26 April 2023
EMA/235041/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bimzelx

International non-proprietary name: bimekizumab

Procedure No. EMEA/H/C/005316/II/0010

Note

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

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List of abbreviations

ADAb	anti-drug antibody(ies)
ADR	adverse drug reactions
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	analysis of covariance
AS	ankylosing spondylitis
ASAS	Assessment of SpondyloArthritis International Society
ASAS20, 40, 5/6	Assessment of SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria
ASAS-PR	Assessment of SpondyloArthritis International Society partial remission
ASDAS	Ankylosing Spondylitis Disease Activity Score
ASDAS-MI	Ankylosing Spondylitis Disease Activity Score major improvement
ASspiMRI-a	Ankylosing Spondylitis spine Magnetic Resonance Imagine-activity a
ASQoL	Ankylosing Spondylitis Quality of Life
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
BA	bioavailability
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BASFI	Bath Ankylosing Spondylitis Functional Index
BASMI	Bath Ankylosing Spondylitis Metrology Index
bimekizumab-AI	bimekizumab auto-injector
bimekizumab-SS	bimekizumab safety syringe
bimekizumab-TN	bimekizumab-True North
BME	bone marrow edema
CFR	Code of Federal Regulations
CI	confidence interval
COVID-19	coronavirus disease 2019
CHMP	Committee for Medicinal Products for Human Use
CPMP	Committee for Proprietary Medicinal Products
CRP	C-reactive protein
csDMARD	conventional synthetic disease-modifying antirheumatic drug
CSR	Clinical Study Report
CTCAE	Common Terminology Criteria for Adverse Events
CV	cardiovascular
CV-CAC	Cardiovascular Clinical Event Adjudication Committee
DDI	drug-drug interaction
DILI	drug-induced liver injury
DILIN	drug-induced liver injury network
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
EAIR	exposure adjusted incidence rate
EAER	exposure adjusted event rate
EAM	extra-articular manifestation
ECG	electrocardiogram
eC-SSRS	electronic Columbia-Suicide Severity Rating Scale
EMA	European Medicines Agency
EudraCT	European Union Drug Regulating Authorities Clinical Trials Database

FACIT-Fatigue	Functional assessment of chronic illness therapy-Fatigue
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HAC	Hepatology Adjudication Committee
HADs	Hospital Anxiety and Depression Scale
HD	high disease
HLA-B27	human leukocyte antigen-B27
HLT	High Level Term
HRQoL	health-related quality of life
HS	hidradenitis suppurativa
hs-CRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
ID	inactive disease
IgG1	immunoglobulin G1
IGRA	Interferon-Gamma Release Assay
IL-17	interleukin-17
IL-17-RA	IL-17 receptor A
IMP	investigational medicinal product
IND	Investigational New Drug
ISAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
iv	intravenous
JAK	janus kinase
LD	low disease
LFT	liver function test
LS	least squares
mAb	monoclonal antibody
MACE	major adverse cardiac event
MASES	Maastricht Ankylosing Spondylitis Enthesitis Index
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
mNY	Modified New York (criteria)
MRI	magnetic resonance imaging
NAb	neutralizing antibody(ies)
NEC	not elsewhere classified
nr-axSpA	nonradiographic axial spondyloarthritis
NRI	nonresponder imputation
NRS	Numeric Rating Scale
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
OMERACT	Outcome Measures in Rheumatology Clinical Trials
PBO	placebo
PD	pharmacodynamics
PFS	prefilled syringe
PGADA	Patient’s Global Assessment of Disease Activity
PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetics

PRO	patient-reported outcomes
PsA	psoriatic arthritis
PSO	psoriasis
PSUR	Periodic Safety Update Report
PT	Preferred Term
Q4W	every 4 weeks
r-axSpA	radiographic axSpA
RA	rheumatoid arthritis
RR	risk ratio
RS	Randomized Set
SAP	Statistical Analysis Plan
sc	subcutaneous(ly)
SCS	Summary of Clinical Safety
SF-36	PCS Short-Form 36-item Health Survey physical component summary
SFU	Safety Follow-Up
SMQ	standardized MedDRA query
SOC	System Organ Class
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
TB	tuberculosis
TEMA	treatment-emergent markedly abnormal
TEAE	treatment-emergent adverse event
TNFα	tumor necrosis factor alpha
UC	ulcerative colitis
ULN	upper limit of normal
WPAI-SHP	Work Productivity and Activity Impairment Questionnaire-specific health problem

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 26 August 2022 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 adults with active axial spondyloarthritis (axSpA), including non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS, radiographic axial spondyloarthritis), based on interim results from two interventional and controlled phase III clinical studies: AS0010 (BE MOBILE 1) and AS0011 (BE MOBILE 2), which provide evidence of the efficacy and safety of bimekizumab in axSpA (nr-axSpA and AS), both compared to placebo treatment. Further supportive data is provided by the results of a phase 2a exploratory study (AS0013), a phase 2b, dose-ranging study (AS0008) and its ongoing follow-on phase 2b open-label extension (OLE) study (AS0009). 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 1.2 of the RMP has also been submitted. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev.1.

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/0456/2020 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0456/2020 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 did seek Scientific Advice at the CHMP. See section 2.1.3 below.

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	26 August 2022
Start of procedure:	17 September 2022
CHMP Rapporteur Assessment Report	14 November 2022
PRAC Rapporteur Assessment Report	17 November 2022
CHMP Co-Rapporteur Assessment	24 November 2022
PRAC Outcome	1 December 2022
CHMP members comments	5 December 2022
Updated CHMP Rapporteur(s) (Joint) Assessment Report	8 December 2022
Request for supplementary information (RSI)	15 December 2022
CHMP Rapporteur Assessment Report	28 February 2023
PRAC members comments	n/a
PRAC Outcome	16 March 2023
CHMP members comments	20 March 2023
Updated CHMP Rapporteur Assessment Report	23 March 2023
Request for supplementary information (RSI)	30 March 2023
CHMP Rapporteur Assessment Report	12 April 2023
PRAC Rapporteur Assessment Report	12 April 2023
PRAC members comments	17 April 2023
CHMP members comments	17 April 2023
Updated PRAC Rapporteur Assessment Report	20 April 2023
Updated CHMP Rapporteur Assessment Report	20 April 2023
Opinion	26 April 2023

2. Scientific discussion

2.1. Introduction

2.1.1. Problem statement

Disease or condition

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases (including axial spondyloarthritis [axSpA], psoriatic arthritis [PsA], reactive arthritis, the arthritis of inflammatory bowel

disease [IBD], and undifferentiated SpA) that have features in common with each other and distinct from other inflammatory arthritides, particularly rheumatoid arthritis.

Axial spondyloarthritis comprises diseases with mainly axial involvement (sacroiliac [SI] joints and spine), including:

• Ankylosing spondylitis (AS; also known as radiographic axSpA [r-axSpA]) requires a diagnosis of definite radiographic damage of the SI joints, as demonstrated by radiographic evidence.

• Nonradiographic axSpA (nr-axSpA) where there is no definite radiographic damage on the SI joints.

The claimed therapeutic indication

The proposed indication for bimekizumab in nr-axSpA and AS is as follows:

Non-radiographic axial spondyloarthritis (nr-axSpA)

Bimzelx is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation as indicated by elevated C-reactive protein (CRP) and/or magnetic resonance imaging (MRI) who have responded inadequately or are intolerant to nonsteroidal anti-inflammatory drugs (NSAIDs).

