEAEs and the 15 bimekizumab-treated study participants with vulvovaginal mycotic infection TEAEs in Pool S1, all events were nonserious, mild or moderate in intensity, and managed with standard antifungal treatment; only 1 vulvovaginal candidiasis TEAE led to study discontinuation. Of these 32 study participants with vulvovaginal candidiasis and vulvovaginal mycotic infection TEAEs, 13 study participants reported use of antibiotics (4 study participants at Baseline and 9 study participants during the Initial Treatment Period), and for 3 events concomitantly used antibiotics were reported as co-suspect. In 12 study participants, the events were not considered drug related (as determined by the Investigator) and had no mention of possible etiology.

In comparison to Pool S1, no increases in the EAIRs of vulvovaginal candidiasis or vulvovaginal mycotic infection were seen with longer exposure in Pool S3 (EAIRs for TEAEs of vulvovaginal candidiasis and vulvovaginal mycotic infection were 6.5/100 participant-years and 5.8/100 participant-years in the bimekizumab total group in Pool S1, respectively, and 2.9/100 participant-years and 3.0/100 participant-years in the Phase 3 bimekizumab total group in Pool S3, respectively).

In Pool S4, no clear imbalance was noted for individual PTs of vulvovaginal candidiasis (0.8% in the bimekizumab total group vs 0.2% in the placebo group) or vulvovaginal mycotic infection (1.0% in the bimekizumab total group vs 0.3% in the placebo group); however, given the male predominance of study participants in the PSO, axSpA, and PsA development programs, a by-gender analysis was performed on vulvovaginal fungal infections (by combining the PTs of vulvovaginal candidiasis and vulvovaginal mycotic infection) in Pool S4. This analysis did show an imbalance in vulvovaginal fungal infections in females, with incidence rates of 4.0% in the bimekizumab total group compared with 1.1% in the placebo group.

The MAH proposed to update the ADR table as a conservative approach to reflect the imbalance in the PTs of vulvovaginal candidiasis and vulvovaginal mycotic infection. In addition, a broader analysis of Pool S4 was done for imbalances in other forms of candidiasis (excluding oral and oropharyngeal forms, which are already listed as ADRs). Based on the observed imbalances and plausible mechanisms of action, a broader term to cover cutaneous and other mucosal forms of candidiasis has already been included as an ADR for bimekizumab.

Adverse events (AEs)

Treatment-emergent AEs were defined as those AEs that have a start date on or following the first dose of study treatment through the final dose of study treatment + 140 days (covering the 20-week SFU Period).

Common TEAEs are defined as those TEAEs occurring in >2% of participants (at the PT level) in any treatment group for the Pool being summarised.

TEAEs:

Pool S1:

In Pool S1, during the Initial Treatment Period, TEAEs were reported at a similar incidence in the bimekizumab total group (63.4%) compared with the placebo group (61.6%).

The incidence of serious TEAEs and TEAEs leading to discontinuation was slightly higher in the bimekizumab total group (2.6% and 3.6%, respectively) compared with the placebo group (0% and 0.7%, respectively). The incidence of severe TEAEs was low overall, with an incidence of 3.3% in the bimekizumab total group and 1.4% in the placebo group. Drug-related TEAEs (as assessed by the

Investigator) were reported at a higher incidence in the bimekizumab total group compared with the placebo group (30.7% vs 13.7%, respectively).

Treatment-emergent AEs were reported at a lower incidence in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (58.6% vs 65.8%, respectively). Incidence of serious TEAEs, TEAEs leading to discontinuation, and severe TEAEs was low and similar in the bimekizumab 320mg Q4W group (2.5%, 3.2%, and 2.8%, respectively) compared with the bimekizumab 320mg Q2W group (2.6%, 3.8%, and 3.5%, respectively). Drug-related TEAEs were reported at a lower incidence in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (26.3% vs 32.8%, respectively).

No deaths were reported in Pool S1.

Pool S3:

EAIRs of TEAEs in the Phase 3 bimekizumab total group in Pool S3 did not increase with extended exposure (261.6/100 participant-years) compared with the bimekizumab total group in Pool S1 (375.9/100 participant-years).

The incidence of any TEAEs, serious TEAEs, TEAEs leading to discontinuation, and severe TEAEs were similar in the Phase 3 bimekizumab 320mg Q4W group (82.2%, 6.0%, 5.4%, and 6.9%, respectively) compared with the Phase 3 bimekizumab 320mg Q2W group (81.9%, 6.9%, 6.4%, and 8.3%, respectively). Drug-related TEAEs were reported at a lower incidence in the Phase 3 bimekizumab 320mg Q4W group compared with the Phase 3 bimekizumab 320mg Q2W group (38.0% vs 43.6%, respectively).

Common TEAEs:

Pool S1:

The most frequently reported TEAEs by PT in Pool S1 in the bimekizumab total group were hidradenitis (8.0%; EAIR: 27.5/100 participant-years [this PT is a combination of different reported terms, with the most frequently reported terms related to HS abscesses, pain due to HS, and worsening of HS), headache (6.4%; EAIR: 21.9/100 participant-years), diarrhoea (6.2%; EAIR: 21.1/100 participant-years), and oral candidiasis (5.6%; EAIR: 18.8/100 participant-years). The most frequently reported TEAEs by PT in Pool S1 in the placebo group were hidradenitis (10.3%; EAIR: 35.3/100 participant-years), headache (6.8%; EAIR: 23.4/100 participant-years), and diarrhoea (4.8%; EAIR: 16.3/100 participant-years).

Of the most common TEAEs by PT (defined as ≥2% in any treatment group), the incidence of oral candidiasis was higher in the bimekizumab total group compared with the placebo group (5.6% vs 0%, respectively), and the incidences of folliculitis and vulvovaginal candidiasis were slightly higher in the bimekizumab total group compared with the placebo group (2.8% vs 0% and 2.0% vs 0%, respectively). The incidence of back pain was slightly lower in the bimekizumab total group compared with the placebo group (0.8% vs 4.8%, respectively).

When comparing the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups, of the most common TEAEs by PT (defined as ≥2% in any treatment group), the incidence of vulvovaginal candidiasis was slightly higher in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (3.9% vs 1.0%, respectively). The incidence of oral candidiasis was slightly lower in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (2.5% vs 7.1%, respectively).

Table 47. Incidence of common TEAEs (i.e, in ⩾2% of study participants by PT in any treatment group) during the ITP (Pool S1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=146 n (%) [#]	BKZ 320mg Q4W N=285 n (%) [#]	BKZ 320mg Q2W N=576 n (%) [#]	BKZ Total N=861 n (%) [#]
Any TEAEs	90 (61.6) [216]	167 (58.6) [543]	379 (65.8) [1224]	546 (63.4) [1767]
Gastrointestinal disorders	20 (13.7) [27]	39 (13.7) [64]	102 (17.7) [156]	141 (16.4) [220]
Diarrhoea	7 (4.8) [8]	17 (6.0) [20]	36 (6.3) [42]	53 (6.2) [62]
Abdominal pain	2 (1.4) [2]	4 (1.4) [5]	13 (2.3) [15]	17 (2.0) [20]
Nausea	3 (2.1) [4]	8 (2.8) [8]	10 (1.7) [12]	18 (2.1) [20]
General disorders and administration site conditions	13 (8.9) [18]	38 (13.3) [48]	90 (15.6) [164]	128 (14.9) [212]
Fatigue	3 (2.1) [3]	8 (2.8) [9]	16 (2.8) [18]	24 (2.8) [27]
Pyrexia	2 (1.4) [3]	8 (2.8) [8]	19 (3.3) [20]	27 (3.1) [28]
Injection site pain	1 (0.7) [1]	8 (2.8) [8]	9 (1.6) [21]	17 (2.0) [29]
Injection site reaction	0	1 (0.4) [1]	14 (2.4) [20]	15 (1.7) [21]
Infections and infestations	30 (20.5) [41]	91 (31.9) [132]	193 (33.5) [308]	284 (33.0) [440]
Oral candidiasis	0	7 (2.5) [7]	41 (7.1) [44]	48 (5.6) [51]
Vulvovaginal candidiasis	0	11 (3.9) [11]	6 (1.0) [6]	17 (2.0) [17]
Folliculitis	0	8 (2.8) [8]	16 (2.8) [17]	24 (2.8) [25]
Nasopharyngitis	3 (2.1) [5]	10 (3.5) [13]	23 (4.0) [25]	33 (3.8) [38]
Urinary tract infection	4 (2.7) [4]	6 (2.1) [6]	9 (1.6) [9]	15 (1.7) [15]
Corona virus infection	2 (1.4) [2]	5 (1.8) [5]	20 (3.5) [20]	25 (2.9) [25]
Investigations	16 (11.0) [18]	23 (8.1) [38]	43 (7.5) [62]	66 (7.7) [100]
Psychiatric evaluation abnormal	2 (1.4) [2]	7 (2.5) [7]	7 (1.2) [7]	14 (1.6) [14]

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=146 n (%) [#]	BKZ 320mg Q4W N=285 n (%) [#]	BKZ 320mg Q2W N=576 n (%) [#]	BKZ Total N=861 n (%) [#]
Musculoskeletal and connective tissue disorders	15 (10.3) [19]	15 (5.3) [19]	38 (6.6) [43]	53 (6.2) [62]
Back pain	7 (4.8) [7]	0	7 (1.2) [7]	7 (0.8) [7]
Nervous system disorders	13 (8.9) [16]	25 (8.8) [33]	54 (9.4) [68]	79 (9.2) [101]
Headache	10 (6.8) [12]	15 (5.3) [23]	40 (6.9) [48]	55 (6.4) [71]
Respiratory, thoracic and mediastinal disorders	5 (3.4) [5]	19 (6.7) [24]	31 (5.4) [35]	50 (5.8) [59]
Oropharyngeal pain	2 (1.4) [2]	4 (1.4) [5]	15 (2.6) [16]	19 (2.2) [21]
Skin and subcutaneous tissue disorders	26 (17.8) [30]	67 (23.5) [99]	148 (25.7) [201]	215 (25.0) [300]
Hidradenitis	15 (10.3) [17]	25 (8.8) [30]	44 (7.6) [51]	69 (8.0) [81]
Eczema	2 (1.4) [2]	5 (1.8) [5]	14 (2.4) [15]	19 (2.2) [20]
Seborrhoeic dermatitis	0	7 (2.5) [7]	11 (1.9) [11]	18 (2.1) [18]
Dermatitis contact	0	4 (1.4) [4]	12 (2.1) [12]	16 (1.9) [16]
Intertrigo	2 (1.4) [2]	8 (2.8) [8]	5 (0.9) [6]	13 (1.5) [14]
Pruritus	1 (0.7) [1]	6 (2.1) [6]	13 (2.3) [15]	19 (2.2) [21]

BKZ=bimekizumab; ISS=Integrated Summary of Safety; ITP=Initial Treatment Period; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; Q2W=every 2 weeks; Q4W=every 4 weeks; SOC=System Organ Class; TEAE=treatment-emergent adverse event

Note: n=number of study participants who reported at least 1 TEAE within SOC/PT.

Note: [#] was the number of individual occurrences of the TEAE.

Note: Only TEAEs that occurred above the reporting threshold of 2% of study participants in any treatment group are included.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, TEAEs in the Phase 3 bimekizumab total group were most frequently reported in the SOCs of Infections and infestations (68.0%), Skin and subcutaneous tissue disorders (49.8%), Gastrointestinal disorders (29.7%), and General disorders and administration site conditions (21.6%).

The most frequently reported TEAEs by PT in Pool S3 in the Phase 3 bimekizumab total group were hidradenitis (24.1%; EAIR: 21.9/100 participant-years), corona virus infection (19.1%; EAIR: 16.6/100 participant-years), oral candidiasis (14.0%; EAIR: 12.1/100 participant-years) and nasopharyngitis (11.2%; EAIR: 11.2/100 participant-years).

Of the TEAEs reported by ≥5% of study participants by PT in any Phase 3 treatment group, slightly lower incidences of oral candidiasis (8.9% vs 12.4%, respectively) and corona virus infection (11.4% vs 14.7%, respectively) were reported in the Phase 3 bimekizumab 320mg Q4W group compared with the Phase 3 bimekizumab 320mg Q2W group.

The incidence of hidradenitis was slightly higher in the Phase 3 bimekizumab 320mg Q4W group compared with the Phase 3 bimekizumab 320mg Q2W group (20.6% vs 16.3%).

Table 48. Incidence of TEAEs reported by ⩾5% of study participants, by PT, in any treatment group – Overall Period (AMS)

MedDRA V19.0 SOC PT	PBO/ BKZ 320mg Q2W N=65 100 participant-years=0.59 n (%) [#] Incidence (95% CI)	BKZ 320mg Q4W/Q4W N=143 100 participant-years=1.17 n (%) [#] Incidence (95% CI)	BKZ 320mg Q2W/Q4W N=145 100 participant-years=1.22 n (%) [#] Incidence (95% CI)	BKZ 320mg Q2W/Q2W N=141 100 participant-years=1.21 n (%) [#] Incidence (95% CI)	BKZ total N=494 100 participant-years=3.99 n (%) [#] Incidence (95% CI)
Any TEAEs	60 (92.3) [352] 326.99 (249.5, 420.9)	122 (85.3) [721] 330.79 (274.7, 395.0)	124 (85.5) [715] 317.43 (264.0, 378.5)	126 (89.4) [753] 347.38 (289.4, 413.6)	425 (86.0) [2413] 328.08 (297.6, 360.8)
Gastrointestinal disorders	19 (29.2) [44] 38.33 (23.1, 59.9)	39 (27.3) [88] 41.77 (29.7, 57.1)	44 (30.3) [66] 45.12 (32.8, 60.6)	40 (28.4) [68] 40.81 (29.2, 55.6)	137 (27.7) [254] 42.47 (35.7, 50.2)
Diarrhoea	7 (10.8) [8] 12.32 (5.0, 25.4)	16 (11.2) [22] 15.04 (8.6, 24.4)	12 (8.3) [16] 10.57 (5.5, 18.5)	15 (10.6) [20] 13.29 (7.4, 21.9)	49 (9.9) [65] 13.24 (9.8, 17.5)
Abdominal pain	4 (6.2) [5] 6.95 (1.9, 17.8)	5 (3.5) [7] 4.41 (1.4, 10.3)	6 (4.1) [6] 5.08 (1.9, 11.1)	4 (2.8) [4] 3.36 (0.9, 8.6)	18 (3.6) [21] 4.63 (2.7, 7.3)
Nausea	2 (3.1) [4] 3.44 (0.4, 12.4)	5 (3.5) [8] 4.40 (1.4, 10.3)	1 (0.7) [1] 0.82 (0.0, 4.6)	8 (5.7) [9] 6.87 (3.0, 13.5)	16 (3.2) [21] 4.10 (2.3, 6.7)
General disorders and administration site conditions	10 (15.4) [17] 18.86 (9.0, 34.7)	26 (18.2) [42] 25.84 (16.9, 37.9)	24 (16.6) [52] 22.70 (14.5, 33.8)	35 (24.8) [57] 34.95 (24.3, 48.6)	89 (18.0) [157] 25.88 (20.8, 31.8)
Pyrexia	3 (4.6) [4] 5.26 (1.1, 15.4)	8 (5.6) [8] 7.07 (3.1, 13.9)	8 (5.5) [9] 6.88 (3.0, 13.5)	7 (5.0) [7] 5.93 (2.4, 12.2)	24 (4.9) [25] 6.21 (4.0, 9.2)
Infections and infestations	43 (66.2) [93] 115.41 (83.5, 155.5)	87 (60.8) [193] 131.42 (105.3, 162.1)	89 (61.4) [235] 124.94 (100.3, 153.8)	91 (64.5) [225] 129.31 (104.1, 158.8)	301 (60.9) [721] 128.20 (114.1, 143.5)
Oral candidiasis	3 (4.6) [4] 5.14 (1.1, 15.0)	13 (9.1) [14] 11.69 (6.2, 20.0)	16 (11.0) [22] 14.14 (8.1, 23.0)	15 (10.6) [26] 13.21 (7.4, 21.8)	47 (9.5) [66] 12.50 (9.2, 16.6)
Influenza	5 (7.7) [6] 8.73 (2.8, 20.4)	2 (1.4) [2] 1.72 (0.2, 6.2)	2 (1.4) [4] 1.66 (0.2, 6.0)	4 (2.8) [4] 3.36 (0.9, 8.6)	12 (2.4) [14] 3.04 (1.6, 5.3)

MedDRA V19.0 SOC PT	PBO/ BKZ 320mg Q2W N=65 100 participant-years=0.59 n (%) [#] Incidence (95% CI)	BKZ 320mg Q4W/Q4W N=143 100 participant-years=1.17 n (%) [#] Incidence (95% CI)	BKZ 320mg Q2W/Q4W N=145 100 participant-years=1.22 n (%) [#] Incidence (95% CI)	BKZ 320mg Q2W/Q2W N=141 100 participant-years=1.21 n (%) [#] Incidence (95% CI)	BKZ total N=494 100 participant-years=3.99 n (%) [#] Incidence (95% CI)
Nervous system disorders	11 (16.9) [13] 20.43 (10.2, 36.6)	21 (14.7) [35] 20.15 (12.5, 30.8)	22 (15.2) [37] 20.51 (12.9, 31.1)	22 (15.6) [31] 20.39 (12.8, 30.9)	73 (14.8) [112] 20.55 (16.1, 25.8)
Headache	7 (10.8) [8] 12.55 (5.0, 25.9)	10 (7.0) [23] 9.02 (4.3, 16.6)	16 (11.0) [24] 14.44 (8.3, 23.4)	12 (8.5) [16] 10.59 (5.5, 18.5)	43 (8.7) [68] 11.56 (8.4, 15.6)
Respiratory, thoracic, and mediastinal disorders	6 (9.2) [8] 10.56 (3.9, 23.0)	15 (10.5) [19] 14.04 (7.9, 23.2)	14 (9.7) [19] 12.40 (6.8, 20.8)	16 (11.3) [22] 13.97 (8.0, 22.7)	50 (10.1) [67] 13.45 (10.0, 17.7)
Oropharyngeal pain	4 (6.2) [4] 6.92 (1.9, 17.7)	4 (2.8) [5] 3.50 (1.0, 9.0)	6 (4.1) [7] 5.09 (1.9, 11.1)	5 (3.5) [5] 4.17 (1.4, 9.7)	18 (3.6) [20] 4.61 (2.7, 7.3)
Skin and subcutaneous tissue disorders	37 (56.9) [59] 92.54 (65.2, 127.6)	63 (44.1) [137] 78.13 (60.0, 100)	63 (43.4) [122] 74.53 (57.3, 95.4)	63 (44.7) [146] 74.29 (57.1, 95.0)	215 (43.5) [444] 76.37 (66.5, 87.3)
Hidradenitis	19 (29.2) [24] 38.07 (22.9, 59.5)	36 (25.2) [57] 36.08 (25.3, 50.0)	27 (18.6) [37] 25.15 (16.6, 36.6)	22 (15.6) [45] 20.36 (12.8, 30.8)	96 (19.4) [153] 27.36 (22.2, 33.4)
Eczema	3 (4.6) [3] 5.15 (1.1, 15.1)	10 (7.0) [10] 8.90 (4.3, 16.4)	8 (5.5) [10] 6.84 (3.0, 13.5)	7 (5.0) [7] 5.87 (2.4, 12.1)	27 (5.5) [29] 6.96 (4.6, 10.1)
Intertrigo	2 (3.1) [2] 3.44 (0.4, 12.4)	9 (6.3) [10] 8.03 (3.7, 15.2)	7 (4.8) [7] 5.87 (2.4, 12.1)	8 (5.7) [10] 6.74 (2.9, 13.3)	25 (5.1) [28] 6.43 (4.2, 9.5)
Seborrhoeic dermatitis	3 (4.6) [4] 5.20 (1.1, 15.2)	6 (4.2) [7] 5.26 (1.9, 11.4)	11 (7.6) [11] 9.46 (4.7, 16.9)	3 (2.1) [3] 2.51 (0.5, 7.3)	23 (4.7) [25] 5.94 (3.8, 8.9)
Pruritus	3 (4.6) [3] 5.19 (1.1, 15.2)	7 (4.9) [7] 6.22 (2.5, 12.8)	3 (2.1) [3] 2.50 (0.5, 7.3)	7 (5.0) [8] 5.99 (2.4, 12.3)	19 (3.8) [20] 4.90 (2.9, 7.6)

MedDRA V19.0 SOC PT	PBO/ BKZ 320mg Q2W N=65 100 participant-years=0.59 n (%) [#] Incidence (95% CI)	BKZ 320mg Q4W/Q4W N=143 100 participant-years=1.17 n (%) [#] Incidence (95% CI)	BKZ 320mg Q2W/Q4W N=145 100 participant-years=1.22 n (%) [#] Incidence (95% CI)	BKZ 320mg Q2W/Q2W N=141 100 participant-years=1.21 n (%) [#] Incidence (95% CI)	BKZ total N=494 100 participant-years=3.99 n (%) [#] Incidence (95% CI)
Folliculitis	2 (3.1) [2] 3.39 (0.4, 12.2)	7 (4.9) [7] 6.18 (2.5, 12.7)	11 (7.6) [13] 9.46 (4.7, 16.9)	8 (5.7) [9] 6.79 (2.9, 13.4)	28 (5.7) [31] 7.25 (4.8, 10.5)
Nasopharyngitis	6 (9.2) [12] 10.72 (3.9, 23.3)	11 (7.7) [16] 9.87 (4.9, 17.7)	12 (8.3) [16] 10.37 (5.4, 18.1)	12 (8.5) [14] 10.54 (5.4, 18.4)	39 (7.9) [53] 10.30 (7.3, 14.1)
Upper respiratory tract infection	2 (3.1) [2] 3.42 (0.4, 12.3)	7 (4.9) [8] 6.07 (2.4, 12.5)	10 (6.9) [11] 8.51 (4.1, 15.7)	8 (5.7) [11] 6.81 (2.9, 13.4)	27 (5.5) [32] 6.95 (4.6, 10.1)
Urinary tract infection	5 (7.7) [6] 8.67 (2.8, 20.2)	7 (4.9) [7] 6.19 (2.5, 12.7)	9 (6.2) [12] 7.68 (3.5, 14.6)	9 (6.4) [9] 7.64 (3.5, 14.5)	29 (5.9) [33] 7.50 (5.0, 10.8)
Corona virus infection	11 (16.9) [11] 19.66 (9.8, 35.2)	16 (11.2) [16] 14.40 (8.2, 23.4)	23 (15.9) [24] 20.45 (13.0, 30.7)	23 (16.3) [23] 20.57 (13.0, 30.9)	71 (14.4) [72] 19.06 (14.9, 24.0)
Investigations	19 (29.2) [33] 39.23 (23.6, 61.3)	30 (21.0) [57] 29.71 (20.0, 42.4)	22 (15.2) [34] 19.61 (12.3, 29.7)	27 (19.1) [66] 25.36 (16.7, 36.9)	90 (18.2) [177] 25.34 (20.4, 31.1)
Aspartate aminotransferase increased	4 (6.2) [6] 7.04 (1.9, 18.0)	0	1 (0.7) [1] 0.82 (0.0, 4.6)	4 (2.8) [5] 3.37 (0.9, 8.6)	8 (1.6) [11] 2.03 (0.9, 4.0)
Psychiatric evaluation abnormal	5 (7.7) [5] 8.70 (2.8, 20.3)	11 (7.7) [11] 9.85 (4.9, 17.6)	4 (2.8) [4] 3.32 (0.9, 8.5)	1 (0.7) [1] 0.83 (0.0, 4.6)	20 (4.0) [20] 5.11 (3.1, 7.9)
Musculoskeletal and connective tissue disorders	15 (23.1) [18] 30.99 (17.3, 51.1)	19 (13.3) [30] 17.56 (10.6, 27.4)	23 (15.9) [30] 21.55 (13.7, 32.3)	16 (11.3) [19] 14.05 (8.0, 22.8)	61 (12.3) [82] 16.64 (12.7, 21.4)
Back pain	6 (9.2) [6] 10.99 (4.0, 23.9)	4 (2.8) [4] 3.45 (0.9, 8.8)	7 (4.8) [7] 5.96 (2.4, 12.3)	3 (2.1) [3] 2.50 (0.5, 7.3)	14 (2.8) [14] 3.57 (2.0, 6.0)

Severe TEAEs:

Pool S1:

The incidence of severe TEAEs was low overall in the bimekizumab total group (3.3%) and placebo group (1.4%).

Severe TEAEs which led to discontinuation all occurred in the bimekizumab total group and included suicidal ideation, depression, psoriasis, pregnancy on contraceptive, folliculitis, colitis, migraine, breast cancer, and hidradenitis (2 study participants).

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the majority of TEAEs were mild or moderate in intensity. The incidence of severe TEAEs was 10.6% in the Phase 3 bimekizumab total group.

When adjusting for exposure, the EAIR of severe TEAEs in the Phase 3 bimekizumab total group in Pool S3 was similar (8.7/100 participant-years) compared with the bimekizumab total group in Pool S1 (10.9/100 participant-years).

Severe TEAEs in the Phase 3 bimekizumab total group in Pool S3 were most frequently reported in the SOC of Skin and subcutaneous tissue disorders (3.4%). Severe TEAEs, by PT, reported by >1 study participant in the Phase 3 bimekizumab total group were hidradenitis (23 study participants [2.3%]); suicidal ideation (7 study participants [0.7%]); AST increased and hyperkalemia (3 study participants [0.3%] each); and cholelithiasis, cellulitis, corona virus infection, road traffic accident, GGT increased, psychiatric evaluation abnormal, depression, nephrolithiasis, renal colic, pain of skin, and psoriasis (2 study participants [0.2%] each).

Table 49. Incidence of severe TEAEs per 100 participant-years in ≥1 study participant by PT in the Phase 3 bimekizumab total treatment group during the combined Initial, Maintenance, and OLE Treatment Period (Pool S3)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 320mg Q4W N=650 100 participant-yrs=5.44 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 320mg Q2W N=823 100 participant-yrs=7.29 n (%) [#] EAIR (95% CI)	Phase 3 BKZ Total N=995 100 participant yrs=12.72 n (%) [#] EAIR (95% CI)
Any severe TEAE	45 (6.9) [71] 8.5 (6.2, 11.4)	68 (8.3) [92] 9.8 (7.6, 12.4)	105 (10.6) [163] 8.7 (7.1, 10.5)
Hepatobiliary disorders	2 (0.3) [4] 0.4 (0.0, 1.3)	1 (0.1) [1] 0.1 (0.0, 0.8)	3 (0.3) [5] 0.2 (0.0, 0.7)
Cholelithiasis	1 (0.2) [1] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [2] 0.2 (0.0, 0.6)
Infections and infestations	13 (2.0) [16] 2.4 (1.3, 4.1)	16 (1.9) [17] 2.2 (1.3, 3.6)	28 (2.8) [33] 2.2 (1.5, 3.2)
Cellulitis	0	2 (0.2) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.2 (0.0, 0.6)
Corona virus infection	1 (0.2) [1] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [2] 0.2 (0.0, 0.6)
Injury, poisoning and procedural complications	2 (0.3) [2] 0.4 (0.0, 1.3)	3 (0.4) [4] 0.4 (0.1, 1.2)	5 (0.5) [6] 0.4 (0.1, 0.9)
Road traffic accident	1 (0.2) [1] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [2] 0.2 (0.0, 0.6)
Investigations	4 (0.6) [5] 0.7 (0.2, 1.9)	3 (0.4) [4] 0.4 (0.1, 1.2)	7 (0.7) [9] 0.6 (0.2, 1.1)
Aspartate aminotransferase increased	1 (0.2) [1] 0.2 (0.0, 1.0)	2 (0.2) [2] 0.3 (0.0, 1.0)	3 (0.3) [3] 0.2 (0.0, 0.7)
Gamma-glutamyltransferase increased	1 (0.2) [1] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [2] 0.2 (0.0, 0.6)
Psychiatric evaluation abnormal	2 (0.3) [2] 0.4 (0.0, 1.3)	0	2 (0.2) [2] 0.2 (0.0, 0.6)
Hyperkalaemia	0	3 (0.4) [3] 0.4 (0.1, 1.2)	3 (0.3) [3] 0.2 (0.0, 0.7)
Psychiatric disorders	5 (0.8) [6] 0.9 (0.3, 2.1)	4 (0.5) [4] 0.5 (0.1, 1.4)	9 (0.9) [10] 0.7 (0.3, 1.3)
Depression	2 (0.3) [2] 0.4 (0.0, 1.3)	0	2 (0.2) [2] 0.2 (0.0, 0.6)
Suicidal ideation	3 (0.5) [3] 0.6 (0.1, 1.6)	4 (0.5) [4] 0.5 (0.1, 1.4)	7 (0.7) [7] 0.6 (0.2, 1.1)
Renal and urinary disorders	2 (0.3) [13] 0.4 (0.0, 1.3)	5 (0.6) [5] 0.7 (0.2, 1.6)	5 (0.5) [18] 0.4 (0.1, 0.9)
Nephrolithiasis	2 (0.3) [7] 0.4 (0.0, 1.3)	2 (0.2) [2] 0.3 (0.0, 1.0)	2 (0.2) [9] 0.2 (0.0, 0.6)
Renal colic	1 (0.2) [2] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [3] 0.2 (0.0, 0.6)
Skin and subcutaneous tissue disorders	12 (1.8) [14] 2.2 (1.1, 3.9)	22 (2.7) [25] 3.1 (1.9, 4.6)	34 (3.4) [39] 2.7 (1.9, 3.8)
Hidradenitis	7 (1.1) [7] 1.3 (0.5, 2.7)	16 (1.9) [18] 2.2 (1.3, 3.6)	23 (2.3) [25] 1.8 (1.2, 2.7)
Pain of skin	1 (0.2) [1] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [2] 0.2 (0.0, 0.6)
Psoriasis	1 (0.2) [1] 0.2 (0.0, 1.0)	1 (0.1) [1] 0.1 (0.0, 0.8)	2 (0.2) [2] 0.2 (0.0, 0.6)

In the bimekizumab total groups in both pools, severe TEAEs were most frequently reported in the SOC of Skin and subcutaneous tissue disorders, and the most frequently reported severe TEAE by PT was hidradenitis.

In the bimekizumab total groups in both pools, severe TEAEs were most frequently reported in the SOC of Skin and subcutaneous tissue disorders, and the most frequently reported severe TEAE by PT was hidradenitis.

Serious adverse event/deaths/other significant events

Deaths

Pool S1:

In Pool S1, during the Initial Treatment Period, no study participant experienced a TEAE leading to death.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, a total of 2 bimekizumab-treated study participants experienced a TEAE leading to death.

Study HS0003: A participant who received 320mg Q2W/Q2W experienced fatal congestive cardiac failure 255 days post first injection and 15 days post last injection. The participant had several co-morbidities including but not limited to diabetes, hypertension, MI with stenting, pacemaker and congestive cardiac failure. The participant was on several concomitant medications at the time of the acute, cardiac failure including the following: metformin, atorvastatin, furosemide, losartan, timolol, warfarin, liraglutide, clotrimazole, carvedilol, betamethasone, metoprolol and nystatin. The participant had a complex clinical history and experienced episodes of minor decompensation while on the study. These episodes were attributed to poor compliance with dietary requirements and medication. The participant was stabilised after these events and resumed treatment until ultimately he was found unresponsive at home. There was no postmortem performed. The death was attributed to decompensation of known CCF in the setting of poor compliance with furosemide.

Study HS0005: A participant with a known history of anxiety, lower respiratory tract infections and anaemia suffered a fatal outcome because of a CNS infection 386 days post first injection and 8 days post last injection. Concomitant medication(s) at the time of infection included the following: clonazepam, citalopram, and quetiapine. The participant presented to hospital with fever- and a documented GCS of 12. CT brain revealed hydrocephalus. CSF cultures were negative. The patient had complex HS with gluteal abscesses invading into coccyx. Blood culture then revealed *P. mirabilis* and *A. baumannii* complex/*haemolyticus* and the wound culture revealed *K. pneumonia* and *P. mirabilis* but the CSF culture remained negative. Despite intensive treatment, the patient never regained consciousness. The patient did not have an autopsy. The cause of death is recorded as brain death, cytotoxic cerebral oedema, septic encephalopathy, multiple organ dysfunction syndrome, soft tissue infection-osteomyelitis, and septic shock.

Serious TEAEs

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of serious TEAEs was low overall, though slightly higher in the bimekizumab total group (2.6%) compared with the placebo group (0%).

Serious TEAEs in the bimekizumab total group were most frequently reported in the SOC of Skin and subcutaneous tissue disorders (0.5%).

By PT, the 2 serious TEAEs reported by >1 study participant in the bimekizumab total group were hidradenitis (3 study participants [0.3%]) and cholelithiasis (2 study participants [0.2%]).

All other serious TEAEs by PT were reported by 1 study participant each in any treatment group.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of serious TEAEs was 9.0% in the Phase 3 bimekizumab total group.