Ankylosing spondylitis (AS, radiographic axial spondyloarthritis)

Bimzelx is indicated for the treatment of adults with active ankylosing spondylitis who have responded inadequately or are intolerant to conventional therapy.

Epidemiology and risk factors, screening tools/prevention

Ankylosing spondylitis

The estimated prevalence of AS ranges from 0.05% to 1.5% (Bohn et al, 2018; Sieper and Poddubnyy, 2017; Curtis et al, 2016; Strand et al, 2013; Reveille et al, 2012).

Nonradiographic axial spondyloarthritis

Data are limited on the prevalence of nr-axSpA. A multinational study found that among patients with inflammatory back pain, 29% met the criteria for nr-axSpA, with variation in the prevalence by geographic region (36% in Asia and 16% in Africa) (Burgos-Vargas et al, 2016). It is estimated that the proportion of patients that present with nr-axSpA is similar to that of patients diagnosed with AS; thus, the total population of patients with axSpA is at least double the proportion reported for AS (Baraliakos and Braun, 2015; van Tubergen, 2015). The prevalence of the disease is highly affected by the background prevalence of HLA-B27, its major genetic association (Navarro-Compán et al, 2021).

Clinical presentation, diagnosis and stage/prognosis

Patients with nr-axSpA and AS develop their first symptoms in late teenage years to mid-twenties, but experience long delays in diagnosis, which impacts the timing of effective treatment. Studies of the Berlin early spondyloarthritis clinic records found that the average time from symptom onset to diagnosis was 8 years for all axSpA patients (Poddubnyy et al, 2012a).

Ankylosing spondylitis

Patients with AS primarily have inflammatory back pain. The disease typically originates in the sacroiliac joints, then progresses to the spine. In the sacroiliac joints and the spine, active inflammation seen on

magnetic resonance imaging (MRI) as bone marrow edema (BME) over time results in chronic lesions such as erosions, sclerosis, fat lesions, and ankylosis. However, the most characteristic feature is new bone formation leading to ankylosis of the sacroiliac joints and syndesmophytes attached to the vertebral bodies. As a result of extended syndesmophyte formation, over time the spine may become fused in some patients with AS (bamboo spine). Objective signs of inflammation such as BME on MRI, elevated C-reactive protein (CRP) and genetic features (such as the presence of human leukocyte antigen-B27 [HLA-B27]) may also be present (Braun, 2012; Rudwaleit et al, 2009c; Braun and Sieper, 2007).

Disability in AS is related to both the degree of inflammatory activity causing pain, stiffness, fatigue, and poor quality of sleep, and to the degree of bony ankylosis, causing loss of spinal mobility and impaired physical function.

Nonradiographic axial spondyloarthritis

Nonradiographic axSpA falls under the umbrella of axSpA and can be seen as an earlier form of axSpA in some patients, however, many patients do not develop structural damage on the sacroiliac joints after years of symptoms and therefore never progress to AS (Navarro-Compán et al, 2021). Robinson et al. (2021) reported rates of progression from nr-axSpA to AS in different cohorts that ranged from 1% to 12% over 2 years, 6% to 46% over 2 to 9 years, and 26% to 59% over >10 years. Despite lack of structural damage on the sacroiliac joint and spine, patients with nr-axSpA have comparable disease burden (disease activity, pain, impairments of physical function and quality of life) to those with AS (Callhoff et al, 2015; Kiltz et al, 2012). This recognition led to development of the Assessment in SpondyloArthritis international Society (ASAS) criteria (Rudwaleit et al, 2009b) to facilitate earlier recognition of axSpA and to identify axSpA patients with and without radiographic sacroiliitis according to 2 possible entry arms: the "imaging arm" (presence of sacroiliitis on radiography or MRI) and the "clinical arm" (presence of HLA-B27).

In both subpopulations and beyond the core signs and symptoms of spinal disease, many patients with AS or nr-axSpA experience peripheral manifestations such as peripheral arthritis, enthesitis, and to a lesser extent, dactylitis and extra-articular manifestations (EAMs) like acute anterior uveitis, IBD, or psoriasis (PSO) which is an additional burden affecting these patients' quality of life (Navarro-Compán et al, 2021). Such patients are in need of a holistic treatment approach.

Many patients continue to suffer from symptoms and residual inflammation despite treatment. This can lead to irreversible structural damage and as a consequence to loss of mobility, impact on daily function, and quality of life.

Management

The goals of treatment of nr-axSpA and AS are to reduce symptom severity, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, decrease disease complications, and to slow progression of structural damage.

Nonsteroidal anti-inflammatory drugs (NSAIDs) are used as first-line treatment and are effective for the symptoms (pain and stiffness) of axSpA, but many patients lose or never have clinically meaningful response, and structural damage often progresses despite their use. Conventional synthetic disease-modifying antirheumatic drugs (cDMARDs; e.g., methotrexate [MTX] and sulfasalazine [SSZ]) have no proven efficacy in axial disease but may benefit patients with peripheral joint disease. Patients with purely axial disease should normally not be treated with cDMARDs; sulfasalazine may be considered in patients with peripheral arthritis. Patients who are intolerant or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have approved treatment options such as tumour necrosis factor alpha (TNFα) inhibitors.

Additionally, the interleukin (IL)-17 cytokine family has been identified as a therapeutic target in axSpA and secukinumab as well as ixekizumab, IL-17A monoclonal antibodies, have been approved as treatment options in active AS and nr-axSpA. Janus kinase inhibitors (upadacitinib and tofacitinib) have recently been approved for the treatment of patients with active AS (upadacitinib and tofacitinib) and nr-axSpA (upadacitinib) in the EU.

2.1.2. About the product

Bimekizumab is a humanised, full-length monoclonal antibody (mAb) of immunoglobulin G1 subclass with 2 identical antigen binding regions that selectively bind with high affinity and neutralise IL-17A, IL-17F, and IL-17AF cytokines. Antibodies targeting IL-17A cytokines have demonstrated efficacy in patients with active axSpA, PSO, and PsA.

Bimekizumab has been granted marketing authorisation in the EU, for the treatment of moderate to severe plaque PSO.

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

The bimekizumab axSpA phase 2 development program included two Phase 2b studies in study participants with AS: AS0008 (completed) to investigate dose-response, efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) and its open-label extension (OLE) study AS0009 (ongoing) to investigate long term safety and efficacy. Data from this Phase 2b study led to dose selection of bimekizumab 160mg Q4W for the Phase 3 studies. One exploratory Phase 2a study (AS0013), evaluated the efficacy and safety of bimekizumab and certolizumab pegol (Cimzia) in adult study participants with active AS.

The bimekizuamb axSpA phase 3 development program consisted of 2 adequate and well controlled pivotal placebo-controlled Phase 3 studies designed in adults with nr-axSpA (AS0010) or AS (AS0011) who suffer from moderate to severe active disease. Efficacy is evaluated through the end of the placebo-controlled Double-Blind Initial Treatment Period at Week 16 and continued for 36 weeks until Week 52 in the Maintenance Period in both studies.

Upon completion of AS0010 and AS0011, eligible study participants could receive continued treatment with bimekizumab 160mg Q4W in an OLE study (AS0014; ongoing), to allow the collection of data on the long-term safety, tolerability, and efficacy of bimekizumab. The MAH performed a data cut (20 Dec 2021) to provide the most complete data for safety and exposure to bimekizumab at the time of initial submission. Study participants who did not enroll into AS0014 entered a 20-week Safety Follow-Up (SFU) Period.

A data cut was taken after the last study participants had their last Week 24 study visit in AS0010 or AS0011 and the following analyses of data were initially presented:

- All efficacy data up to the Week 24 Visit, ie, including the Week 16 primary analysis time point and an additional 8 weeks of treatment in the Maintenance Period up to the Week 24 Visit.
- All available safety data at the time of the Week 24 data cut-off, ie, including the 16-week Double-Blind Treatment Period and Maintenance Period up to the Week 24 cut-off date. This included safety data for all study participants up to their Week 24 Visit as well as all available safety data beyond Week 24 for participants who have continued further in the study.
- Complete immunogenicity data (anti-drug antibody(ies) [ADAb], and neutralising antibody(ies) [NAb]) up to Week 24 (from 100% of study participants) and all available immunogenicity data

(ADAb, NAb) up to Week 52/Early Termination/SFU (representing 69.7% of study participants in AS0010 and 75.6% in AS0011; data cut-off: 20 Dec 2021) were provided.

Prior to initiating the global Phase 2 and Phase 3 studies, EMA Scientific Advice was obtained on the initial clinical development plan in axSpA in July 2016 (EMEA/H/SA/3306/3/2016/II). The overall proposed clinical programme for axSpA was considered acceptable by the CHMP at that time.

Following this interaction and input from the USA FDA, several adjustments were incorporated into the programme. Results from the Phase 2b dose-ranging study in AS (AS0008) and the updated *Guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis* (EMA/CPMP/EWP/4891/03 Rev. 1), effective 01 May 2018, further informed the development of the Phase 3 program.

The revised program was presented to EMA in a follow up Scientific Advice meeting (EMEA/H/SA/3306/3/FU/1/2018/II) and was found acceptable.

2.2. Non-clinical aspects

No new non-clinical data have been submitted in this application. The MAH has cross referenced to data submitted in a parallel procedure (EMEA/H/C/005316/II/0011) for an extension of indication in psoriatic arthritis. The assessment henceforth refers to said data, where relevant, for the proposed indication in axial spondyloarthritis, including non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS, radiographic axial spondyloarthritis).

The data for consideration included primary pharmacodynamic studies relevant to the proposed indication and an updated carcinogenicity assessment document (CAD).

2.2.1. Pharmacology

Primary pharmacodynamic studies

In vitro pharmacodynamics

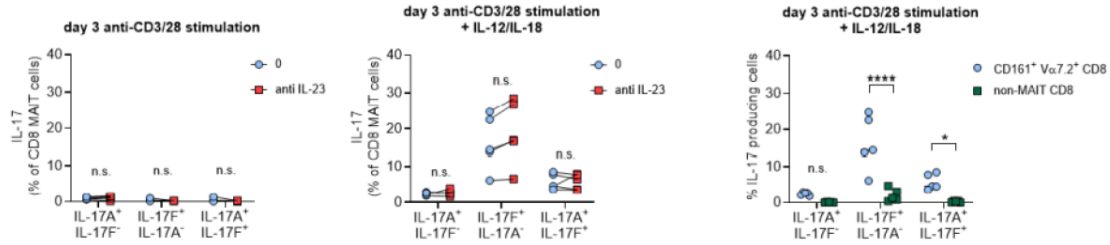
IL-17F is produced in larger amounts than Il-17A by innate immune cells and independently of Il-23

Interleukin-17A and IL-17F are produced by cells from the adaptive and innate immune system. Flow cytometry was used to examine the capability of mucosal-associated invariant T cells (MAIT cells) and γδ T cells (innate immune system) and cluster differentiation (CD)4+ T cells (adaptive immune system) from peripheral blood from 5 human donors to produce IL-17A and IL-17F in response to T cell receptor (TCR) stimulation with or without IL-12/IL-18 and in the presence or absence of an antibody neutralising IL-23.

CD8+ MAIT cells produce negligible amounts of IL-17A or IL-17F upon anti-CD3/CD28 stimulation alone. Following addition of IL-12 and IL-18, both cytokines were produced with a strong bias towards IL-17F, which is independent of IL-23. The majority of IL-17A and IL-17F produced from CD8+ T cells was shown to be issued from MAIT cells (identified as Vα7.2+CD161+CD8+) (Figure 1).

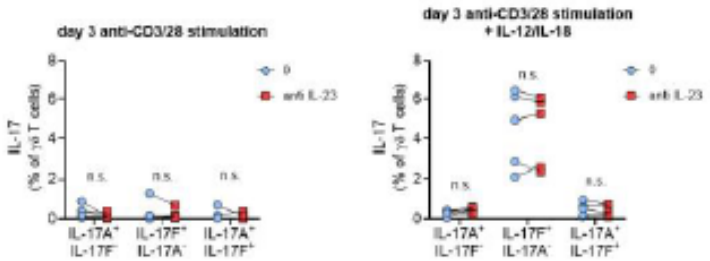
As MAIT cells, γδ T cells produced very little IL-17A or IL-17F upon anti-CD3/CD28 stimulation alone and produced mainly IL-17F upon addition of IL-12 and IL-18 but independently of the presence of IL-23 (Figure 2).

In contrast, CD4+ T cells produced IL-17A and IL-17F upon anti-CD3/CD28 stimulation alone, which was reduced by an IL-23 neutralising antibody.



The proportion of Vα7.2$^+$CD161$^+$CD8$^+$ MAIT cells positive for IL-17A, IL-17F or IL-17A and IL-17F was evaluated upon anti-CD3/CD28 stimulation (TCR) alone (left panel) or in the presence of IL12/IL-18 (central panel) with (red squares) or without (blue circles) 10µg/mL of an IL-23 neutralizing antibody. The right panel demonstrated that most of the CD8$^+$ IL-17-producing cells were MAIT cells (blue circles), as indicated by the Vα7.2$^+$CD161$^+$ labeling (red squares)

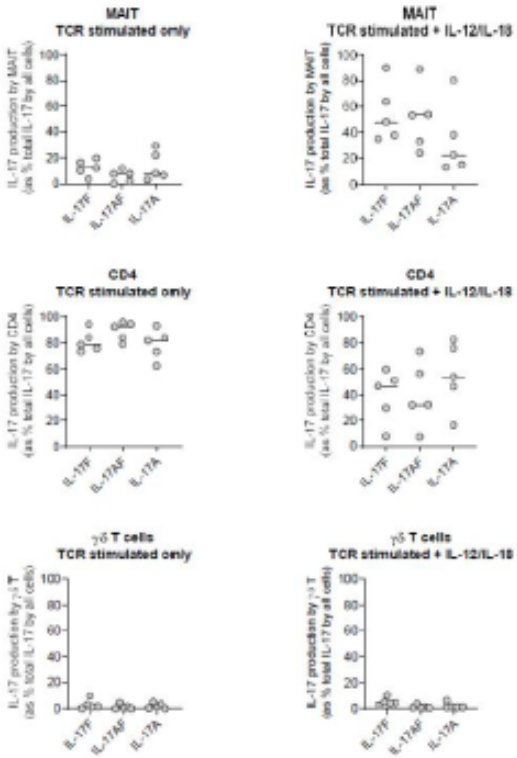
Figure 1: IL-17A and IL-17F production by MAIT cells



The proportion of γδ T cells positive for IL-17A, IL-17F or IL-17A and IL-17F was evaluated upon anti-CD3/CD28 stimulation (TCR) alone (left panel) or in the presence of IL12/IL-18 (central panel) with (red squares) or without (blue circles) 10µg/mL of an IL-23 neutralizing antibody.