Serious TEAEs in the Phase 3 bimekizumab total group were most frequently reported in the SOCs of Infections and infestations (2.1%), Skin and subcutaneous disorders (1.8%), and Gastrointestinal disorders (1.0%). Serious TEAEs, by PT, reported by >1 study participant in the Phase 3 bimekizumab total group were hidradenitis (14 study participants [1.4%]); suicidal ideation (5 study participants [0.5%]); cellulitis (3 study participants [0.3%]); and colitis ulcerative, cholelithiasis, corona virus infection, meniscus injury, road traffic accident, pregnancy on contraceptive, depression, nephrolithiasis, ureterolithiasis, pain of skin, and deep vein thrombosis (2 study participants [0.2%] each).

Overall period:

During the Overall Period in the treated population, 8.1% of study participants in the bimekizumab total group reported serious TEAEs. The incidence of serious TEAEs was similar in the bimekizumab 320mg Q4W/Q4W group (9.1%) compared with the bimekizumab 320mg Q2W/Q2W group (9.2%).

In the bimekizumab total group, the following serious TEAEs, by PT, were reported in >1 study participant: hidradenitis (7 study participants), suicidal ideation (4 study participants), cellulitis (2 study participants), and nephrolithiasis (2 study participants).

Treatment related adverse events:

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of any drug-related TEAE (as assessed by the Investigator) was higher in the bimekizumab total group (30.7%) compared with the placebo group (13.7%).

As expected, drug-related TEAEs in the bimekizumab total group were primarily reported in the SOC of Infections and infestations (14.3%), which was higher compared with the placebo group (2.7%). The most frequently reported drug-related TEAE by PT was oral candidiasis, which was only reported in the bimekizumab total group (4.6%). In addition to oral candidiasis, the most commonly reported drug-related TEAEs (reported in ≥2% of study participants) in the bimekizumab total group were diarrhea (2.1%) and headache (2.0%); the incidences of these events were similar in the bimekizumab total and placebo groups. The most frequently reported drug-related TEAE by PTs in the placebo group were diarrhoea and headache (2.1% each). The incidence of drug-related TEAEs was lower in the bimekizumab 320mg Q4W group (26.3%) compared with the bimekizumab 320mg Q2W group (32.8%). Of the most common drug-related TEAEs by PT (reported in ≥2% of study participants in any treatment group), the incidence of oral candidiasis was slightly lower in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (2.1% vs 5.9%).

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, drug-related TEAEs (as assessed by the Investigator) were reported by 50.7% of study participants in the Phase 3 bimekizumab total group.

Drug-related TEAEs in the Phase 3 bimekizumab total group in Pool S3 were primarily reported in the SOC of Infections and infestations (33.8%). The most frequently reported drug-related TEAE by PT (reported in ≥5% of study participants in the Phase 3 bimekizumab total group) was oral candidiasis (12.0%).

The incidence of drug-related TEAEs was lower in the Phase 3 bimekizumab 320mg Q4W group (38.0%) compared with the Phase 3 bimekizumab 320mg Q2W group (43.6%).

The most frequently reported drug-related TEAE by PT, oral candidiasis, was reported at a slightly lower incidence in the Phase 3 bimekizumab 320mg Q4W group (7.5%) compared with the Phase 3 bimekizumab 320mg Q2W group (10.4%).

Overall period:

During the Overall Period in the treated population, the incidence of serious drug-related TEAEs (relatedness determined by the Investigator) was low and similar in both the bimekizumab 320mg Q4W/Q4W (2.8%) and the bimekizumab 320mg Q2W/Q2W (1.4%) groups. In the bimekizumab 320mg Q4W/Q4W group, serious drug-related TEAEs of keratitis, genital candidiasis, oropharyngeal candidiasis, and suicidal ideation were reported by 1 study participant each (keratitis and suicidal ideation were reported during the Initial Treatment Period). In the bimekizumab 320mg Q2W/Q2W group, serious drug-related TEAEs of drug-induced liver injury and hidradenitis were reported by 1 study participant each (drug-induced liver injury was reported during the Initial Treatment Period).

Adverse Events of Special Interest (AESIs):

Potential Hy's Law was the only AESI defined for the HS program. Potential Hy's Law, defined as ≥3x upper limit of normal (ULN) alanine aminotransferase (ALT) or aspartate aminotransferase (AST) with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality, had to be reported as an AESI.

Hepatic events and LFT elevations

Pool S1:

In Pool S1, the incidence of hepatic TEAEs during the Initial Treatment Period was similar between the bimekizumab total group (2.2%) and the placebo group (2.7%).

Hepatic TEAEs reported in >1 study participant in the bimekizumab total group were aspartate aminotransferase increased (0.8%); alanine aminotransferase increased (0.6%); gamma-glutamyltransferase increased (0.5%); and hepatic steatosis, blood bilirubin increased, and hepatic enzyme increased (0.2% each).

Liver TEAEs in Pool S1 were generally mild or moderate with the exception of 3 participants. Only one of these events was considered related to the study drug and is detailed below.

HS0003: A serious TEAE of drug-induced liver injury (DILI) was experienced by a participant with no known history of prior liver disease. They were noted to have elevated liver enzymes with no known cause on two prior occasions in 2018 and 2020, prior to enrolment in HS0003. In the initial treatment period, the assigned treatment was Bimekizumab 320mg subcutaneous (sc) every 2 weeks (Q2W).

On 13 March 2021, the participant received the first dose of Covid-19 vaccine. Concomitant medication(s) at the time of the drug-induced liver injury included the following: dienogest with ethinylestradiol and ibuprofen.

At Screening, ALT, AST, ALP, GGT, and total bilirubin were within the normal range of reference. At Baseline, prior to receiving the first dose of bimekizumab, ALT, AST, and GGT were reported to be elevated to CTCAE Grade 1. Two weeks after the first dose of bimekizumab, ALT and AST were elevated to CTCAE Grade 3, and GGT remained elevated to Grade 1. Thereafter, there was a persistent decrease in ALT, AST, and GGT over the next 2 to 3 weeks. The event resolved 29 days after the onset, with complete normalisation of LFTs. ALP and total bilirubin remained normal throughout the course of this

event. Other hepatology work-up including viral serology, relevant immunology parameters, and drug screen were also normal.

The drug was withdrawn, and the event was considered related to bimekizumab by the Investigator although there were multiple confounding factors including recent covid 19 vaccination, alcohol consumption and a known history of elevated liver enzymes without a clear cause. There was no liver biopsy or review by a hepatologist making definitive determination of causality difficult.

In Pool S1, during the Initial Treatment Period, the incidence of ALT or AST elevations >3xULN was low in the bimekizumab total group (1.2%), and no study participants in the placebo group reported ALT or AST elevations >3xULN.

In the bimekizumab total group, 10 study participants (1.2%; EAIR: 3.8/100 participant-years) had either ALT or AST elevations >3xULN, including 3 study participants (0.4%; EAIR: 1.1/100 participant-years) with either ALT or AST elevations >5xULN. Of these, 2 study participants (0.2%) had either ALT or AST elevations >8xULN, and 1 study participant (0.1%) had either ALT or AST elevations >10xULN.

For all 3 study participants with ALT or AST >5xULN, the HAC causality assessment scoring for drug-induced liver injury was unlikely (likelihood of <25%). No study participants met the criteria for Hy's law.

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of any hepatic TEAEs in the Phase 3 bimekizumab total group was 6.9%. No increased risk over time was observed for the incidence of any hepatic TEAE in the Phase 3 bimekizumab total group in Pool S3 (EAIR: 5.7/100 participant-years) when compared with the bimekizumab total group in Pool S1 (EAIR: 7.3/100 participant-years). The most frequently reported hepatic TEAEs by PT in the Phase 3 bimekizumab total group in Pool S3 were AST increased (2.4%), ALT increased (1.7%), and GGT increased (1.6%).

The majority of the hepatic event TEAEs reported in the Phase 3 bimekizumab total group were nonserious, were mild or moderate in intensity, were considered not drug related (as assessed by the Investigator), did not lead to study discontinuation, and resolved.

Of the 69 study participants in the Phase 3 bimekizumab total group who had hepatic event TEAEs in Pool S3:

- One study participant had a serious hepatic event TEAE of DILI that was considered drug related (as assessed by the Investigator) and led to study discontinuation. This is detailed in the discussion of Pool S1.
- Three study participants reported a total of 5 severe hepatic event TEAEs.
- Five study participants discontinued the study due to a hepatic event TEAEs.
- A total of 12 study participants had hepatic event TEAEs that were considered drug-related (as assessed by the Investigator). The events were in the PTs: ALT increased, AST increased, GGT increased, transaminases increased, DILI, blood bilirubin increased, bilirubin conjugated increased, and hepatocellular injury.

In pool S3, 46 study participants (4.7%) had either ALT or AST elevations >3xULN. Of these, 13 study participants (1.3%) had either ALT or AST elevations >5xULN, including 6 study participants (0.6%) with either ALT or AST elevations >8xULN, 3 study participants (0.3%) with either ALT or AST elevations >10xULN, and 1 study participant (0.1%) with either ALT or AST elevations >20xULN. One study participant in the Phase 3 bimekizumab total group met the protocol-defined laboratory criteria for PDILI (ALT or AST >3xULN and total bilirubin ≥1.5xULN). The total bilirubin remained below 2xULN (i.e., event did not meet criteria for Hy's Law), and the site considered these elevations to be related to diet.

No study participants in the Phase 3 bimekizumab total group met the criteria for Hy's Law.

No increased risk over time for the incidence of liver function elevations was observed in the Phase 3 bimekizumab total group from Pool S3 (1.3%; EAIR: 1.0/100 participant-years) when compared with the bimekizumab total group from Pool S1 (0.4%; EAIR: 1.1/100 participant-years).

All 13 cases of TEMA liver enzyme elevations (ALT or AST >5xULN) in the Phase 3 bimekizumab total group were independently adjudicated in a blinded manner by the HAC; 1 study participant each had at least 1 laboratory value adjudicated as probable (likelihood: 50% to 74%) or possible (likelihood: 25% to 49%), and the remainder were adjudicated as unlikely (likelihood: <25%). None of the TEMA cases of liver enzyme elevations across the HS development program were adjudicated as definitely or highly likely related to study medication. Both the probable and possible cases were confounded by concurrent medical histories such as underlying IBD, obesity, type 2 diabetes mellitus, hyperlipidemia, intestinal malabsorption, or concomitant use of medications labelled for hepatic enzyme abnormalities.

The following were events where participants experienced ALT or AST elevations >5xULN that were possibly related (as assessed by the Investigator) to bimekizumab; these were adjudicated as probable and unlikely, respectively per HAC.

Table 50. Cases of LFT elevation (>5xULN of ALT or AST) for bimekizumab-treated study participants with HS (n=13)

Study[a]	ID Age (years)/ Gender/ Weight (kg) Country	Liver TEAEs by PT (TTO – from first BKZ injection)	Medical history/ ConMeds/ LFTs at Baseline	Peak LFT values (U/L)	BKZ dose	Investigator's causality/ Severity/ Pattern/ Action with BKZ/ Hy's law [a] HAC overall causality assessment	UCB comment/Relevant event details/ Outcome (time to resolution)
HAC causality assessment: probable							
HS0004		Hepatocellular injury (239 days)	Cushing's syndrome, IBS, overweight, nausea, vomiting (for several years), and chronic diarrhea/ ethinylestradiol with levonorgestrel, Clobetasol, loperamide, betamethasone/ Normal LFTs at Baseline	W36: AST: 82 U/L ALT: 243 U/L GGT: 46 U/L	BKZ 320mg Q4W	Related/ Moderate/ Continuous/ Drug withdrawn/ No Hy's law Probable	The event of hepatocellular injury was followed by a serious AE of Crohn's disease. At W36 the level of ALT was >3x and <5xULN and the event was not resolved at the time of reporting. Considering possibility of co-existing elevation of liver enzymes in patients with IBD, the signs and symptoms of hepatocellular injury in this participant could have occurred with onset of symptoms of Crohn's disease.
HAC causality assessment: unlikely							
HS0003		Drug-induced liver injury (14 days)	Hepatic enzyme increased (unknown etiology); elevated liver enzymes in 2018 and 2020, occasional alcohol use/ ienogest with ethinylestradiol and ibuprofen/ Elevated AST, ALT, and GGT at Baseline	Baseline: AST 73 U/L ALT 97 U/L GGT 42 U/L W2: AST 514 U/L ALT 978 U/L GGT 56 U/L	BKZ 320mg Q2W	Related/ Moderate/ Continuous/ Drug withdrawn/ No Hy's law Unlikely	Confounded by medical history of LFT elevations before study entry: Grade 3 elevation of AST and ALT and Grade 1 elevation of GGT in Feb 2018 and >3xULN elevation of ALT with Grade 1 elevation of AST and GGT in Oct 2020. ALT, AST and GGT started to rise prior to administration of the first BKZ dose but the cause of these Grade 1 elevations were not reported. The participant continued alcohol intake during the study and GGT levels were elevated to Grade 1 throughout the course of this event. The participant had recently received COVID-19 vaccine; per the Investigator, the immune reaction due to COVID-19 vaccination might have contributed to the increase of the liver enzymes. In addition, the participant was not seen by hepatic consult and liver biopsy was not performed, which precluded appropriate assessment of causality.

Of note, a participant, experienced TEAEs of GGT increased, ALT increased (>5xULN), and AST increased (>5xULN), which were all nonserious, moderate in intensity, were considered drug related (as assessed by the Investigator), did not lead to study discontinuation, and resolved or were resolving.

Overall period:

During the Overall Period in the treated population, hepatic events were reported by 5.1% of study participants in the bimekizumab total group. The incidence of hepatic events was lower in the bimekizumab 320mg Q4W/Q4W group (1.4%) compared with the bimekizumab 320mg Q2W/Q2W group (8.5%).

In the bimekizumab total group, the most common hepatic TEAEs were ALT increased (8 study participants), AST increased (8 study participants), and gamma-glutamyltransferase increased (6 study participants). In the bimekizumab 320mg Q4W/Q4W group, no TEAE, by PT, was reported by >1 study participant. In the bimekizumab 320mg Q2W/Q2W group, the most common hepatic TEAEs were AST increased (4 study participants), gamma-glutamyltranferase increased (4 study participants), and ALT increased (3 study participants).

Other safety topics of interest:

Infection:

Pool S1

In Pool S1, during the Initial Treatment Period, TEAEs were most frequently reported in the SOC of Infections and infestations and were more commonly reported in the bimekizumab total group (33.0%) compared with the placebo group (20.5%).

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, TEAEs in the Phase 3 bimekizumab total group were most frequently reported in the SOC of Infections and infestations (68.0%). No increased incidence rate of infections was observed in the Phase 3 bimekizumab total group in Pool S3 (EAIR: 104.7/100 participant-years) when compared with the bimekizumab total group in Pool S1 (EAIR: 132.2/100 participant-years).

By PT, the most frequently reported infections in the Phase 3 bimekizumab total group in Pool S3 were corona virus infection (19.1%), oral candidiasis (14.0%), and nasopharyngitis (11.2%).

Most infections in the Phase 3 bimekizumab total group in Pool S3 were nonserious, mild or moderate in intensity, and did not lead to study discontinuation.

Infections predefined to be of particular interest for bimekizumab were serious infections, opportunistic (including TB) infections, and fungal infections.

Serious Infections:

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of serious infections was low overall in the bimekizumab total group (0.1%). One study participant in the bimekizumab 320mg Q2W group reported a serious infection of cellulitis which was severe in intensity, did not lead to study discontinuation, was not considered drug related by the investigator. There were no reports of serious infection in the placebo group.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of serious infections was low overall in the Phase 3 bimekizumab total group (2.1%; EAIR: 1.7/100 participant-years). Serious infections reported by >1 study participant by HLT (followed by PTs) in the Phase 3 bimekizumab total group were:

-Abdominal and gastrointestinal infections in 4 study participants: appendicitis (0.1%), diverticulitis (0.1%), gastroenteritis (0.1%), and peritonitis (0.1%)

-Bacterial infections in 4 subjects: cellulitis (0.3%) and periorbital cellulitis (0.1%)

-Viral infections NEC in 3 subjects: corona virus infection (0.2%) and gastroenteritis viral (0.1%)

-Candida infections in 2 subjects: genital candidiasis (0.1%) and oropharyngeal candidiasis (0.1%)

-Female reproductive tract infections in 2 subjects: bartholinitis (0.1%) and vulval abscess (0.1%)

-Infections NEC in 2 subjects: groin infection (0.1%) and wound infection (0.1%)

Of the 21 study participants who reported a total of 24 serious infections in the Phase 3 bimekizumab total group in Pool S3: fifteen study participants had serious infection TEAEs that were reported as severe in intensity; five study participants discontinued due to a serious infection TEAE (groin infection, periorbital cellulitis, wound infection, central nervous system infection, and rash pustular); and four study participants had drug-related serious infection TEAEs.