Figure 2: IL-17A and IL-17F production by γδ T cells

MAIT cells were significant contributors to the production of total IL-17A, IL-17F and IL-17AF in the presence of IL-12/IL-18 whereas CD4 cells were the main contributors under TCR stimulation (Figure 3).



Cell proportions were evaluated by flow cytometry, using gating on either IL-17A$^-$IL-17F$^+$, IL-17A$^+$IL-17F$^-$ or IL-17A$^+$IL-17F$^+$, and the percentage of CD3$^+$CD4$^+$ (CD4$^+$ T cells), CD3$^+$CD8$^+$Vα7.2$^+$ (MAIT) or CD3$^+$CD4$^-$CD8$^-$ γδTCR$^+$ cells.

Figure 3: Proportion of IL-17A and IL-17F isoforms produced by MAIT, CD4 or γδ T cells as compare to totat cells number

Based on these *in vitro* experiments, innate-like T cells such as MAIT and γδT cells can produce IL-17A and IL-17F, with a bias towards greater IL-17F, upon stimulation with IL-12 and IL-18, which is IL-23 independent. In contrast, adaptive CD4+ T cells show greater dependency on IL-23.

Il-17F plays an important role in psoriatic arthritis (Glatt et al, 2018)

The MAH has demonstrated the presence of both IL-17A and IL-17F in synovial tissue from patients with PsA using mRNA expression analysis. The 2 cytokines induce the release of inflammatory mediators by signaling through the receptor complex IL17RA/RC present in both synoviocytes and skin cells. Whereas neither IL-17A nor IL-17F demonstrate substantial activity by themselves, their potency is significantly increased in the presence of TNFα.

The inhibition of both Il-17A and IL-17F by bimekizumab or a cocktail of antibodies against IL-17A and IL-17F blocked more effectively the production of IL-8 and MMP3 by synoviocytes from patients with PsA stimulated by the supernatant of polyclonal Th17 cells than antibodies selectively inhibiting each of the cytokines. Similar results were obtained on the secretion of IL-8 by normal dermal fibroblasts. Bimekizumab also induced a more profound down regulation of a large panel of inflammation-related genes in synoviocytes and normal human dermal fibroblasts stimulated by Th17 cell supernatants than inhibition of IL-17A alone and confirmed a more profound inhibition of neutrophil chemotaxis than antibodies neutralising selectively each of the cytokines as previously demonstrated (Study 40001876).

Altogether, the MAH considered that these results suggest that although IL-17F appears to be less potent than IL-17A, it plays an important role in chronic inflammation.

Il-17F potently enhances osteogenic differentiation from human periosteum-derived cells and *in vitro* bone formation (Shah et al, 2020)

The MAH in collaboration with academic groups has demonstrated that IL-17A and IL-17F potently enhance osteogenic differentiation from human periosteum-derived cells and *in vitro* bone formation from human periosteal cells that are hypothesised to orchestrate pathological bone formation in AS. These effects are more efficiently inhibited by bimekizumab than by the specific inhibition of IL-17A or IL-17F.

IL-17A and IL-17F induce the transient expression of the periosteal stem cell marker SOSTDC1 indicating differentiation away from a 'stem cell' phenotype and the simultaneous increased expression of the osteo-commitment marker RUNX2, the IL-17A and IL-17F receptors and BMP2. The 2 cytokines are approximately equipotent in enhancing osteogenic differentiation based on the determination of markers SP7, BGLAP, VEGFA and PHOSPHO1. γδ T cells or Th17 cell supernatants (containing IL-17A and IL-17F) induce potent increases in all osteogenic markers and in matrix mineralisation in human periosteum-derived cells. Serum from AS patients also promotes the osteogenic differentiation of human periosteum-derived cell as suggested by increased RUNX2 expression.

The dual neutralisation of IL-17A and IL-17F induces a deeper suppression of osteogenic gene expression in human periosteum-derived cells than the neutralisation of either cytokine alone, and a suppression of matrix mineralisation. Similarly, the pre-incubation of serum from 2 out of 3 AS patients with bimekizumab more effectively blocks RUNX2 expression in human periostal derived cells than the preincubation with antibodies specific to IL-17A or IL-17F (Shah et al, 2020).

Secondary pharmacodynamic studies

Bimekizumab, as secukinumab, is an IgG1 with a potent Fc function that can be influenced by the structure of the N-linked oligosaccharide moiety of the CH2 region of the Fc domain. However, the mechanism of action of bimekizumab (binding soluble IL-17A and IL-17F to prevent their interaction with the IL-17RA/IL-17RC complex) does not involve the Fc effector function. In these conditions, the risk of Fc effector-driven adverse events (cytotoxicity) is low, and the composition of the N-linked oligosaccharide moiety is not expected to influence the efficacy or potency (Jiang et al, 2011). The absence of risk for antibody-dependent cell-mediated cytotoxicity (ADCC) or complement-dependent cytotoxicity (CDC) was nevertheless assessed using *in vitro* assays.

ADCC was previously investigated by evaluating the viability of normal human dermal fibroblasts (effector cells) pre-stimulated with human IL-17A or IL-17F and cultured with natural killer (NK) effector cells in the presence of bimekizumab (Study 40001865). To address a question raised during the review of the MA dossier for the PSO indication, the risk of ADCC and CDC was evaluated on IL-17-producing cells. Peripheral blood mononuclear cells (IL-17-producing cells) were preincubated with anti-CD28 and anti-CD3 antibodies and therefore incubated with complement active human serum and increasing concentrations of bimekizumab or secukinumab (IgG1 anti-IL-17A, used as negative control). Under the experimental conditions, none of the antibodies induced CD4+ IL-17+ T cell depletion; by contrast peripheral blood mononuclear cells incubated with complement active human serum and increasing concentrations of ocrelizumab or rituximab (with known ADCC and CDC properties for B cells) led to depletion of CD20+ B cells (Study 40001929). Results showed that bimekizumab does not elicit Fc receptor mediated cytotoxicity, either by ADCC or by CDC on IL-17 effector cells or on IL-17-producing cells.

2.2.2. Toxicology

Carcinogenicity

The CAD reviewing the full weight-of-evidence for the role of IL-17A and IL-17F in carcinogenesis and tumour progression, the mode of action of bimekizumab, information from *in vitro* and *in vivo* tumour models, published data from patients with tumours, and published safety data has been updated with most recent publications on therapeutic antibodies targeting the IL-17 pathway for the PSO, PsA, and AS indications.

Published safety data from marketed antibodies targeting IL-17A or IL-17RA demonstrated no increased risk of tumour so far for PSO, PsA, or AS (Genovese et al, 2020; Combe et al, 2020; Lebwohl et al, 2021).

2.2.3. Ecotoxicity/environmental risk assessment

Bimekizumab does not contain non-natural amino acids or modifications. It is expected to be subject to the same *in vivo* degradation pathways as natural proteins and to have the same environmental impact as naturally occurring human antibodies. According to the Guideline on the Environmental Risk Assessment on Medicinal Products for Human Use (EMEA/CHMP/SWP/4447/00), amino acids, peptides and proteins are exempted because they are unlikely to result in significant risk to the environment. Consequently, no Environmental Risk Assessment for bimekizumab is required.