One additional serious infection was reported during the Phase 2 study (HS0001); this serious infection was an event of empyema that was severe in intensity, did not lead to study discontinuation, was not considered drug related, and has resolved.

During the Overall Period in the treated population, the incidences of serious infection TEAEs were low in the bimekizumab total group (2.2%) and similar in the bimekizumab 320mg Q4W/Q4W (1.4%) and bimekizumab 320mg Q2W/Q2W (3.5%) groups.

Opportunistic Infections:

Pool S1:

In Pool S1, during the Initial Treatment Period, 3 study participants (0.3%) in the bimekizumab total group reported opportunistic infections. Two study participants (1 study participant each in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups) reported localised opportunistic infections of oesophageal candidiasis, and 1 study participant in the bimekizumab 320mg Q4W group reported a localised opportunistic infection of oropharyngeal candidiasis; all of these opportunistic infections were resolved at the time of the data cut. No study participants in the placebo group reported opportunistic infections.

Pool S3:

The opportunistic infections seen in pool S3, were localised mucocutaneous fungal infections. In Pool S3, the incidence of any opportunistic infection in the combined Initial, Maintenance, and OLE Treatment Period in the Phase 3 bimekizumab total group was 12 study participants [1.2%]; EAIR: 0.9/100 participant-years).

Opportunistic infections reported in >1 study participant in the Phase 3 bimekizumab total group were oropharyngeal candidiasis (6 study participants [0.6%]) and oesophageal candidiasis (2 study participants [0.2%]). All other opportunistic infections were reported by 1 study participant.

In the Phase 3 bimekizumab total group in Pool S3, 2 opportunistic infection events were serious. These are discussed as part of the 'Fungal Infection' sub-section below.

All other opportunistic infections were nonserious, mild or moderate in intensity, and did not lead to study discontinuation or withdrawal of study medication. All of the opportunistic infections resolved.

No additional opportunistic infections were reported during the Phase 2 study (HS0001).

No study participant developed active TB in Pool S3.

Overall period:

During the Overall Period in the treated population, the incidences of opportunistic infections were low and similar in the bimekizumab 320mg Q4W/Q4W group (2.1%) and the bimekizumab 320mg Q2W/Q2W group (0.7%).

Fungal infection:

Pool S1:

The incidence of any fungal infection was higher in the bimekizumab total group (12.8%) compared with the placebo group (0.7%).

Oral candidiasis was the most frequently reported PT in the bimekizumab total group (5.6%), followed by vulvovaginal candidiasis (2.0%) and vulvovaginal mycotic infection (1.7%). These events were not reported in the placebo group. All other PTs were reported in <1% of study participants in either the bimekizumab total or the placebo group. When comparing the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W groups, of the most frequently reported fungal infections by PT, the incidence of oral candidiasis was slightly lower in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (2.5% vs 7.1%, respectively), and the incidence of vulvovaginal candidiasis was slightly higher in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (3.9% vs 1.0%, respectively).

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of any fungal infection in the Phase 3 bimekizumab total group was 29.0% (EAIR: 28.6/100 participant-years).

In the Phase 3 bimekizumab total group, fungal infections were reported in the HLTs of candida infections (19.1%), fungal infections NEC (9.7%), tinea infections (4.3%), and coccidioides infections (0.1%). By PT, oral candidiasis (14.0%), vulvovaginal mycotic infection (3.7%), vulvovaginal candidiasis (3.6%), fungal skin infection (3.1%), skin candida (2.4%), oral fungal infection (2.1%), and tinea pedis (2.5%) were reported with an incidence ≥2% in the Phase 3 bimekizumab total group. The incidence of any fungal infection was slightly lower in the Phase 3 bimekizumab 320mg Q4W group (20.8%; EAIR: 28.9/100 participant-years) compared with the Phase 3 bimekizumab 320mg Q2W group (23.1%; EAIR: 31.5/100 participant-years). This difference was mainly driven by a slightly lower incidence of the PT of oral candidiasis in the Phase 3 bimekizumab 320mg Q4W group (8.9%) compared with the Phase 3 bimekizumab 320mg Q2W group (12.4%).

Table 51. Incidence of fungal infections per 100 participant-years with an incidence of ⩾2% by PT in any treatment group during the combined Initial, Maintenance, and OLE Treatment Period (Pool S3)

MedDRA v19.0 High Level Term Preferred Term	Phase 3 BKZ 320mg Q4W N=650 100 participant-yrs=5.44 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 320mg Q2W N=823 100 participant-yrs=7.29 n (%) [#] EAIR (95% CI)	Phase 3 BKZ Total N=995 100 participant-yrs=12.72 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ Total N=1041 100 participant-yrs=12.97 n (%) [#] EAIR (95% CI)
Any fungal infection	135 (20.8) [203] 28.9 (24.3, 34.3)	190 (23.1) [313] 31.5 (27.2, 36.3)	289 (29.0) [516] 28.6 (25.4, 32.0)	293 (28.1) [524] 28.3 (25.2, 31.7)
Candida infections	91 (14.0) [129] 18.6 (14.9, 22.8)	125 (15.2) [192] 19.1 (15.9, 22.8)	190 (19.1) [321] 17.2 (14.8, 19.8)	193 (18.5) [328] 17.1 (14.8, 19.7)
Oral candidiasis	58 (8.9) [81] 11.3 (8.6, 14.6)	102 (12.4) [148] 15.3 (12.4, 18.5)	139 (14.0) [229] 12.1 (10.2, 14.3)	142 (13.6) [233] 12.1 (10.2, 14.3)
Vulvovaginal candidiasis	21 (3.2) [23] 4.0 (2.5, 6.1)	16 (1.9) [20] 2.2 (1.3, 3.6)	36 (3.6) [43] 2.9 (2.0, 4.0)	37 (3.6) [46] 2.9 (2.1, 4.0)
Skin candida	12 (1.8) [13] 2.2 (1.1, 3.9)	12 (1.5) [16] 1.7 (0.9, 2.9)	24 (2.4) [29] 1.9 (1.2, 2.8)	24 (2.3) [29] 1.9 (1.2, 2.8)
Fungal infections NEC	42 (6.5) [60] 8.0 (5.8, 10.9)	60 (7.3) [83] 8.7 (6.7, 11.2)	97 (9.7) [143] 8.2 (6.6, 9.9)	98 (9.4) [144] 8.1 (6.6, 9.8)
Vulvovaginal mycotic infection	17 (2.6) [23] 3.2 (1.9, 5.1)	22 (2.7) [26] 3.1 (1.9, 4.7)	37 (3.7) [49] 3.0 (2.1, 4.1)	38 (3.7) [50] 3.0 (2.1, 4.1)
Fungal skin infection	16 (2.5) [18] 3.0 (1.7, 4.8)	17 (2.1) [18] 2.4 (1.4, 3.8)	31 (3.1) [36] 2.5 (1.7, 3.5)	31 (3.0) [36] 2.4 (1.7, 3.5)
Oral fungal infection	5 (0.8) [9] 0.9 (0.3, 2.2)	16 (1.9) [22] 2.2 (1.3, 3.6)	21 (2.1) [31] 1.7 (1.0, 2.6)	21 (2.0) [31] 1.6 (1.0, 2.5)
Tinea infections	13 (2.0) [14] 2.4 (1.3, 4.1)	31 (3.8) [37] 4.4 (3.0, 6.2)	43 (4.3) [51] 3.5 (2.5, 4.7)	43 (4.1) [51] 3.4 (2.5, 4.6)
Tinea pedis	8 (1.2) [8] 1.5 (0.6, 2.9)	17 (2.1) [18] 2.4 (1.4, 3.8)	25 (2.5) [26] 2.0 (1.3, 3.0)	25 (2.4) [26] 2.0 (1.3, 2.9)

Two study participants reported serious fungal infections.

In HS0003, a participant with concurrent psoriasis experienced multiple SAEs of genital candidiasis, intertrigo, and skin *Candida* (between toes left feet) from 282 to 298 days after the first and 29 to 45 days after the most recent bimekizumab injections. He was hospitalised for genital candidiasis (second event) and intertrigo, a swab culture was positive for *Streptococcus dysgalactiae* subspecies (ssp) *equisimilis* and he received treatment with clindamycin and metamizole. Per the Investigator, the area involving candidiasis did not overlap with the psoriasis (small plaques on lower leg).

Bimekizumab was withdrawn due to the genital candidiasis (first and second events), intertrigo, and skin *Candida* (second event). The genital candidiasis (second event) and intertrigo resolved 19 days after onsets and skin *Candida* (second event) resolved on 31 days after onset. The genital candidiasis (first event) was reported as not resolved at the time of this report. The study participant completed the study but did not roll into the open-label extension study, HS0005. All events except for intertrigo were considered related by the Investigator. Based on mechanism of action of the study drug and clinical data to date, the Sponsor deems the events of genital candidiasis and skin *Candida* (second event) as probably related and intertrigo as unlikely related to bimekizumab.

A study participant experienced an SAE of moderate oropharyngeal candidiasis 259 days after the first and 7 days after the most recent bimekizumab injections. Oral candidiasis had become severe and affected her esophagus leading to dysphonia and odynodysphagia. A buccal swab was positive for *Candida dubliniensis* (no other species of *Candida* were isolated); She received treatment for the event. She withdrew consent and discontinued the study (consent withdrawn, not due to an adverse event). The

event resolved 24 days after onset. The event was considered related by the Investigator. Based on mechanism of action of the study drug and clinical data to date, the Sponsor deems the event as probably related to bimekizumab.

Overall period:

During the Overall Period in the treated population, fungal infection TEAEs were reported in 22.7% of study participants in the bimekizumab total group. The incidence of fungal infection TEAEs was similar in the bimekizumab 320mg Q4W/Q4W group (24.5%) compared with the bimekizumab 320mg Q2W/Q2W group (23.4%).

In the bimekizumab total group, the most common fungal infection TEAEs were oral candidiasis (9.5%), fungal skin infection (3.6%), and vulvovaginal mycotic infection (2.8%).

In the bimekizumab 320mg Q4W/Q4W group, the most common fungal infection TEAEs were oral candidiasis (9.1%), vulvovaginal mycotic infection (4.2%), and fungal skin infection (2.8%).

In the bimekizumab 320mg Q2W/Q2W group, the most common fungal infection TEAEs were oral candidiasis (10.6%), vulvovaginal candidiasis (3.5%), and fungal skin infection (3.5%).

No systemic fungal infections were reported during the Overall Period.

Vulvovaginal candidiasis:

According to the MAH, the imbalance in the incidence of TEAEs of vulvovaginal mycotic infection and vulvovaginal candidiasis in Pool S1 may be due to the following baseline characteristics that could predispose study participants in the bimekizumab group more than the placebo group; these include a higher number of female study participants, a higher proportion of study participants with a BMI >30kg/m2, and more frequent use of concomitant systemic hormonal contraceptives in the bimekizumab total group.

Of the 17 bimekizumab-treated study participants with vulvovaginal candidiasis TEAEs and the 15 bimekizumab-treated study participants with vulvovaginal mycotic infection TEAEs in Pool S1, all events were nonserious, mild or moderate in intensity, and managed with standard antifungal treatment; only 1 vulvovaginal candidiasis TEAE led to study discontinuation. Of these 32 study participants with vulvovaginal candidiasis and vulvovaginal mycotic infection TEAEs, 13 study participants reported use of antibiotics (4 study participants at Baseline and 9 study participants during the Initial Treatment Period), and for 3 events concomitantly used antibiotics were reported as co-suspect. In 12 study participants, the events were not considered drug related (as determined by the Investigator) and had no mention of possible etiology.

No increases in the EAIRs of vulvovaginal candidiasis or vulvovaginal mycotic infection were seen with longer exposure in Pool S3 (EAIRs for TEAEs of vulvovaginal candidiasis and vulvovaginal mycotic infection were 6.5/100 participant-years and 5.8/100 participant-years in the bimekizumab total group in Pool S1, respectively, and 2.9/100 participant-years and 3.0/100 participant-years in the Phase 3 bimekizumab total group in Pool S3, respectively).

Major adverse cardiovascular events (MACE):

Pool S1:

In Pool S1, during the Initial Treatment Period, no adjudicated MACE was reported in the bimekizumab total group or the placebo group.

In Pool S1, during the Initial Treatment Period, the incidence of any extended MACE in the bimekizumab total group was 0.1% (1 study participant who reported 2 TEAEs: cardiac failure and cardiac failure acute; this study participant also later experienced an event adjudicated as MACE during the Maintenance

Treatment Period). This fatal event is discussed in the 'Deaths' section of this report. No extended MACE was reported in the placebo group.

Pool S3:

Adjudicated MACE were reported for 4 study participants in the Phase 3 bimekizumab total group (0.4%; EAIR: 0.3/100 participant-years) and included PTs of cardiac failure congestive, acute coronary syndrome, cerebral infarction, and ruptured cerebral aneurysm (0.1% each). Treatment-emergent adverse events adjudicated as MACE included cardiac failure congestive, acute coronary syndrome, cerebral infarction, and ruptured cerebral aneurysm (0.1%; EAIR: 0.1/100 participant years each). The adjudicated MACE occurred in study participants with a history of atherosclerosis (e.g., coronary artery disease) and/or multiple CV risk factors (e.g., hypertension, hyperlipidemia, significant smoking history, and high BMI).

Except for 1 case of fatal cardiac failure congestive, study medication was resumed following resolution of the MACE. Six extended MACE were reported for 4 study participants in the Phase 3 bimekizumab total group (0.4%; EAIR: 0.4/100 participant-years) and included the adjudicated MACE described above plus cardiac failure and cardiac failure acute TEAEs that occurred during the ITP. Thirty-six CV-related TEAEs were adjudicated for 30 study participants in the Phase 3 bimekizumab total group (3.0%; EAIR: 2.4/100 participant-years). No particular trend was observed, and 17 of the 36 events were adjudicated as non-cardiovascular. The majority of the events were resolved at the time of the data cut.

During the Overall Period in the safety set, mean and median changes from Baseline for ECG results were generally small and not considered to be clinically meaningful.

Suicidal ideation and behaviour:

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of adjudicated SIB was 0,2% in bimekizumab total group (2 study participants [0.2%]; PTs: psychiatric evaluation abnormal and suicidal ideation), and no study participants in the placebo group reported TEAEs that were adjudicated as SIB. Both of these adjudicated SIB events were classified as suicidal ideation.

In addition to the safety data submitted originally, 1 additional TEAEs was adjudicated as SIB (suicidal ideation) in Pool S1 after the clinical cut-off date (0.3% in the bimekizumab total group).

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of adjudicated SIB in the Phase 3 bimekizumab total group was 0.7% (EAIR:0.6/100 participant-years).

7 study participants in the Phase 3 bimekizumab total group had 8 events adjudicated as SIB. There were no events of completed suicide. There were 2 events adjudicated with the event type suicide attempt (0.2%; EAIR: 0.2/100 participant-years) and 7 events adjudicated with the event type suicidal ideation (0.7%; EAIR: 0.6/100 participant-years).

Of the 7 study participants who reported 8 events adjudicated as SIB:

- Five study participants reported serious SIB events. Three of these events were reported as serious due to hospitalisation and 2 events were reported as life-threatening. Action taken with bimekizumab was drug withdrawn in 2 cases, not applicable in 2 cases, and dose not changed in 1 case. All serious SIB events resolved.
- Six study participants reported 7 severe SIB events.
- Four study participants discontinued the study due to SIB events.

- Two study participants reported SIB events that were considered drug related (as assessed by the Investigator).
- Six SIB events resolved, 1 event was not resolved, and 1 event had an unknown outcome.

In addition to the safety data submitted originally, 5 additional TEAEs were adjudicated after the clinical cut-off date (EAIR 0.94/100 participant-years). There were no additional completed suicide or events adjudicated as suicide attempt.

IBD:

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of adjudicated definite/probable IBD was 0.5% in the bimekizumab total group and no adjudicated definite/probable IBD was reported in the placebo group. Overall, in the bimekizumab total group, 10 study participants (1.2%) had 13 events adjudicated as possible IBD; no study participants had events adjudicated as possible IBD in the placebo group.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, 8 study participants in the Phase 3 bimekizumab total group (0.8%) had 16 TEAEs adjudicated as definite/probable IBD, which included 7 study participants (0.7%) with 12 events of definite IBD and 2 study participants (0.2%) with 4 events of probable IBD (1 study participant had TEAEs adjudicated as both definite and probable IBD).

Eight study participants in the Phase 3 bimekizumab total group had a documented history of IBD. One TEAE adjudicated as definite or probable IBD was reported in a study participant with a history of IBD.

No increased incidence rate of definite/probable IBD events was observed in the Phase 3 bimekizumab total group in Pool S3 (EAIR: 0.6/100 participant-years) when compared with the bimekizumab total group in Pool S1 (EAIR: 1.5/100 participant-years).