2.2.4. Discussion on non-clinical aspects

The rationale for IL-17 modification in axial spondyloarthritis is supported by the pharmacodynamic studies conducted by the MAH. The predominant secretion of IL-17 from innate immune cells, independent of IL-23, may partially explain the failure of targeting IL-23 in axial spondyloarthritis thus far. While IL-17A is considered more potent than IL-17F, evidence suggested that they may have equal potency in their pro-osteogenic effects. Elevated IL-17 promoted osteogenic markers, including BMP2 and RUNX2, the latter of which has been observed at elevated levels in the serum of patients with ankylosing spondylitis (AS). IL-17F isoform is predominantly expressed in inflammatory diseases including AS. Pre-incubation of AS serum with bimekizumab reduced RUNX2 expression to a greater extent than antibodies targeting either Il-17A or Il-17F alone. SmPC section 5.1. has been updated accordingly. The pharmacodynamic studies discussed provide a solid rationale for the use of bimekizumab in AS. No data was submitted specifically in support of non-radiographic axial spondyloarthritis, this is acceptable as the update to SmPC relates to the broader mechanism of action of bimekizumab.

The MAH also provided an update to the Carcinogenicity Assessment Document (CAD). Overall, evidence collected in the post-marketing setting including with other Il-17 inhibitors did not indicate an increased risk of malignancies in psoriasis, psoriatic arthritis or AS.

2.2.5. Conclusion on the non-clinical aspects

The non-clinical package submitted in support of an indication in axial spondyloarthritis is acceptable. Bimekizumab is not expected to pose a risk to the environment.

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.

2.3.2. Pharmacokinetics

In the context of this new indication for the treatment of adults with active axial spondyloarthritis (axSpA), additional PK data were collected and submitted by the MAH. Bimekizumab doses ranged from 16 mg up to 320 mg.

The Table 1 below gives an overview of the studies contributing data to the AxSpA summary of clinical pharmacology:

Table 1: Summary of studies contributing data to the axSpA clinical pharmacology

Study Number	Study Objectives	Pop-PK	PK/ Efficacy[a]	PK Sampling
Phase 1 study in healthy study participants				
UP0067	Single-dose study to evaluate the safety, tolerability, and PK in Chinese healthy study participants			Intensive
Phase 2 efficacy and safety studies in axSpA				
AS0008 (Phase 2b)	Dose-ranging study to evaluate efficacy, safety, PK, and PD in the treatment of active AS	X[b]	X[c]	Sparse
AS0009 (Phase 2b)	Long-term safety, efficacy, and PK study for participants who complete AS0008			Sparse
AS0013 (Phase 2a)	Exploratory study of the safety and efficacy of bimekizumab and certolizumab pegol in active AS	X[b]		Sparse
Phase 3 pivotal efficacy and safety studies in axSpA				
AS0010	Comparison of bimekizumab to placebo in the treatment of active nr-axSpA	X[b]	X[c]	Sparse
AS0011	Comparison of bimekizumab to placebo in the treatment of active AS	X[b]	X[c]	Sparse
Additional study in PsA which contributed to summary of clinical pharmacology in axSpA				
DV0004	Clinical-use device presentation substudy of PA0012			Sparse
Additional study in PSO which contributed to summary of clinical pharmacology in axSpA				
PS0015	Comparison of bimekizumab to secukinumab in study participants with PSO	X[b]		Sparse

AS=ankylosing spondylitis; ASAS=Assessment of SpondyloArthritis International Society criteria; axSpA=axial spondyloarthritis; nr-axSpA=nonradiographic axSpA; PD=pharmacodynamics; PK=pharmacokinetics; Pop-PK=population pharmacokinetics; PsA=psoriatic arthritis; PSO=psoriasis

[a] PD or efficacy data were collected in these studies.

[b] CL0538: Population PK analysis of bimekizumab in participants with axSpA, PsA, and PSO.

[c] CL0539: Population PK-PD modeling of ASAS response following bimekizumab subcutaneous administration in participants with axSpA.

Bioanalytical methods

An overview of the bioanalytical methods used for analyses of plasma bimekizumab concentrations (4 methods), anti-bimekizumab antibody (ADAb) assessments (5 methods), and anti-bimekizumab NAb determination (1 method with 2 parts [IL-17AA and IL-17FF specific]) in clinical studies relevant to the psoriatic arthritis (PsA), axial spondyloarthritis (axSpA), and psoriasis (PSO) indications are shown in Table 2 (study numbers related to the PsA and axSpA submissions are in bold font).

Table 2: Bioanalytical methods used

Study numbers	Study phase	Bioanalytical method		
		Plasma BKZ concentration method	Anti-BKZ antibody method	Neutralizing anti-BKZ antibody method
UP0008	1	PK Method #1	ADAb-1	Not evaluated
PA0007		PK Method #1	ADAb-1	
RA0124	1	PK Method #1	ADAb-1	Not evaluated
UP0031		PK Method #1	ADAb-2	
UP0033		PK Method #2	ADAb-4	
UP0034		PK Method #3	ADAb-5	
UP0042		PK Method #1	ADAb-3	
UP0067		PK Method #4	ADAb-5	
PS0010 (2b)	2	PK Method #1	ADAb-3	Not evaluated
PS0011 (2b)		PK Method #1	ADAb-3	
PS0016 (2a)		PK Method #1	ADAb-3	
PS0018		PK Method #1	ADAb-3	
PA0008 (2b)	2	PK Method #1	ADAb-3	Not evaluated
PA0009 (2b)		PK Method #2	ADAb-3	
AS0008 (2b)		PK Method #1	ADAb-3	
AS0009 (2b)		PK Method #1	ADAb-3	
AS0013 (2a)		PK Method #1 and #2	ADAb-4	
PS0008	3	PK Method #2	ADAb-5	CLBA
PS0009		PK Method #2	ADAb-5	CLBA
PS0013		PK Method #2	ADAb-5	CLBA
PS0014		PK Method #2	ADAb-5	CLBA
DV0002 [a]		PK Method #2	ADAb-5	CLBA
DV0006 [a]		PK Method #2	ADAb-5	CLBA
PS0015		PK Method #2	ADAb-5	CLBA
PA0010	3	PK Method #3	ADAb-5	CLBA
PA0011		PK Method #3	ADAb-5	CLBA
PA0012		PK Method #3	ADAb-5	CLBA
DV0004 [b]		PK Method #3	ADAb-5	CLBA
AS0010 [c]		PK Method #3 and #4	ADAb-5	CLBA
AS0011 [c]		PK Method #3 and #4	ADAb-5	CLBA

axSpA=axial spondyloarthritis; ADAb=antidrug antibody; BKZ=bimekizumab; CLBA=competitive ligand binding assay; NA=not applicable; NAb=neutralizing antibody; PK=pharmacokinetic; PsA=psoriatic arthritis; PSO=psoriasis

Note: Information on study numbers in bold font is being newly provided with the PsA and axSpA submissions; information on the other listed studies was previously provided with the PSO submission.

[a] DV0002 and DV0006 are device presentation substudies of PS0014 and bioanalytical reports are part of the PS0014 bioanalytical report.

[b] DV0004 is a device presentation substudy of PA0012 and the bioanalytical report is part of the PA0012 bioanalytical report (see Section 2.2).

[c] For the AS0010 and AS0011 samples from China, PK Method #4 was used; for all other AS0010 and AS0011 samples, PK Method #3 was used.