Overall, of the 8 study participants who had definite or probable IBD TEAEs in the Phase 3 bimekizumab total group in Pool S3, 3 study participants had serious IBD events, 2 study participants had severe IBD TEAEs, 4 study participants discontinued due to IBD TEAEs, and 5 study participants had drug-related IBD TEAEs. The majority of definite or probable IBD TEAEs (62.5%) were reported as resolved.

Malignancy

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of malignancy TEAEs during the Initial Treatment Period was low in the bimekizumab total group (0.1%), and no study participant reported a malignancy TEAE while receiving placebo. One study participant in the bimekizumab 320mg Q2W group experienced a TEAE of breast cancer that was serious, severe, led to study discontinuation, was not considered drug related (as assessed by the Investigator), and was not resolved.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Periods, the incidence of malignancy TEAEs was 0.9%; EAIR: 0.7/100 participant-years in the Phase 3 bimekizumab total group. Excluding non-melanomic skin cancers, the incidence rate of malignancies was 0.7%; EAIR: 0.6/100 participant-years in the Phase 3 bimekizumab total group. By PT, all malignancy TEAEs were reported by 1 study participant each (0.1%).

In the Phase 3 bimekizumab total group in Pool S3, during the combined Initial, Maintenance, and OLE Treatment Periods, a total of 9 malignancy TEAEs were reported. The TEAEs of breast cancer, clear cell

renal cell carcinoma, papillary thyroid cancer, and Hodgkin's disease were serious, severe, and led to study discontinuation; the TEAE of intraductal proliferative breast lesion was serious, severe, and did not lead to study discontinuation; the TEAE of adrenal gland cancer was severe and led to study discontinuation (seriousness was not reported); the TEAE of squamous cell carcinoma of the tongue was serious, not severe, and did not lead to study discontinuation; and the TEAEs of basal cell carcinoma and keratoacanthoma were nonserious, mild and moderate in intensity, respectively, and did not lead to study discontinuation. One of the malignancies (squamous cell carcinoma of the tongue) was considered drug related (as assessed by the Investigator), and no malignancy had a fatal outcome.

Three of the malignancies were reported as resolved and 6 were reported as not resolved.

One malignancy was considered related to the study treatment by the investigator. The event of squamous cell carcinoma of tongue occurred 400 days and 63 days after the first bimekizumab injections in HS0003 and HS0005, respectively. This occurred in a 51-year-old subject with a known smoking history. The onset of the event was 34 days after last dose in the study following withdrawal due to seborrheic dermatitis event and resolved 150 days after onset. Based on the mechanism of action of study drug, clinical data to date and past history of prolonged smoking (cigarettes and cigars), the Sponsor considers a contributory role for bimekizumab as unlikely for this event.

Hypersensitivity

Pool S1:

In Pool S1, during the Initial Treatment Period, hypersensitivity reactions were reported at a higher incidence in the bimekizumab total group (10.1%) compared with the placebo group (3.4%).

The highest incidences of hypersensitivity reactions were reported in the SOC of Skin and subcutaneous tissue disorders (8.7% in the bimekizumab total group vs 3.4% in the placebo group), mainly from the HLTs Dermatitis and eczema (5.8% in the bimekizumab total group and 2.7% in the placebo group) and Urticarias (1.2% in the bimekizumab total group and 0% in the placebo group). The most frequently reported hypersensitivity reaction TEAEs by PT in the SOC of Skin and subcutaneous tissue disorders were eczema (2.2% in the bimekizumab total group and 1.4% in the placebo group), dermatitis contact (1.9% in the bimekizumab total group and 0% in the placebo group), and urticaria (1.0% the bimekizumab total group and 0% in the placebo group). The majority of hypersensitivity reactions (77.8%) were reported as resolved.

The incidence of any hypersensitivity reaction was slightly lower in the bimekizumab 320mg Q4W group (8.1%) compared with the bimekizumab 320mg Q2W group (11.1%).

Pool S3

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Periods, the incidence of hypersensitivity reactions in the Phase 3 bimekizumab total group was 23.7% (EAIR: 21.9/100 participant years).

The majority of hypersensitivity reactions in the Phase 3 bimekizumab total group were reported in the SOC of Skin and subcutaneous tissue disorders (21.4%); mainly from the HLT Dermatitis and eczema (16.1%). The most frequently reported hypersensitivity reactions by PT were eczema (7.6%), dermatitis contact (4.8%), and dermatitis (2.3 %). The following additional hypersensitivity reactions by PT were reported in ≥5 study participants in the Phase 3 bimekizumab total group: urticaria 2.0%), dermatitis atopic (1.7%), rash (1.5%), eczema nummular (1.2%), dermatitis psoriasiform (1.2%), rhinitis allergic (0.9%), and conjunctivitis allergic (0.8%).

No increased incidence rate of hypersensitivity reactions was observed in the Phase◦3 bimekizumab total group in Pool S3 (EAIR: 21.9/100 participant-years) when compared with the bimekizumab total group in Pool S1 (EAIR: 34.9/100 participant-years).

The majority of hypersensitivity reactions in the Phase 3 bimekizumab total group in Pool S3 were non-serious, mild or moderate in intensity, and did not lead to study discontinuation. Of the 236 study participants in the Phase 3 bimekizumab total group who had hypersensitivity reaction TEAEs in Pool S3:

- One study participant had a serious hypersensitivity reaction. This serious event of rash pustular was moderate in intensity, considered drug related (as assessed by the Investigator), led to study discontinuation, and was resolving.
- One study participant had a severe hypersensitivity reaction.
- Four study participants discontinued due to a hypersensitivity reaction (rash generalised, eczema nummular, rash pustular, and eczema).
- Eighty-six study participants had a hypersensitivity reaction considered drug related.
- The majority of hypersensitivity reactions were reported as resolved (71.0%) or resolving (7.8%).

Injection site reactions:

In Pool S1, during the Initial Treatment Period, all the administration or injection site reactions were identified within the Injection site reactions HLT. The incidence of Injection site reactions was higher in the bimekizumab total group (5.8%) compared with the placebo group (1.4%). By PT, the most frequently reported administration or injection site reaction TEAEs in the bimekizumab total group were injection site pain (2.0%), injection site reaction (1.7%), and injection site erythema (0.9%).

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of any administration or injection site reactions in the Phase 3 bimekizumab total group was 7.3% (EAIR: 6.1/100 participant years).

In the Phase 3 bimekizumab total group, administration or injection site reactions were most frequently reported in the Injection site reactions HLT (7.0%). By PT, the most frequently reported administration or injection site reaction TEAEs in the Phase 3 bimekizumab total group were injection site reaction (2.6%), injection site pain (2.2%), and injection site erythema (1.2%).

The incidence of any administration or injection site reactions was slightly lower in the Phase 3 bimekizumab 320mg Q4W group (3.8%; EAIR: 4.7/100 participant-years) compared with the Phase 3 bimekizumab 320mg Q2W group (6.3%; EAIR: 7.5/100 participant-years).

In the Phase 3 bimekizumab total group, all administration or injections site reactions were nonserious and mild or moderate in intensity. One study participant discontinued due to a mild TEAE of injection site erythema, which was considered drug related (as assessed by the Investigator) and resolved; no other injection site reaction TEAEs led to study discontinuation. The majority of injection site reactions were considered drug related (as assessed by the Investigator) and were resolved.

Seven additional study participants reported 11 injection site reactions during the Phase 2 study (HS0001); these injection site reactions were events of injection site pain (3 events in 3 study participants), injection site reaction (4 events in 3 study participants), injection site erythema (2 events in 1 study participant), and injection site pruritus (2 events in 2 study participants). None of these injection site reactions were serious, severe, or led to study discontinuation. The majority of these events were considered drug related (as assessed by the Investigator) and all were resolved.

ADAb

An ISI Addendum was included to provide new information on the bimekizumab immunogenicity profile in the HS indication.

The exposure-adjusted incidence rate (EAIR) of TEAEs in study participants on or after becoming ADAb positive (367.24/100 participant-years) was lower than in study participants prior to becoming ADAb positive (456.85/100 participant-years) and higher than in study participants who were always ADAb negative (286.75/100 participant-years).

Laboratory findings

Haematology:

Pool S1:

In Pool S1, during the Initial Treatment Period, the incidence of TEMA hematology values was low and the same in the bimekizumab total and placebo groups (0.7%) (ISS Table 52). The most frequently reported TEMA hematology value in the bimekizumab total group was hemoglobin low (<80g/L) (0.4%). Markedly abnormal findings:

Table 52. Markedly abnormal hematology data during the ITP (Pool S1)

	Placebo N=146 n/Nsub (%)	BKZ 320mg Q4W N=285 n/Nsub (%)	BKZ 320mg Q2W N=576 n/Nsub (%)	BKZ Total N=861 n/Nsub (%)
Any TEMA hematology laboratory value	1/144 (0.7)	2/282 (0.7)	4/572 (0.7)	6/854 (0.7)
Hemoglobin low (<80g/L)	0/144	1/282 (0.4)	2/572 (0.3)	3/854 (0.4)
Hemoglobin high (>40g/L above ULN)	0/144	0/282	0/572	0/854
Lymphocytes low (<0.5x10^9/L)	0/144	1/282 (0.4)	0/572	1/854 (0.1)
Lymphocytes high (>20x10^9/L)	0/144	0/282	0/572	0/854
Neutrophils low (<1x10^9/L)	1/144 (0.7)	0/282	1/572 (0.2)	1/854 (0.1)
Platelets low (<50x10^9/L)	0/144	0/282	1/572 (0.2)	1/854 (0.1)
WBC count low (<2.0x10^9/L)	0/144	0/282	0/572	0/854
WBC count high (>100x10^9/L)	0/144	0/282	0/572	0/854

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Periods, the incidence of TEMA hematology values was low in the Phase 3 bimekizumab total group (1.9%). The most frequently reported TEMA hematology values in the Phase 3 bimekizumab total group were neutrophils low (<1x109/L), lymphocytes low (<0.5x109/L), and hemoglobin low. None of the CTCAE Grade 3 or Grade 4 neutrophil count values were associated with a serious infection.

Table 53. Markedly abnormal hematology data during the combined Initial, Maintenance, and OLE Treatment Periods (Pool S3)

	Phase 3 BKZ 320mg Q4W N=650 n/Nsub (%)	Phase 3 BKZ 320mg Q2W N=823 n/Nsub (%)	Phase 3 BKZ Total N=995 Nsub (%)
Any TEMA hematology laboratory value	13/642 (2.0)	8/815 (1.0)	19/988 (1.9)
Hemoglobin low (<8.0g/dL)	3/642 (0.5)	3/815 (0.4)	5/988 (0.5)
Hemoglobin high (>40 above ULN)	0/642	0/815	0/988
Lymphocytes low (<0.5x10^9/L)	5/642 (0.8)	1/815 (0.1)	6/988 (0.6)
Lymphocytes high (>20x10^9/L)	0/642	0/815	0/988
Neutrophils low (<1x10^9/L)	5/642 (0.8)	3/815 (0.4)	8/988 (0.8)
Platelets low (<50x10^9/L)	1/642 (0.2)	1/814 (0.1)	1/988 (0.1)
WBC count low (<2.0x10^9/L)	1/642 (0.2)	0/815	1/988 (0.1)
WBC count high (>100x10^9/L)	0/642	0/815	0/988

Neutropenia:

Pool S1:

In pool S1, during the ITP, no neutropenia TEAEs were reported in the bimekizumab total group or the placebo group.

Pool S3:

In pool S3, during the combined Initial, Maintenance, and OLE Treatment Periods, the incidence of neutropenia TEAEs was low in the Phase 3 bimekizumab total group (2 study participants [0.2%]; EAIR: 0.2/100 participant-years). Both of the neutropenia TEAEs (neutropenia and neutrophil count decreased) were non-serious, mild in intensity, not considered drug related (as assessed by the Investigator), did not lead to study discontinuation or withdrawal of study medication, and resolved.

Biochemistry:

In Pool S1, during the Initial Treatment Period, the incidence of TEMA biochemistry laboratory values was low and similar in the bimekizumab total (4.7%) and placebo groups (4.9%). The most frequently reported TEMA biochemistry value was glucose high (3.5% each in the bimekizumab total and placebo groups). Except for glucose high, the proportion of study participants who experienced other TEMA biochemistry laboratory values in the bimekizumab total group was below 1.0%. There were no markedly abnormal elevations in total cholesterol during the Initial Treatment Period.

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of markedly abnormal biochemistry values was 9.1% in the Phase 3 bimekizumab total group and mainly driven by glucose high, reported in 44 study participants (4.5%).

All other markedly abnormal biochemistry values occurred in <1.5% of study participants. There were no markedly abnormal elevations in total cholesterol during the combined Initial, Maintenance, and OLE Treatment Period.

Vital signs:

Pool S1:

No clinically meaningful changes in mean vital signs measurements were noted across treatment groups during the Initial Treatment Period.

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period the proportion of study participants who experienced post-Baseline markedly abnormal pulse rate, systolic BP, or diastolic BP was below 4% in the Phase 3 bimekizumab total group.

Safety in special populations

Pregnancy and breastfeeding:

As of the clinical cut-off date (15 November 2022), a total of 8 maternal bimekizumab exposure pregnancies in 7 study participants were reported in the studies included in Pool S3. No safety signals emerged from the very limited number of pregnancies reported throughout the program.

No clinical data on lactation are available since all study participants who became pregnant were withdrawn from the study as per predefined withdrawal criteria specified in the protocols.

Age:

There were only 2 study participants between 75 to <85 years of age and no study participants ≥85 years of age therefore subgroup analyses by age were only performed in the following age categories: <40 years of age, between 40 to <65 years of age, and ≥65 years of age. In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, discontinuation rates in the Phase 2/3 bimekizumab total group across age categories were generally similar for study participants in the <40 years of age, 40 to <65 years of age, and ≥65 years of age groups (34.0%, 36.5%, and 27.8%, respectively). The primary reason for discontinuation in study participants <40 years of age, 40 to <65 years of age, and ≥65 years of age was consent withdrawn (16.5%, 13.1%, and 16.7%, respectively), followed by AE (5.9%, 12.3%, and 11.1%, respectively). The incidence of discontinuation due to AE was lowest in study participants in the <40 years of age group compared with study participants in the 40 to <65 years of age and ≥65 years of age groups.

In pool S3 Phase 2/3 bimekizumab total group, TEAE analyses by age subgroups showed a higher EAIR in the older (≥65 years) age group (374.4/100 participant-years) compared with the <40 years (247.0/100 participant-years) and 40 to <65 years (289.4/100 participant-years) age groups.

Body weight:Pool S1:

In Pool S1, during the Initial Treatment Period, within the bimekizumab total group, TEAEs were reported at a lower incidence rate when accounting for exposure in study participants with the lower baseline body weights of <70 kg and ≥70 to <95 kg (EAIR: 331.5/100 participant-years and 326.0/100 participant-years, respectively) compared with study participants with heavier baseline body weights of ≥95 to <120 kg and ≥120 kg (EAIRs: 425.4/100 participant-years and 438.9/100 participant-years, respectively). Similarly, within the placebo group, TEAEs were reported at a lower incidence rate in study participants with lower baseline body weights of <70kg (EAIR: 387.0/100 participant-years) and ≥70 to <95 kg (EAIR: 272.9/100 participant-years) compared with study participants with heavier baseline body weights of ≥95 to <120 kg (EAIR: 465.8/100 participant-years) and ≥120 kg (EAIR: 402.0/100 participant-years).

Pool S3:

No meaningful differences were noted across the Baseline weight groups for TEAEs leading to discontinuation (range: 5.6% to 9.7%) or TEAEs considered drug related (as assessed by the Investigator) (range: 47.2% to 50.6%). There was a slightly lower incidence of serious and severe TEAEs in study participants with a Baseline weight of <70 kg (5.6% and 6.5%, respectively) compared with study participants with a Baseline weight of ≥70 to <95kg (9.2% and 11.4%, respectively), ≥95 to <120 kg (7.9% and 9.7%, respectively), and ≥120kg (11.7% and 11.7%, respectively). The 2 TEAEs leading to death occurred in study participants with a Baseline weight of ≥70 to <95 kg.

In Pool S3, the incidence of any TEAEs in the Phase 2/3 bimekizumab total group when accounting for exposure was generally similar across the baseline weight groups of <70kg, ≥70 to <95kg, ≥95 to <120kg, and ≥120kg (261.0/100 participant-years, 236.0/100 participant-years, 297.8/100 participant-years, and 272.9/100 participant-years).