Determination of bimekizumab concentrations in plasma

Method life cycle information for each of the 4 PK methods is presented in Table 3. PK Method #1 was developed and used to analyse samples in Phase 1 studies (except UP0033, UP0034, and UP0067) and all PsA, axSpA, and PSO Phase 2 studies (except PA0009). The method is based on coating with anti-bimekizumab idiotypic antibody and detection with a sheep anti-human IgG1 antibody. PK Method #1 was updated into PK Method #2 to yield improved robustness going into the Phase 2 studies PA0009 and AS0013 (and was also used in the Phase 3 PSO studies). The main improvements for PK Method #2 were based on using both coating and detection with anti-bimekizumab idiotypic antibodies and raising the lower limit of quantification (LLOQ) to 250ng/mL. For future testing, PK Method #2 was transferred successfully to another vendor and validated as PK Method #3. PK Method #3 was used for the Phase 3 studies in PsA and axSpA as well as the stand-alone study UP0034. PK Method #3 was transferred to a

Chinese vendor and validated as PK Method #4. Subsequently, PK Method #4 was cross-validated with PK Method #3. Thus far, PK Method #4 has only been used in the Chinese Phase 1 study UP0067. PK Method #1 and PK Method #2 were cross-validated to facilitate population PK analysis using combined data from Phase 2 and Phase 3 studies.

Table 3: Bioanalytical PK method life cycle information

	Method validation #1 (PK Method #1)	**Method validation #2 (PK Method #2)**	**Method validation #3 (PK Method #3)**	**Method validation #4 (PK Method #4)**
Analyte	Bimekizumab (UCB4940)	Bimekizumab	Bimekizumab	Bimekizumab
Validation type	Full validation	Full validation	Full validation	Full validation
eCTD reference number	PSO Module 2.7.1 Table 4-2	PSO Module 2.7.1 Table 4-3, NCD3091rep stab add1, NCD3091rep stab add2 and NCD3091rep stab add3	PSO Module 2.7.1 Table 4-4, NCD3248rep add3 and NCD3248rep add4	NCD3219rep, NCD3219rep add1 and NCD3427rep
Method ID	MWI4676 and MWI3958	MWI4741	ICD 730	20BASM049V1
Duration of time method is in use	Feb 2013 – Apr 2019	Mar 2019 - Present	Sep 2019 - Present	Sep 2020 - Present
Matrix	Lithium Heparin Plasma			
Platform	Electrochemiluminescence Immunoassay (ECLIA) (MSD)			
Format	A validated sandwich format using an anti-idiotypic Bimekizumab rabbit monoclonal antibody as capture and a sheep anti-human IgG1 antibody for detection.	A validated sandwich format using an anti-idiotypic Bimekizumab rabbit monoclonal antibody as capture and an anti-idiotypic rabbit IgG1 antibody for detection.	A validated sandwich format using an anti-idiotypic Bimekizumab rabbit monoclonal antibody as capture and an anti-idiotypic rabbit IgG1 antibody for detection.	A validated sandwich format using an anti-idiotypic Bimekizumab rabbit monoclonal antibody as capture and an anti-idiotypic rabbit IgG1 antibody for detection.
Stock reference, lot number, expiration date	Reference drug UCB4940, lot CELz009, expiration date 15 Feb 2014, lot CELa001, expiration date 31 Oct 2015, lot 272527 ARS, expiration date 05 April 2017, UCB4940 reference UCB4940-RS-003, lot 160542 expiration date 24 May 2020	Reference drug UCB4940, lot 160542, expiration date 24 May 2020	Reference drug UCB4940, lot 160542, expiration date 24 May 2020	Reference drug UCB4940, lot 160542, expiration date 24 May 2021
Calibration range from LLOQ to ULOQ	150ng/mL to 18,000ng/mL	250ng/mL to 20,000ng/mL	250ng/mL to 20,000ng/mL	250ng/mL to 20,000ng/mL
Matrix study population	Healthy individuals and Subjects with psoriasis, psoriatic arthritis, rheumatoid arthritis, axial spondylarthritis or ulcerative colitis.	Healthy individuals and individuals with psoriasis.	Healthy individuals and individuals with psoriasis, psoriatic arthritis or Ankylosing Spondylitis.	Healthy individuals and individuals with Ankylosing Spondylitis.
Link to reports and applicable amendments	The PK assay validation was amended with a partial validation to include psoriatic, psoriatic arthritis and ulcerative colitis (MWI3958, report code: NCD2857rep [QBR113785QB10])	The PK assay validation was amended with a Long-Term Stability (LTS) study.	The PK assay validation was amended with an LTS study (PPD study code RJQL3)	The PK assay validation was amended with an LTS, selectivity and parallelism study (report code: NCD3219rep add1)

	Method validation #1 (PK Method #1)	Method validation #2 (PK Method #2)	Method validation #3 (PK Method #3)	Method validation #4 (PK Method #4)
Synopsis of amendment history	Assessment of UCB4940 frozen stability at -80°C and -20°C (up to 629 days)	Assessment of UCB4940 Freeze/Thaw (6 cycles), Room Temperature up to 336 hours (see report NCD3091rep stab [LGC314867QB40]), Long-term stability (LTS) up to 1028 days (see report NCD3091rep stab add3 [LGC314867QB40]).	Assessment of UCB4940 Freeze/Thaw (6 cycles), Room Temperature up to 338 hours, Frozen stability at -25° and -80° C (LTS) up to 914 days (see report NCD3248rep add4).	Long-term stability assessed up to 731 days.

Antidrug antibody methods

The ADAb assay was optimised during clinical development with respect to 1) development of a tiered analysis approach and changing from quantitative evaluation using a calibrator curve to semi-quantitative titer evaluation, and 2) optimisation regarding drug and target tolerance requirements. The ADAb data in the clinical studies were generated using bioanalytical methods that were validated according to the relevant guidelines at the time of validation.

In support of the early clinical studies, e.g., PA0007, a homogenous Meso Scale Discovery (MSD)-based ADAb assay was used applying a calibration curve (ADAb-1). Presence of ADAb was only evaluated using a screening and confirmatory assay (drug displacement assay), no titration was performed. The level of ADAb was reported as unit/mL where 1 unit is equivalent to 1µg of calibrator. This assay was validated.

The ADAb assay was redeveloped and re-established (ADAb-2), which included the transition from reporting relative concentration units to implementing a 3-tiered sample analysis approach, consisting of a screening assay, confirmatory assay (i.e. drug displacement assay to confirm the true positivity of the ADAb-positive samples), and a titration assay to semi-quantify the ADAb responses. This assay was validated.

Subsequently, this assay was improved (ADAb-3) and used in support of Phase 2 studies AS0008, AS0009, PA0008, and PA0009. This assay was validated.

Based on the clinical ADAb data obtained during clinical development, the ADAb assay was further optimized to improve target tolerance to allow sensitive detection of treatment emergent ADAb during the drug treatment period. This assay was validated (ADAb-4) and used in analysis of samples from AS0013.

Subsequently, this assay was transferred and validated (ADAb-5) and used in UP0067 and Phase 3 studies PS0015, AS0010, AS0011, PA0010, PA0011, and PA0012 (including substudy DV0004). Supplemental validation was performed to establish additional freeze/thaw stability, drug tolerance assessment in the confirmatory tier, and additional positive control qualification.