Race:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, discontinuation rates in the Phase 2/3 bimekizumab total group were lowest in Asian (17.1%), followed by White (34.7%), Black (38.8%), and Other (43.8%) study participants. The primary reason for discontinuation across these periods for Asian, White, Black, and Other study participants in the Phase 2/3 bimekizumab total group was consent withdrawn (4.9%, 15.6%, 13.8%, and 20.8%, respectively), followed by AE (4.9%, 8.3%, 10.3%, and 6.3%, respectively).

Pool S1:

In Pool S1, during the Initial Treatment Period, within the bimekizumab total group, TEAEs when adjusted for exposure were reported at the lowest incidence in Asian study participants (EAIR: 287.2/100 participant-years), followed by White study participants (EAIR: 353.0/100 participant-years), Black study participants (EAIR: 541.7/100 participant-years), and Other study participants (EAIR: 591.5/100 participant-years).

Within the placebo group, TEAEs were reported at the lowest incidence in White study participants (EAIR: 310.2/100 participant-years), followed by Black study participants (EAIR: 507.3/100 participant-years), Other study participants (EAIR: 668.1/100 participant-years, respectively), and Asian study participants (EAIR: 712.2/100 participant-years).

Pool S3:

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the median study medication duration in the Phase 2/3 bimekizumab total group was highest in Asian study participants (547.0 days), followed by White, Black, and Other study participants (450.0 days, 358.5 days, and 336.0 days, respectively). As of the clinical cut-off date, study medication exposures of at least 12 months were achieved mostly by White study participants (512), followed by Black, Asian, and Other study participants (58, 35, and 21, respectively). The total time at risk was highest for White study participants (1046.3 participant-years), followed by Black, Asian, and Other study participants (131.8, 61, and 51.2 participant-years).

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of any TEAE in the Phase 2/3 bimekizumab total group when accounting for exposure was lower in White and Asian study participants (EAIRs: 253.7/100 participant-years and 241.4/100 participant-years, respectively) compared with Black and Other study participants (EAIR: 323.9/100 participant-years and 350.7/100 participant-years, respectively).

Gender:

In the Pool S3 Phase 2/3 bimekizumab total group, similar incidences of TEAEs by gender subgroup were observed in female study participants (90.4%) compared with male (88.7%) study participants. Overall, no clinically relevant imbalances beyond known gender-based differences were observed. In the HLT of Dermatitis and eczema, a higher incidence of TEAEs was noted in female participants compared with male participants (24.9% vs 19.5%, respectively).

Geographical location:

No clinically significant pattern was observed with respect to geographic region for TEAE categories, including SAEs, severe TEAEs, and TEAEs leading to discontinuation.

Baseline antibiotic use:

In Pool S1, during the Initial Treatment Period, within the bimekizumab total group, TEAEs were reported at a higher incidence rate in study participants with Baseline antibiotic use (EAIR: 563.8/100 participant-years) compared with study participants with no Baseline antibiotic use (EAIR: 362.4/100 participant-years), and a similar trend was present in the placebo group (EAIR: 557.6 participant-years vs 336.3/100 participant-years, respectively).

In Pool S3, the incidence of any TEAEs in the Phase 2/3 bimekizumab total group was lower in study participants with no Baseline antibiotic use (EAIR: 255.5/100 participant-years) compared with study participants who had Baseline antibiotic use (EAIR: 371.8/100 participant years).

- Skin and subcutaneous tissue disorders: Higher incidence with Baseline antibiotic use (EAIR: 92.0/100 participant-years) compared with no Baseline antibiotic use (EAIR: 56.8/100 participant-years).
- HLT TEAE differences (EAIR difference of ≥5.0/100 participant-years) observed in:

  Apocrine and eccrine gland disorders: EAIRs: 31.1/100 participant-years vs 22.6/100 participant-years, respectively.

  Dermatitis and eczema: EAIRs: 33.6/100 participant-years vs 20.6/100 participant-years, respectively.

Prior biologic use:

In study participants with prior biologic use for any indication, the EAIR of any TEAE was higher (326.7/100 participant-years) than in study participants with no prior biologic use (249.2/100 participant-years).

In Pool S3, the sample size in the Phase 2/3 bimekizumab total group for prior and no prior biologic use for any indication was 192 and 803 study participants.

Safety related to drug-drug interactions and other interactions

No DDI studies have been conducted with bimekizumab. Given the mode of action of bimekizumab, minimal impact is expected on the exposure of drugs metabolised by the cytochrome P450 (CYP450) system. Population PK modelling found no evidence of a significant impact for use of medications concomitantly administered with bimekizumab in rheumatologic indications (MTX, corticosteroids, or csDMARDs) on bimekizumab. This information is captured in section 4.5 of the SmPC.

Discontinuation due to adverse events

In Pool S1, during the ITP, the incidence of TEAEs leading to discontinuation was low overall, though slightly higher in the bimekizumab total group (3.6%) compared with the placebo group (0.7%).

By SOC, all TEAEs leading to discontinuation were reported in <1% of study participants in both the bimekizumab total and placebo groups. Treatment-emergent AEs leading to discontinuation were spread across SOCs with no obvious trend.

By PT, TEAEs leading to study discontinuation reported by >1 study participant in the bimekizumab total group were hidradenitis (4 study participants [0.5%] each); psychiatric evaluation abnormal (3 study participants [0.3%]); and diarrhoea, oral candidiasis and nasopharyngitis (2 study participants [0.2%] each).

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the incidence of TEAEs leading to discontinuation was 8.8% in the Phase 3 bimekizumab total group.

The EAIR of TEAEs leading to study discontinuation in the Phase 3 bimekizumab total group in Pool S3 did not increase with extended exposure (7.0/100 participant-years) compared with the bimekizumab total group in Pool S1 (12.0/100 participant-years).

Treatment-emergent AEs leading to discontinuation in the Phase 3 bimekizumab total group in Pool S3 were most frequently reported in the SOCs of Skin and subcutaneous tissue disorders (2.5%), Infections and infestations (2.0%), and Gastrointestinal disorders (1.7%).

Treatment-emergent AEs, by PT, leading to discontinuation that were reported in >1 study participant in the Phase 3 bimekizumab total group were hidradenitis (15 study participants [1.5%]); psychiatric evaluation abnormal (9 study participants [0.9%]); diarrhoea (8 study participants [0.8%]); oral candidiasis (5 study participants [0.5%]); folliculitis, depression, and psoriasis (3 study participants [0.3%] each); and colitis microscopic, Crohn's disease, nasopharyngitis, pregnancy on contraceptive, and suicidal ideation (2 study participants [0.2%] each).

Post marketing experience

Bimekizumab is currently not approved for moderate to severe HS.

Post-marketing data for the other approved indications are provided in PSURs. The cumulative the post-authorisation patient exposure outside of clinical studies to bimekizumab is estimated to be approximately 4810 patient-years.

2.5.1. Discussion on clinical safety

To support this application, the MAH performed 2 pivotal Phase 3 double-blind studies in HS (HS0003 and HS0004), one Phase 2 study (HS0001) and an ongoing Open-label Extension (OLE) study (HS0005) and safety data from these studies was pooled to perform the overall safety assessment. Upon CHMP request, the MAH has provided longer safety data up to a cut-off point of 19 May 2023. No new safety signals have been identified. The final results of the OLE study HS0005 will be submitted for assessment once they become available (see RMP).

In the HS clinical development program, 861 study participants in Pool S1 (short term safety up to 16 weeks), 995 study participants in Pool S2 (continuous dosing for participants originally randomised to bimekizumab Q2W who switched to bimekizumab Q4W, and for bimekizumab Q2W and bimekizumab Q4W perpetual groups), and 995 study participants in the more comprehensive Pool S3 (patients who

received at least one dose) were exposed to bimekizumab with total times at risk accounting for 262.3, 845.1, and 1271.8 participant-years, respectively.

The dosing interval for the HS indication (320 mg Q2W (week 0-16) then 320 mg Q4W) has been halved relative to PSO indication (320 mg Q4W (week 0-16) then 320 mg Q8W).

Patient exposure

893 patients in the BKZ total group have been exposed for at least 4 months. 291 patients have been exposed to the recommended dose regimen BKZ 320 mg Q2W/Q4W in pool S2, of which 259 (89%) had a cumulative duration of exposure of at least 4 months. 285 patients have been exposed to the more frequent dose regimen BKZ Q2W/Q2W in pool S2 of which 257 (90.2%) had at least 4 months exposure. The exposure is considered sufficient as this is a new indication for bimekizumab in HS patients in addition to already approved indications in PSO, PsA and AxSpA; as for a 90 kg individual, the median steady state concentration at a dose of 320mg Q4W was approximately 40% lower in HS compared to other indications; as the safety profile in the HS population is similar to the one in the other indications.

In pool S3, 765 patients had at least 8 months exposure, and 630 patients at least 12 months. This is considered sufficient by the CHMP. However, as the dosing interval in the HS population was halved versus that in the PSO population, long-term data in patients with HS are required to follow long-term safety and possible impact on adverse drug reactions that occur less frequently or for which an increase in the background incidence should be investigated. Long-term safety data will be provided post-approval (see RMP).

Demographics were generally well balanced; although it is noted that there is a lower number of black or African American study participants included in this study given the prevalence of HS in this population; there is no evidence, at this time, to suggest that the safety of bimekizumab is different in this population. In pool S1 and S3, there was a slightly higher proportion of female participants (56.7%) which is expected. In the general population, the prevalence of HS in women is 3 times that of men. The comorbidities observed in the bimekizumab HS study participants at baseline were consistent with those described in the literature for this population.

Treatment emergent adverse events (TEAEs)

In pool S1, rates of TEAEs were similar between placebo and treatments groups. There were slightly higher rates of TEAEs leading to discontinuation than serious TEAES in the treatment group (3.6% and 2.6%, respectively) versus the placebo group (0.7% and 0%, respectively). This was not seen in pool S3 where the incidences of serious TEAEs and TEAEs leading to discontinuation were similar. In pool S3, the incidence of serious TEAEs, TEAEs leading to discontinuation, and severe TEAEs were similar in the Phase 3 bimekizumab 320mg Q4W group (6.0%, 5.4%, and 6.9%, respectively) compared with the Phase 3 bimekizumab 320mg Q2W group (6.9%, 6.4%, and 8.3%, respectively).

There was an increase of TEAEs in pool S1 but not in pool S3 for the bimekizumab 320 mg Q2W group versus the bimekizumab 320mg Q4W group (any TEAEs: Pool S1: Q4W 58.6%, Q2W 65.8%; Pool S3: Q4W 82.2%, Q2W 81.9%).

The incidence of any TEAEs was the same for the 320 mg Q4W dosing in PSO and HS (58.6% in HS and 58.8% in PSO).

There was an increase of drug-related TEAEs in pool S1 and pool S3 for the bimekizumab 320mg Q2W group versus bimekizumab 320mg Q4W group: (Pool S1: Q4W 26.3%, Q2W 32.8%; Pool S3: Q4W 38.0%, Q2W 43.6%).

There was a slight increase in serious AEs in the HS indication versus the PSO indication for the 320 mg Q4W dosing group (2.5% in HS and 1.6% in PSO indication), but it was similar for the Q2W and Q4W dosing groups in pool S1 and pool S3: (Pool S1 Q4W 2.5%, Q2W 2.6%; Pool S3 Q4W 6.0%; Q2W 6.9%).

In Pool S3, during the combined Initial, Maintenance, and OLE Treatment Period, the most frequently reported TEAEs by PT in the Phase 3 bimekizumab total group were hidradenitis (24.1%), corona virus infection (19.1%), oral candidiasis (14.0%), and nasopharyngitis (11.2%). Excluding hidradenitis, these are in keeping with the common TEAEs seen in the trials in the already approved Bimzelx indications.

For Pool S1, the incidence of severe TEAEs was low overall in the bimekizumab total group (3.3%) and placebo group (1.4%). For Pool S3, the incidence of severe TEAEs in the Phase 3 bimekizumab total group was 10.6%. In the bimekizumab total groups in both pools, severe TEAEs were most frequently reported in the SOC of Skin and subcutaneous tissue disorders, and the most frequently reported severe TEAE by PT was hidradenitis. When adjusting for exposure, the EAIR of severe TEAEs in the Phase 3 bimekizumab total group in Pool S3 was similar (8.7/100 participant-years) compared with the bimekizumab total group in Pool S1 (10.9/100 participant-years).

Deaths

Two deaths occurred during the clinical development program for treatment of HS. The investigator does not consider either death to be related to the study drug and this is accepted.

Drug-related TEAEs

Drug-related TEAEs were reported at a lower incidence in the Phase 3 bimekizumab 320mg Q4W group compared with the Phase 3 bimekizumab 320mg Q2W group.

Lower incidences of drug-related TEAEs (as assessed by the Investigator) and TEAEs of oral candidiasis, nasopharyngitis, and corona virus infection occurred in the bimekizumab 320mg Q4W/Q4W group compared with the bimekizumab 320mg Q2W/Q2W group. There were similar incidences of serious TEAEs, severe TEAEs, and TEAEs leading to discontinuation between the dosing groups. Compared with the bimekizumab 320mg Q4W/Q4W and bimekizumab 320mg Q2W/Q2W groups in Pool S2, overall similar incidences of TEAEs were reported in the bimekizumab 320mg Q2W/bimekizumab 320mg Q4W switchers group.

AESIs

Potential Hy's Law was the only AESI defined for the HS program. No participant in the study met the criteria for Hy's Law. For most study participants with ALT or AST > 5xULN in the HS pool S3, the HAC causality assessment scoring for DILI was unlikely, 1 study participant each had at least 1 laboratory value adjudicated as probable (likelihood: 50% to 74%) or possible (likelihood: 25% to 49%). However, the observed transaminase elevations were mainly driven by the less specific AST marker, were mostly transient, with rapid normalization even with continued bimekizumab administration or shortly after bimekizumab discontinuation and did not result in clinical sequelae.

The rates and patterns of infection in the HS development program are in keeping with those seen in the earlier development program from PSA and axSpA. This information has been reflected in SmPC section 4.8.

The reported serious infection TEAEs were resolved or resolving at the cut-off point of 19 May 2023.

No active TB was reported during the study period. All opportunistic infections resolved.

In Pool S1, the incidence of any fungal infection was higher in the bimekizumab total group (12.8%) compared with the placebo group (0.7%). The fungal infections of oral candidiasis (5.6%), vulvovaginal

candidiasis (2.0%) and vulvovaginal mycotic infection (1.7%) were seen in the participants treated with bimekizumab and not in those who received placebo.

In pool S1, the incidence of oral candidiasis was lower in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (2.5% vs 7.1%, respectively), and the incidence of vulvovaginal candidiasis was slightly higher in the bimekizumab 320mg Q4W group compared with the bimekizumab 320mg Q2W group (3.9% vs 1.0%, respectively). Confounding factors like the higher number of female participants in the Q4W group could have contributed to this imbalance.

Of note in Pool S1, the fungal infections of oral candidiasis, vulvovaginal candidiasis and vulvovaginal mycotic infection were seen in the participants treated with bimekizumab and not in those who received placebo. This may be due to the larger number of female participants and rates of antibiotic use. Despite these confounding factors, it is agreed that it is considered appropriate to update the ADR table to reflect the imbalance in the PTs of vulvovaginal candidiasis and vulvovaginal mycotic infection. This has been added to section 4.8 of the SmPC.

In pool S3, the incidence of any fungal infection was slightly lower in the Phase 3 bimekizumab 320mg Q4W group (20.8%, event rate 37.3) compared with the Phase 3 bimekizumab 320mg Q2W group (23.1%, event rate 42.9). This difference was mainly driven by a lower incidence of oral candidiasis in the Phase 3 bimekizumab 320mg Q4W group (8.9%, event rate 14.9) compared with the Phase 3 bimekizumab 320mg Q2W group (12.4%, event rate 20.3).

HS is associated with an increased risk of MACE including cerebrovascular accident (CVA), myocardial infarction (MI), and cardiovascular-associated mortality. The events of MACE seen throughout the studies occurred in those with known cardiac co-morbidities. There was one fatal event of MACE which was not related to bimekizumab. Based on the data provided there does not appear to be an increased MACE risk with bimekizumab in the HS development program, when compared to the background rate observed in the study populations with a known history of CV risk factors. These safety concerns will be followed-up post-approval (see RMP).

There is a known increased risk of depression, anxiety and other psychiatric disorders in patients with HS. Protocol amendment 3 included removal of depression as a safety topic of interest. However, depression continues to be monitored as a safety parameter by the PHQ-9 and is captured via adverse event (AE) reporting during the bimekizumab clinical studies. Monitoring for the risk of suicidality and depression during the bimekizumab clinical studies, using the specific scales for depression and suicidality and the external adjudication committee for SIB events, continued.

In the HS Phase 3 studies with bimekizumab, participants with a history of suicidality were not excluded from study participation, unless they had a suicidal attempt within the last 5 years or active suicidal ideation in the last month, as these participants are generally not considered appropriate candidates for enrolment in blinded controlled studies. Psychiatric disorders were among the most frequently reported medical history conditions (24.4% in the Phase 2/3 bimekizumab total group), with depression disorders (14.6%) and anxiety symptoms (9.9%) the most frequent HLTs. Suicidal and self-injurious behavior was reported by 1.2% of study participants.

The clinical trial design excluded those at very high risk of suicidality. The data includes participants who have reported symptoms of depression or anxiety without a background history of either. Confounding factors are highlighted, including HS diagnosis and history of trauma. There was no imbalance between the placebo and bimekizumab treated patients in the incidence of psychiatric disorders TEAEs in HS study participants without documented medical history of events within the Psychiatric disorder SOC. The minor imbalances noted for the incidence of anxiety symptoms TEAEs in study participants without documented medical history of events within the anxiety symptoms HLT (0.4% vs 0.2%) and for the incidence of depressive disorders TEAEs in study participants without documented medical history of events within the

depressive disorders HLT (0.3% vs 0.2%) across indications, require further attention. Based on a cumulative review of all SI/B cases across the bimekizumab development program and from post marketing data that was provided by the MAH upon request in the latest PSUR, a causal relationship between SI/B events and bimekizumab could not be established at this point. There is thus insufficient evidence to warrant a PI update for bimekizumab regarding SI/B. Nevertheless, the MAH should continue to closely monitor this safety topic in future PSURs.

Depression was assessed using the HADS in the Phase 2 study and the PHQ-9 in Phase 3 studies. Due to differences in the methods of data collection used across the Phase 2 and Phase 3 studies, data from the Phase 2 study (HS0001) was not pooled with data from the Phase 3 studies. For the Phase 3 bimekizumab total group, 44 study participants (4.5%) had a PHQ-9 Total Score of ≥15 points at any post-Baseline Visit during the combined Initial, Maintenance, and OLE Treatment Period. Thirteen study participants (1.3%) had a PHQ-9 Total Score ≥20 at any post-Baseline Visit. Across Phase 3 studies, in general, there was no evidence of development or worsening of depression as measured by the PHQ-9 in study participants treated with bimekizumab. No safety concerns emerged from questionnaires used to monitor depression.

Patients with HS have an increased risk of developing inflammatory bowel disease (IBD). There was a slightly increased incidence of IBD in those treated with bimekizumab in this study when compared to background rates. However, the numbers are small which makes interpretation difficult. Risk differences between the bimekizumab total group and placebo group with CIs greater than and not including "0", indicating a higher risk with bimekizumab treatment, were observed for adjudicated definite or probable IBD. IBD is included as an uncommon ADR in SOC gastro-intestinal disorders in the SmPC section 4.8. Currently section 4.4 of the SmPC states that bimekizumab is not recommended in patients with inflammatory bowel disease and if a patient develops signs and symptoms of inflammatory bowel disease or experiences an exacerbation of pre-existing inflammatory bowel disease, bimekizumab should be discontinued and appropriate medical management should be initiated. This remains an appropriate warning.

One participant was considered to have a malignancy (Tongue SCC) which was considered related to bimekizumab by the investigator. Nevertheless, the sponsor was of the view that it is unlikely that this event is related to the study drug. Given the confounding factors, including a smoking history, the sponsor's position is acceptable to the CHMP.

There was an increased incidence of hypersensitivity reactions with bimekizumab compared to placebo, driven by events related to dermatitis and eczema. This was also observed in PSO Pool S1: 4.2% hypersensitivity reactions with bimekizumab compared to 0.6% with placebo, 1.9% dermatitis and eczema events with bimekizumab compared to 0% with placebo. Rates for both placebo and bimekizumab groups in patients with HS were above the ones observed in the PSO studies. There was a slightly higher incidence of hypersensitivity in the Q2W group (11.1%) versus Q4W group (8.1%) during the placebo-controlled period, while the incidence in the placebo group was 3.4%.

The incidence of injection site reactions was slightly higher with bimekizumab treatment in the patients with HS than with PSO. In pool S1 of the bimekizumab studies in the PSO indication, the incidence of injection site reactions was reported by 2.8% in the bimekizumab 320mg Q4W group and by 1.2% of study participants in the placebo group.

In Pool S1 for the HS indication, the incidence of injection site reactions was reported by 1.4% in the placebo group; a higher rate was observed in the Q4W group (4.6% in Pool S1) and an even higher rate was observed in the Q2W group (6.4% in Pool S1) versus Q4W group.

In Pool S3, the incidence of injection site reactions was slightly lower in the Phase 3 bimekizumab 320mg Q4W group (3.4%; EAIR: 4.2/100 participant-years) compared with the Phase 3 bimekizumab 320mg Q2W group (6.2%; EAIR: 7.4/100 participant-years).

The incidence of injection site reactions was similar to that previously seen in the bimekizumab development program and are already included in section 4.8 of the SmPC.

No notable clinically meaningful trends were observed in ADAb positivity and safety, as assessed by TEAE incidence relative to antibody status. SmPC section 4.8 was updated to reflect information on immunogenicity in HS.

No clinically meaningful pattern was observed in the incidence of markedly abnormal haematology values, biochemistry values or vital signs were seen in the safety data provided.

There is no clinically meaningful pattern of neutropenia observed in the phase 3 studies. Neutropenia is already included in section 4.8 of the SmPC as a known, uncommon ADR for bimekizumab.

There is limited data available for use in pregnant or breastfeeding women. Section 4.6 of the SmPC advises use of contraception while receiving bimekizumab and for at least 17 weeks after treatment and that it is preferable to avoid breastfeeding. This is appropriate given the available data and no PI update is therefore warranted by the CHMP.

The majority of participants in this study were aged under 40 which fits with the natural history of HS. The number of participants over 65 years of age was limited. Study medication exposures of at least 12 months were achieved by 10 participants in this category. TEAE analyses by age subgroups showed a higher EAIR in the older (≥65 years) age group but interpretation of this result is difficult given the low number of participants in that age group. Of note, there was no increased risk of infections (including candida infections) or skin disorders (including dermatitis and eczema) in study participants ≥65 years of age.

The incidences of TEAEs and the observed safety profile of bimekizumab in the Pool S3 Phase 2/3 bimekizumab total group was generally similar across the Baseline weight groups. There were no clinically relevant differences in the incidences of TEAEs between weight groups in the data provided. Higher incidences of certain TEAEs in the highest body weight group (≥120 kg) may be due to comorbidities in overweight study participants. There were no TEAEs with >5% difference in the lower bodyweight groups, particularly there was no difference in rates of infection or skin disorders.

The incidence of any TEAEs in the Phase 2/3 bimekizumab total group was lower in study participants with no Baseline antibiotic use (EAIR: 255.5/100 participant-years) compared with study participants who had Baseline antibiotic use (EAIR: 371.8/100 participant years) the main difference was observed in the SOC of Skin and subcutaneous tissue disorders driven by the HLTs Apocrine and eccrine gland disorders and Dermatitis and eczema. Those needing baseline antibiotics have worse or active disease which may account for the higher incidence of skins AEs in this population.

A higher incidence of TEAEs was seen in those with prior biologic use. There was a significant imbalance between those with prior biologic use and those with none which makes the data difficult to interpret. Overall, in the data presented the incidence of TEAEs was distributed across SOCs, with no obvious trend.

In Pool S3 during the combined Initial, Maintenance, and OLE Treatment Period, TEAEs leading to discontinuation in the Phase 3 bimekizumab total group were most frequently reported in the SOCs of Skin and subcutaneous tissue disorders (2.5%), Infections and infestations (2.0%), and Gastrointestinal disorders (1.7%) which is in keeping with the known safety profile of bimekizumab.

2.5.2. Conclusions on clinical safety

In conclusion, the safety profile seen in the hidradenitis suppurativa indication was generally in keeping with that of the already approved indications with the most common TEAEs being in infections and skin disorders SOC. The CHMP concluded that the safety profile of bimekizumab in treatment of adult patients with moderate to severe HS is acceptable. The OLE HS0005 study is listed as a category 3 study in the agreed RMP and will further address long-term safety data as missing information post-approval (see RMP).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The CHMP received the following PRAC Advice on the submitted Risk Management Plan:

The PRAC considered that the risk management plan version 1.12 is acceptable.

The CHMP endorsed this advice without changes.

The CHMP endorsed the Risk Management Plan version 1.12 with the following content:

Safety concerns

Summary of safety concerns	
Important identified risks	Serious infections
	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
Important potential risks	Serious hypersensitivity reactions
	Major adverse cardiovascular events
	Malignancy
Missing information	Use during pregnancy and lactation
	Long-term safety data

Pharmacovigilance plan

Study Status	**Summary of objectives**	**Safety concerns addressed**	**Milestones**	**Due dates**
Category 3 - Required additional pharmacovigilance activities				

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
PS0038: Bimekizumab real-world outcomes study Planned	The goal of this study is to evaluate any potential increase in the risk of safety outcomes of interest in bimekizumab exposed PSO, PsA, axSpA, and HS patients compared to PSO, PsA, axSpA, and HS patients exposed to other biologics (eg, antiTNF, anti-IL-23, but not antiIL17).	Serious infections Serious hypersensitivity reactions MACE Malignancy IBD	Final protocol	Draft protocol for PSO submitted on 16 Dec 2022, final CHMP opinion received on 30 Mar 2023. Protocol amendment 1 submitted 01 Sep 2023 is under review at time of this RMP internal approval. Revised protocol to be submitted within 3 months after approval of HS indication in the EU.
			Interim reports	2 standalone interim reports will be submitted in Q3 2027 and in Q3 2030 respectively.
			Study progress updates	Will be included in PSUR submissions according to EURD list.
			Final study report	31 Dec 2034
PS0036: Bimekizumab pregnancy exposure and outcome registry Planned	To monitor the safety of bimekizumab use in pregnancy.	Missing information: Use during pregnancy and lactation	Final protocol	Approved 30 Mar 2023
			Annual recruitment report	01 Jun 2024 and annually thereafter until recruitment close
			Interim feasibility assessment	End of third year from start of recruitment
			Final study report	31 Dec 2034
PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy Planned	To monitor the safety of bimekizumab use in pregnancy.	Missing information: Use during pregnancy and lactation	Final protocol	Draft protocol submitted on 25 Nov 2021, endorsed 10 Nov 2022; protocol amendment 1 submitted 31 Aug 2023 is under review at time of this RMP internal approval.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Progress report (Phase 1-monitoring of bimekizumab use during pregnancy)	31 Dec 2024 (annually until 50 bimekizumab-exposed pregnant women are identified).
			Interim report (Phase 2 – causal inference analysis)	Annually after end of Phase 1
			Final study report	31 Jun 2035
PS0014 (EudraCT Number: 2016-003427-30) A multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO Ongoing	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of interim clinical study report	15 Aug 2023
			Submission of final clinical study report	31 Dec 2024
PS0015 (EudraCT Number: 2017-003784-35) A multicenter, randomized, double-blind,	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be	Submission of interim clinical study report	31 Jan 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque PSO Ongoing		characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of final clinical study report	31 Jul 2024
PA0012 (EudraCT Number: 2018-004725-86) A multicenter, open label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active PsA. Ongoing	Assess the safety and efficacy of long-term use of bimekizumab in PsA	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of clinical study report	Estimated clinical study report date 18 Sep 2026
AS0014 (EudraCT Number: 2019-004163-47) A multicenter, open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active axSpA (radiographic and non-radiographic) Ongoing	Assess the safety and efficacy of long-term use of bimekizumab in axSpA (radiographic and non-radiographic)	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of interim clinical study report	30 Sep 2024
			Submission of clinical study report	15 Dec 2026

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
HS0005 (EudraCT Number: 2020-004179-42) An open-label, parallel group, multicenter, extension study evaluating the long-term treatment of bimekizumab in study participants with moderate to severe HS Ongoing	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of final clinical study report	08 Dec 2026

axSpa=axial spondyloarthritis; CHMP= Committee for Medicinal Products for Human Use; EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; EURD=European Union reference date; HS= hidradenitis suppurativa; IBD=inflammatory bowel disease; IL=interleukin; MACE=major adverse cardiovascular events; PsA=psoriatic arthritis; PSO=psoriasis; PSUR=periodic safety update report; Q3=third quarter; TNF=tumor necrosis factor

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		
Serious infections	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindication) Risk of infections is discussed under SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005

Safety concern	Risk minimization measures	Pharmacovigilance activities
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Important potential risks		
Serious hypersensitivity reactions	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindication) SmPC Section 4.4 (Special warnings and Precautions) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Major adverse cardiovascular events	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Malignancy	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012; AS0014; HS0005
Missing Information		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Use during pregnancy and lactation	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0036: Bimekizumab pregnancy exposure and outcomes registry PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy
Long-term safety	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0014; PS0015; PA0012; AS0014; HS0005

PhV=pharmacovigilance; PL=patient information leaflet; SmPC=summary of product characteristics

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

2.7.1. User consultation

No full user consultation with target patient groups on the package leaflet has been performed on the basis of a bridging report making reference to Bimzelx (bimekizumab). The bridging report submitted by the MAH has been found acceptable.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Hidradenitis suppurativa (HS) is a chronic, inflammatory, and recurrent skin condition characterised by painful, deep-seated, and inflamed lesions typically located in the intertriginous areas of the body (e.g., axillae, inguinal, and anogenital regions). The nodules are often inflamed, can progress to abscess (AB) formation, and may rupture to form fistulas and subsequent scarring. Thus, many patients with HS develop permanent sequelae of past inflammation that are only remediable through surgical excision of the involved skin areas. The visible manifestations of disease among patients with HS impact interpersonal relationships, self-esteem, and perception of self-image and public image, resulting in depression and embarrassment. HS can progress to become a debilitating skin disease with disfiguring

scarring; as a result, it has the highest negative impact on patients' quality of life. HS is associated with significant comorbidity burden regardless of age, sex, racial, and disease severity group, which is beyond the skin manifestations, and includes metabolic, cardiovascular (CV), endocrine, gastrointestinal, rheumatologic, and psychiatric disorders, which collectively decrease the QOL of patients among all assessed dermatological conditions. HS is estimated to affect about 1% of the adult European population, with a female to male ratio of approximately 3:1. Most patients have mild or moderate disease with the majority typically having moderate disease, though severe disease has been reported in 4 to 28 percent of patients. Risk factors for more severe disease include higher body mass index (BMI)/obesity, smoking and duration of disease.

3.1.2. Available therapies and unmet medical need

The extent of skin involvement and the presence of secondary lesions, including skin tunnels and scarring influences, as well as patient psychosocial burden, affect the approach to treatment. There have been a variety of treatment modalities used in HS, many without high quality supportive efficacy data.

Treatment modalities with strong and uniform support across international guidelines include intralesional corticosteroids, topical clindamycin, oral tetracyclines, combination clindamycin and rifampicin therapy, adalimumab, and wide local excision. Specifically, the European S1 HS guideline suggests that the disease should be treated based on its individual subjective impact and objective severity. Locally recurring lesions can be treated by classical surgery or laser techniques, whereas medical treatment either as monotherapy or in combination with radical surgery is more appropriate for widely spread lesions. Further treatment of HS depends on the extent and activity of the disease and include medical treatments, antiandrogen treatment in women, systemic retinoids, and metformin, as well as surgical treatments (e.g., radical excision, marsupialization, and deroofing), and laser treatment.

Adalimumab (Humira) and Secukinumab (Cosentyx) are approved in the EU for the treatment of moderate to severe HS in subjects in adults (and adolescents for Humira) with an inadequate response to conventional systemic HS therapy. However, considering the limited treatment armamentarium, an unmet need exists for additional systemic therapies.

3.1.3. Main clinical studies

The bimekizumab HS clinical development program consisted of 2 identically designed, adequate and well-controlled, pivotal Phase 3 studies. HS0003 and HS0004 are randomised, double-blind, placebo-controlled, multicentre studies designed to evaluate the efficacy and safety of bimekizumab study participants with moderate to severe HS. Both HS0003 and HS0004 were placebo-controlled during the 16-week double-blind periods. The eligibility criteria of HS0003 and HS0004 were identical. Participants were randomised at Baseline and stratified by Hurley Stage and antibiotic use. The study participant entry criteria are indicative of the target population and reflect the complexity of a moderate to severe HS population in terms of demographics, disease characteristics, and comorbid diseases associated with HS. They also reflected the current clinical practice of HS in terms of concomitant therapies including prior biologics, antibiotics, analgesics, and HS rescue therapies. Both studies used the same doses, dosage forms, and dosing schedules from Week 0 to Week 48.