Although the same assay was validated at 2 CROs (ADAb-4 and ADAb-5), the ADAb samples within a clinical study were analysed by only 1 laboratory. In addition, all samples from the pivotal Phase 3 studies were analysed using the same method (i.e. ADAb-5) allowing for the data to be pooled. Therefore, no formal reproducibility evaluation was performed to establish full comparison of the data produced by each laboratory as the samples within a study were only evaluated by one laboratory. However, as demonstrated in Table 4, the assay performance characteristics between both laboratories are comparable.

Statistical assessment of the cut points was performed according to the white paper of Devanarayan et al, 2017 and screening, confirmatory, and titre cut points were determined. Statistical evaluation was performed to evaluate study-specific false positivity rate and to compare validation cut points with those assessed in-study.

Table 4: ADAb assay life cycle information

	ADAb-1 (QBR113786QB02rep val)[a]	**ADAb-2** (NCD2781rep val)[a]	**ADAb-3** (NCD3064rep val)[a]	**ADAb-4** (NCD3095rep)[a]	**ADAb-5** (NCD3207rep[a], NCD3207rep add1, NCD3207rep add3)
Analyte	Anti-drug antibodies				
Method ID	MW13659	MWI3873	MWI3986	Method 8200	ICDIM 383
Validation ID	Validation of an ECL immunoassay for the detection of anti-UCB4940 antibodies in human plasma	Validation of an ECL immunoassay for the detection of anti-UCB4940 antibodies in human plasma from healthy volunteers	Validation of an ECL immunoassay for the detection of anti-UCB4940 antibodies in human plasma from healthy and disease state populations (ulcerative colitis, psoriasis, psoriatic arthritis and rheumatoid arthritis)	Re-validation of an ADAb method for the determination of UCB4940 antibodies in human plasma in healthy individuals using the MSD platform	Validation of an MSD-ECL method for the detection of anti-UCB4940 antibodies in human plasma
Validation type	Full validation	Full validation	Full validation	Full validation	Full validation
Tiered analysis approach	Screening, confirmatory	Screening, confirmation, titration (end-point titers)	Screening, confirmation, titration (end-point titers)	Screening, confirmation, titration (end-point titers)	Screening, confirmation, titration (interpolated titers)
Platform	ECL MSD Sector Imager 6000	ECL MSD Sector Imager 6000	ECL MSD Sector Imager 600 and 6000	ECL MSD Sector Imager 600	ECL MSD Sector S 600
Assay Format	Homogeneous Bridging Assay	Semi-homogeneous Bridging Assay	Homogeneous Bridging Assay	Homogeneous Bridging Assay	Homogeneous Bridging Assay
Sample pre-treatment	No	No	Acid dissociation (50mM glycine HCl)	Acid dissociation (300mM acetic acid [pH3] for 1h)	Acid dissociation (300mM acetic acid [pH3] for 1h)
Capture reagent	Biotinylated BKZ 0.25µg/mL (MasterMix concentration)	Biotinylated BKZ 0.5µg/mL (MasterMix concentration)	Biotinylated BKZ 1.5µg/mL (MasterMix concentration)	Biotinylated BKZ 1µg/mL (MasterMix concentration)	Biotinylated BKZ 1µg/mL (MasterMix concentration)
Detection reagent	Sulfo-tagged BKZ 0.25µg/mL (MasterMix concentration)	Sulfo-tagged BKZ 0.25µg/mL (MasterMix concentration)	Sulfo-tagged BKZ 0.5µg/mL (MasterMix concentration)	Sulfo-tagged BKZ 3µg/mL (MasterMix concentration)	Sulfo-tagged BKZ 3µg/mL (MasterMix concentration)
Positive control	Anti-UCB4940 idiotypic monoclonal antibody (CA182-01878.0_P42)	Anti-UCB4940 idiotypic monoclonal antibody (CA182-01878.0_P42)	Anti-UCB4940 idiotypic monoclonal antibody (anti-UCB4940 idiotype CA182-01884.0_P42 and CA182_01878.0_P42)	Anti-UCB4940 idiotypic monoclonal antibody (anti-UCB4940 idiotype CA182-01884.0_P42)	Anti-UCB4940 idiotypic monoclonal antibody (anti-UCB4940 idiotype CA182-01884.0_P42)
Negative control	Pooled healthy lithium heparin plasma	Pooled healthy lithium heparin plasma	Pooled healthy lithium heparin plasma	Pooled healthy lithium heparin plasma	Pooled healthy lithium heparin plasma
Matrix	Lithium heparin plasma	Lithium heparin plasma	Lithium heparin plasma	Lithium heparin plasma	Lithium heparin plasma
MRD	1:10	1:5	1:10	1:100	1:100
Sensitivity	290ng/mL (95% CI; screening assay)	350ng/mL (screening assay)	24.4 - 50ng/mL (95% CI; screening and confirmatory assay)	Screening assay: 10.77ng/mL (95% CI); 16.9ng/mL (99% CI) Confirmatory assay: 27.08ng/mL (95% CI); 39.0ng/mL (99% CI)	Screening assay: 15.7ng/mL Confirmatory assay: 13.7ng/mL

	ADAb-1 (QBR113786QB02rep val)[a]	ADAb-2 (NCD2781rep val)[a]	ADAb-3 (NCD3064rep val)[a]	ADAb-4 (NCD3095rep)[a]	ADAb-5 (NCD3207rep[a], NCD3207rep add1, NCD3207rep add3)
Drug tolerance	500ng/mL PC: ≤12.5µg/mL BKZ 7500ng/mL PC: ≥100µg/mL BKZ	350ng/mL PC: ≤5µg/mL BKZ 7500ng/mL PC: 50µg/mL BKZ	100ng/mL PC: 10µg/mL BKZ 250ng/mL PC: 15 - 25µg/mL BKZ	Screening: 16.9ng/mL PC: 100µg/mL BKZ; 100ng/mL PC: 200µg/mL BKZ Confirmatory: 39.0ng/mL PC: 200µg/mL BKZ; 100ng/mL PC: 200µg/mL BKZ	Screening: 28.6ng/mL PC: 24.3µg/mL BKZ; 100ng/mL PC: 200µg/mL BKZ Confirmatory: 28.6ng/mL PC: 100µg/mL BKZ; 100ng/mL PC: 200µg/mL BKZ
Target tolerance	ND	ND	ND	At ≤4000pg/mL target no effect observed in absence of PC (both screening and confirmatory tier)	28.6ng/mL PC: ≥4000pg/mL target 75,000ng/mL PC: ≥4000pg/mL target In absence of PC no false positive responses observed.
Used in clinical studies	PA0007		AS0008, AS0009, PA0008, PA0009	AS0013	PS0015, UP0067, AS0010, AS0011, PA0010, PA0011, PA0012 (including substudy DV0004)

ADAb=anti-drug antibody; BKZ=bimekizumab; CI=confidence interval; ECL=electrochemiluminescent; ID=identification; ISI=Integrated Summary of Immunogenicity; MRD=minimum required dilution; MSD=Meso Scale Discovery; ND=not determined; PC=positive control; PSO=psoriasis; Sector S=sector imager; UCB4940=bimekizumab