The HS Phase 3 clinical studies evaluated the following dose regimens: bimekizumab 320mg Q2W from Weeks 0 to 48, bimekizumab 320mg Q4W from Weeks 0 to 48, bimekizumab 320mg Q2W to Week 16 followed by 320mg Q4W from Weeks 16 to 48, and placebo to Week 16 followed by bimekizumab 320mg Q2W from Weeks 16 to 48.

The primary endpoint was HiSCR50 response at Week 16. Secondary ranked endpoints at Week 16 were HiSCR75, Change from baseline in DLQI, Change from baseline in Skin Pain as assessed by worst skin pain item in HSSDD and Pain response assessed using HSSDD. For Study HS0004, the ranked secondary endpoints included an additional endpoint 'Flare by week 16' as the second ranked secondary endpoint.

3.2. Favourable effects

Statistically significant and clinically relevant differences compared to placebo were observed on the primary endpoint for both the bimekizumab 320mg Q2W and 320mg Q4W doses in HS0004 and for the bimekizumab 320mg Q2W dose in HS0003. Some variability was seen between the two studies; notably, in study HS0004 the response rate for the primary endpoint HiSCR50 was numerically higher for the Q4W regimen compared with the Q2W regimen. In pooled data, the magnitudes of the treatment effects with Q2W and Q4W were overall very similar.

The secondary endpoint of HiSCR75 at Week 16 was statistically and clinically significant for both the bimekizumab 320mg Q2W and Q4W doses in HS0004 and for the bimekizumab 320mg Q2W dose in HS0003. The secondary endpoint of change from Baseline in DLQI total score and change from Baseline in HSSDD worst skin pain score at Week 16 was statistically and clinically significant for the bimekizumab 320mg Q2W dose in HS0003.

No differentiation between the Q2W and Q4W dose regimens was observed during the maintenance treatment phase (MTP) on multiple efficacy endpoints.

Responder rates for the HiSCR50, HiSCR75, and HiSCR90 were generally maintained from Week 16 through Week 48.

Similar numerical results were achieved across both studies for the Q2W and Q4W dose regimens for lesion-, symptom-, and health-related quality of life outcomes (IHS4, HS-PGA, AN50, AN75, and AN90, HSSDD, and HSSQ) for the initial 16 weeks. Responses were maintained or further improved across these endpoints for all treatment groups through Week 48.

3.3. Uncertainties and limitations about favourable effects

Despite the marked effect of body weight on bimekizumab exposure, the PK/PD simulation data and clinical data do not support a separate posology for overweight patients. As such, the CHMP agreed that recommended posology of 320 mg Q2W followed by 320 mg Q4W after Week 16 is appropriate for all HS patients, including those with body weight >100 kg.

There are no data on impact of treatment breaks and maintenance of effect over longer term period, however this would provide important information regarding the effects of stopping treatment and on the sustainability of clinical response to bimekizumab. This will be addressed post-approval in an adequately designed clinical trial (with a randomised withdrawal design) to assess durability of effect upon withdrawal or treatment pause in HS patients responding to treatment with bimekizumab. In addition, further long-term data will be provided post-approval with the ongoing extension study HS0005.

3.4. Unfavourable effects

In pool S1 (short term safety up to 16 weeks), there were slightly higher rates of TEAEs leading to discontinuation than serious TEAEs in the treatment group (3.6% and 2.6%, respectively) versus the placebo group (0.7% and 0%, respectively). This was not seen in pool S3 (continuous dosing) where the incidence was of serious TEAEs and TEAEs leading to discontinuation were similar. In pool S3, the

incidence of serious TEAEs, TEAEs leading to discontinuation, and severe TEAEs were similar in the Phase 3 bimekizumab 320mg Q4W group when compared with the Phase 3 bimekizumab 320mg Q2W group.

There was an increase of drug-related TEAEs in pool S1 and pool S3 for the bimekizumab 320mg Q2W group versus bimekizumab 320mg Q4W group: (Pool S1: Q4W 26.3%, Q2W 32.8%; Pool S3: Q4W 38.0%, Q2W 43.6%)

Vulvovaginal mycotic infection (including vulvovaginal candidiasis) has been added as an ADR (frequency common) due to imbalance in rates between placebo and those treated with bimekizumab.

While there was no imbalance between the placebo and bimekizumab treated patients in the incidence of psychiatric disorders TEAEs in HS study participants without documented medical history of events within the Psychiatric disorder SOC, minor imbalances were noted for the incidence of anxiety symptoms TEAEs in study participants without documented medical history of events within the anxiety symptoms HLT (0.4% vs 0.2%) and for the incidence of depressive disorders TEAEs in study participants without documented medical history of events within the depressive disorders HLT (0.3% vs 0.2%) across indications. The MAH should continue to closely monitor this safety topic in future PSURs.

3.5. Uncertainties and limitations about unfavourable effects

The long-term safety profile is limited. Further long-term safety data will be provided post-approval (see RMP).

Participants with a recent history of suicidal ideation or suicide attempts in the preceding five years were excluded from the pivotal studies. The issue of a potential association between SIB and bimekizumab was reviewed and a causal relationship between SI/B events and bimekizumab could not be established at this point. The MAH agreed to follow up this issue in subsequent PSURs.

3.6. Effects Table

Effects Table for Bimekizumab in treatment of hidradenitis suppurativa (data cut-off: week 16)

Effect	Short Description	Unit	BKZ 320mg Q2W vs Placebo	BKZ 320mg Q4W vs Placebo	Uncertainties/ Strength of evidence	References (Studies)
Favourable Effects						
HiSCR50 response rates at Week 16 including logistic regression (MI using MCMC/Monotone Regression)	Proportion of participants who achieved a HiSCR50, response at Week 16 (vs placebo)	%	$HiSCR_{50}$ at Week 16 Pool E1: BKZ 320mgQ2W: 47.7% (n=580) Placebo: 28.8% (n=146)	$HiSCR_{50}$ at Week 16 Pool E1: BKZ 320mgQ4W: 47.4% (n=288) Placebo: 28.8% (n=146)	Odds Ratio BKZ 320mg Q2W vs placebo: 2.252 (95% CI: 1.514, 3.349) Odds Ratio BKZ 320mg Q4W vs placebo: 2.227 (95% CI: 1.447, 3.427)	**Pool E1:** Efficacy data during placebo-controlled periods of HS0003 and HS0004 were combined to yield efficacy of treatment effect of bimekizumab vs placebo from Baseline to Week 16 **Pool E2:** Efficacy data for the
HiSCR75 response rates at Week 16	Proportion of participants who achieved a HiSCR50,	%	$HiSCR_{75}$ at Week 16 Pool E1	$HiSCR_{75}$ at Week 16 Pool E1	Odds Ratio BKZ 320mg Q2W vs placebo:	

Effects Table for Bimekizumab in treatment of hidradenitis suppurativa (data cut-off: week 16)

Effect	Short Description	Unit	BKZ 320mg Q2W vs Placebo	BKZ 320mg Q4W vs Placebo	Uncertainties/ Strength of evidence	References (Studies)
including logistic regression (MI using MCMC/Monotone Regression)	response at Week 16 (vs placebo)		BKZ 320mgQ2W: 36.4% (n=580) Placebo: 18.2% (n=146)	BKZ 320mgQ4W: 31.2% (n=288) Placebo: 18.2% (n=146)	2.584 (95% CI: 1.608, 4.150) Odds Ratio BKZ 320mg Q4W vs placebo: 2.039 (95% CI: 1.220, 3.408)	double-blind 48-week treatment period of HS0003 and HS0004 (including both ITP and MTP) were combined in a pool designated as Pool E2
HSSDD worst skin pain response at Week 16	Pain response status at Week 16, as assessed by the 'worst pain' item (11-point numeric rating scale) in the HSSDD, is defined as an improvement in the weekly worst pain score of at least 3 units versus Baseline among study participants with a Baseline score of 3 or greater.	%	Pool E1: BKZ 320mgQ2W: 33.0% (n=580) Placebo: 13.2% (n=146)	Pool E1: BKZ 320mgQ4W: 25.6% (n=288) Placebo: 13.2% (n=146)	Odds Ratio BKZ 320mg Q2W vs placebo: 3.258 (95% CI: 1.624, 6.536) Odds Ratio BKZ 320mg Q4W vs placebo: 2.268 (95% CI: 1.064, 4.837)	
Unfavourable effects						
Serious infections	SAEs reported under Infections and infestations SOC	%, EAIR	Pool S1 BKZ 320mgQ2W=0.2% (n=576) Placebo: 0.0% (n=146)	Pool S1 BKZ 320mgQ4W=0.0 % (n=285) Placebo: 0.0% (n=146)	Majority of infections seen with BKZ were nonserious, mild to moderate, and did not lead to study discontinuation. The incidence of serious infections was low overall.	**Pool S1**: Data pooled to assess safety of BKZ vs placebo through Week 16 in Phase 3 placebo-controlled studies (HS0003, HS0004). **Pool S3**: Data from all blinded HS studies and their respective OLE studies (HS0001, HS0003, HS0004, HS0005) for investigation of long-term exposure and safety data in
			Pool S3 Phase 3 BKZ Total group=2.1% (EAIR:1.7/100 participant-years)			
Fungal infections	TEAEs reported under HLGT Fungal infectious disorder	%, EAIR	Pool S1 BKZ 320mg Q2W=13.0% (n=576) Placebo= 0.7% (n=146)	Pool S1 BKZ 320mg Q4W=12.3% (n=285) Placebo= 0.7% (n=146)	Majority were mild-to-moderate and did not lead to treatment discontinuation. None were systemic.	
			Pool S3 Phase 3 BKZ Total group=29.0% (EAIR:28.6/100 participant-years)			
Cutaneous hypersensitivity	TEAEs reported under Dermatitis and eczema HLT	%, EAIR	Pool S1 BKZ 320mg Q2W=6.1% (n=576)	Pool S1 BKZ 320mg Q4W=5.3% (n=285)	No anaphylactic reactions due to BKZ observed. Potential	

Effects Table for Bimekizumab in treatment of hidradenitis suppurativa (data cut-off: week 16)

Effect	Short Description	Unit	BKZ 320mg Q2W vs Placebo	BKZ 320mg Q4W vs Placebo	Uncertainties/ Strength of evidence	References (Studies)
	within MedDRA SMQ Hypersensitivity		Placebo= 2.7% (n=146)	Placebo= 2.7% (n=146)	cutaneous hypersensitivity observed, all but one were mild-moderate.	all bimekizumab-treated study participants with HS
			Pool S3 Phase 3 BKZ Total group=16.1% (EAIR: 14.1/100 participant-years)			
IBD	TEAEs adjudicated as definite or probable IBD events	%, EAIR	Pool S1 BKZ 320mg Q2W=0.2% (n=576) Placebo=0.0% (n=146)	Pool S1 BKZ 320mg Q4W=1.1% (n=285) Placebo=0.0% (n=146)	IBD is considered a class effect AE with IL-17 inhibitors, adjudicated IBD observed were slightly higher with BKZ than background population.	
			Pool S3 Phase 3 BKZ Total group=0.8% (EAIR: 0.6/100 participant-years)			

Abbreviations: BKZ=bimekizumab; EAIR=exposure-adjusted incidence rate; HiSCR50,75=a ≥50%, ≥75%, reduction in the total abscess and inflammatory nodule count with no increase from Baseline in abscess or draining tunnel count; HLGT=MedDRA High Level Group Term; HLT=MedDRA High Level Term; HS=hidradenitis suppurativa; HSSDD=hidradenitis suppurativa symptom daily diary; IBD=inflammatory bowel disease; ITP=Initial Treatment Period; MedDRA=Medical Dictionary for Regulatory Activities; MTP= Maintenance Treatment Period; OLE=open label extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SAE=serious adverse event; SOC=MedDRA System Organ Class; TEAE=treatment emergent adverse event

Notes: For Benefits, values at Week 16 are based on MI-MCMC (All-Abx)

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The Q2W dose demonstrated statistically significant differences vs placebo for the primary endpoint HiSCR50 and the more stringent ranked secondary endpoint of HiSCR75 at Week 16. The magnitude of the treatment effect observed with bimekizumab is considered to be clinically relevant in the context of a second line treatment for a distressing condition with limited treatment options.

Although a positive treatment effect was noted for both bimekizumab 320mg Q2W and 320mg Q4W doses in the initial treatment phase of both pivotal trials this was more consistent for the Q2W regimen across the HISCR50 primary endpoint and key ranked HiSCR75 secondary endpoints and change from baseline in inflammatory nodule count. The proposed Q2W dosing regimen for the initial treatment phase followed by a Q4W regimen after 16 weeks is therefore agreed.

Improvements over placebo up to Week 16 for both Q2W and Q4W were reported across a range of efficacy endpoints measuring disease signs and symptoms as well as disease activity (HiSCR50, HiSCR75, HiSCR90, IHS4, HS-PGA, Lesion counts, HSSDD, and HSSQ). Improvements in HRQoL-based outcome measures were evident at week 16 and were maintained or improved up to week 48.

With respect to the proposed indication, the totality of the data assessing the primary endpoint of HiSCR50 response and secondary endpoint of HiSCR75 response demonstrate that bimekizumab has a clinically relevant response versus placebo for important subgroups defining both less severe disease

(although still moderate HS) and more severe disease. It is thereby agreed that the indication can cover patients with moderate to severe HS as a second line treatment (i.e. (i.e. who have had insufficient response or intolerance to oral antibiotics). In addition, the MAH agreed to update the indication to mention 'active' in it, as a qualifier for disease state. The indication is therefore acceptable for the CHMP.

The impact of treatment withdrawal or pause in HS patients responding to treatment with bimekizumab will be addressed post-approval in an adequately designed clinical trial (with a randomised withdrawal design).

The short term and long-term safety data available indicate that the safety profile of bimekizumab in the treatment of moderate to severe HS is consistent with the known safety profile of the medicinal product.

Vulvovaginal mycotic infection (including vulvovaginal candidiasis) is added as an ADR (frequency common) due to an imbalance in rates between placebo and those treated with bimekizumab.

No new or unexpected safety signals were evident. A causal relationship between bimekizumab and suicidality could not be established. The safety topic on SI/B will continue to be closely monitored in future PSURs.

Long-term safety is identified as missing information in the RMP. The long-term extension study HS0005 is listed as Category 3 study in the RMP and will provide further long-term safety data and further data on durability of effect.

3.7.2. Balance of benefits and risks

The treatment effect for bimekizumab in HS, as shown by data at Week 16, is adequately demonstrated and clinically relevant. A consistent treatment effect was evident across lesion-, symptom- and HRQoL-based outcome measures for both Q4W and Q2W for the overall study population and across relevant subgroups. The lack of differentiation between the Q2W and Q4W dose regimens during the MTP supports bimekizumab 320mg Q4W dosing after Week 16. The clinical relevance is supported by safety data that is in line with the known profile observed in previous studies in other approved conditions as well as post-marketing experience. Long-term data from the HS studies support maintenance of effect as well as an acceptable safety profile until Week 48. Further long-term data will be submitted post-approval once the final results of the long-term extension study HS0005 become available.

3.8. Conclusions

The overall B/R of bimekizumab is positive in the following indication:

Hidradenitis suppurativa (HS)

Bimzelx is indicated for the treatment of active moderate to severe hidradenitis suppurative (acne inversa) in adults with an inadequate response to conventional systemic HS therapy (see section 5.1).

4. Recommendations

Outcome

Based on the review of the submitted data, the CHMP considers the following variation acceptable and therefore recommends the variation to the terms of the Marketing Authorisation, concerning the following change:

Variation accepted		Type	Annexes affected
C.I.6.a	C.I.6.a - Change(s) to therapeutic indication(s) - Addition of a new therapeutic indication or modification of an approved one	Type II	I and IIIB

Extension of indication to include treatment of moderate to severe hidradenitis suppurativa (HS) in adults, based on final results from study HS0003 (BE HEARD I) and study HS0004 (BE HEARD II). These are phase 3, randomised, double blind, placebo controlled, multicenter, pivotal studies evaluating the efficacy and safety of bimekizumab in study participants with moderate to severe HS. Further supportive data are based on the results of phase 2 study HS0001 and phase 3 currently ongoing open-label extension study HS0005. As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated in accordance. RMP version 1.12 is acceptable. Furthermore, the PI is brought in line with the latest QRD template version 10.4.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annex(es) I and IIIB and to the Risk Management Plan are recommended.

5. EPAR changes

The EPAR will be updated following Commission Decision for this variation. In particular the EPAR module 8 "*steps after the authorisation*" will be updated as follows:

Scope

Please refer to the Recommendations section above.

Summary

Please refer to Scientific Discussion 'Bimzelx-H-C-005316-II-Var.0020'

Attachments

1. Product information as adopted by the CHMP on 21 March 2024.