Determination of neutralising antibodies

The competitive ligand binding assay (CLBA) method comprised 2 NAb assays, with specificity for IL-17AA and IL-17FF, respectively. In these NAb assays, ADAb compete with labelled target to bind to the drug. Neutralisation of IL-17AA and IL-17FF binding to the drug is assessed in each respective assay separately. Both NAb assays are electrochemiluminescence (ECL)-based assays using solid-phase extraction with acid dissociation (SPEAD) sample pre-treatment. To remove any interfering drug potentially present in the samples, a 2-step acid dissociation was utilised. In the first step, samples were acidified to dissociate any potential NAb immune complexes. Biotinylated drug to compete with unlabelled drug was added to the acidic solution. The acidic solution was neutralised directly on a streptavidin-coated high bind plate to capture the biotinylated drug/NAb complexes. After incubation and washing, the ADAb/NAb present were dissociated from the biotinylated drug through acidic conditions (second acid step; NAb elution). In parallel, streptavidin MSD plates were blocked and coated with a defined amount of biotinylated drug. Acidified supernatants were split in halves and transferred to the precoated MSD plates for detection with target IL-17AA or IL-17FF, respectively. The acidic supernatants were directly neutralised on the respective MSD plates and incubated. Detection of the resulting drug/NAb immune complexes was achieved through competition of the NAb with labelled IL-17AA or IL-17FF, respectively. Bound target was detected by ECL using an MSD reader. In these CLBAs, potential NAb present in the samples will concentration-dependently reduce the ECL signal. This approach assured sufficient drug and target tolerance to allow for an accurate determination of NAb levels in clinical samples. In addition, specificity testing using an UCB4940 framework control human IgG1 antibody consisting of drug identical framework and unrelated complementarity determining regions, demonstrated that the current CLBA assays are specific for determining the neutralising capacity of bimekizumab. The neutralising antibody assays are only composed of a screening tier.

The NAb assays were developed and validated. In addition, based on evaluation from the PSO submission studies, the NAb assays were partially revalidated to verify the assay sensitivity and the suitability of the assay controls. Assay characteristics and detailed summaries of the (re-) validation parameters were submitted by the MAH. The NAb methods were used in support of the Phase 3 studies PS0015, AS0010, AS0011, PA0010, PA0011, and PA0012.

Bioavailability

No additional bioavailability or bioequivalence studies have been conducted to specifically support the axSpA indication. However, additional considerations for the axSpA (and PsA) indications regarding bioavailability are outlined below.

Study UP0067

UP0067 was a Phase 1, randomised, double-blind, placebo-controlled single dose study to evaluate the PK, safety, and tolerability of bimekizumab in healthy Chinese volunteers. A total of 36 healthy Chinese study participants were randomised and enrolled to 1 of 2 cohorts, bimekizumab 160mg (N=18) or 320mg (N=18). Within each cohort, study participants were randomised in a 2:1 ratio to receive either bimekizumab (N=12) or placebo (N=6) given by subcutaneous (sc) injection. The Pharmacokinetic Per Protocol Set (PK-PPS) consisted of all randomised study participants included in the safety set (SS) who also completed the study without any important protocol deviations (IPDs) with respect to PK, and had plasma concentration data to calculate reliable estimates for the PK variables; 18 study participants were included in the PK-PPS.

The primary objective of this study was to evaluate the PK profile of bimekizumab following a single sc dose administered in healthy Chinese study participants. The PK sampling time-points were as follows: predose, 5h, 24h, 48h, 96h, and at Days 7, 14, 21, 28, 42, 56, 70, 84, 112, and 140.

As shown in Table 5, increasing bimekizumab dose from 160mg to 320mg led to a proportional increase in bimekizumab exposure. For both dose groups, the AUCextr% were <6%, indicating the PK sampling captured the terminal elimination phase of bimekizumab well. Across the dose range tested, the tmax, Vz/F, t1/2, and CL/F were consistent, with no dose dependency observed.

Table 5: Pharmacokinetics parameters of bimekizumab (PK-PPS)

Parameter (unit)	Statistic	BKZ 160mg N=7	BKZ 320mg N=11
AUC (day*µg/mL)	GeoMean	511.7	998.5
	GeoCV (%)	13.9	23.7
$AUC_{(0-t)}$ (day*µg/mL)	GeoMean	495.7	974.1
	GeoCV (%)	14.6	23.6
$AUC_{(0-14)}$ (day*µg/mL)	GeoMean	169.2	321.8
	GeoCV (%)	20.7	23.8
AUCextr (%)	GeoMean	3.022	2.143
	GeoCV (%)	30.2	54.3
C_{max} (µg/mL)	GeoMean	14.97	28.52
	GeoCV (%)	21.6	24.0
t_{max} (day)	Median	6.015	6.012
	Min, max	4.03, 13.1	3.99, 13.1
$t_{1/2}$ (day)	GeoMean	21.88	23.37
	GeoCV (%)	8.8	16.9
V_z/F (L)	GeoMean	9.869	10.81
	GeoCV (%)	16.2	20.1
CL/F (L/day)	GeoMean	0.3127	0.3205
	GeoCV (%)	13.9	23.7

AUC=area under the plasma concentration-time curve from time 0 to infinity; $AUC_{(0-t)}$=area under the plasma concentration-time curve from 0 to last quantifiable concentration; $AUC_{(0\text{-}14\ days)}$=area under the plasma concentration-time curve over the first 14 days; AUCextr%=area under the plasma concentration-time curve extrapolated from the time of last quantifiable concentration to infinity; BKZ=bimekizumab; CL/F=apparent total body clearance; C_{max}=maximum plasma concentration; CV=coefficient of variation; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; max=maximum; min=minimum; PK-PPS=Pharmacokinetic Per-Protocol Set; $t_{½}$=apparent terminal half-life; t_{max}=time of occurrence of C_{max}; V_z/F=apparent volume of distribution

Following body weight-normalisation, dose proportionality between the two groups was maintained (Table 6).

Table 6: Body weight-normalised pharmacokinetic parameters of bimekizumab (PK-PPS)

Parameter (unit)	Statistic	BKZ 160mg N=7	BKZ 320mg N=11
AUC/BW (day*µg/mL/70kg)	GeoMean	466.7	921.3
	GeoCV (%)	18.8	26.6
$AUC_{(0-t)}$/BW (day*µg/mL/70kg)	GeoMean	452.0	898.8
	GeoCV (%)	19.3	26.2
C_{max}/BW (µg/mL/70kg)	GeoMean	13.65	26.31
	GeoCV (%)	26.1	31.4

AUC/BW=body weight-normalized area under the plasma concentration-time curve from time 0 to infinity; $AUC_{(0-t)}$/BW=body weight-normalized area under the plasma concentration-time curve from 0 to last quantifiable concentration; BKZ=bimekizumab; C_{max}/BW=body weight-normalized maximum plasma concentration; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; PK-PPS=Pharmacokinetic Per-Protocol Set

Device use study (DV0004)

DV0004 was a Phase 3, multicenter, open-label, randomised, non-comparator, North America and Europe substudy to PA0012. PA0012 is an ongoing study evaluating the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with PsA who completed 1 of the feeder studies (PA0010 or PA0011).

In the DV0004 substudy, participants were randomly assigned to 1 of the 2 self-injecting device presentations (ie, 1mL bimekizumab auto-injector [bimekizumab-AI-1mL] and 1mL bimekizumab safety syringe [bimekizumab-SS-1mL]) and self-administered bimekizumab at Baseline and at Week 4 in the thigh or abdomen. Within each device presentation arm, study participants were divided into tertiles by BMI. Bimekizumab trough concentrations were collected at baseline, Week 4 and Week 8.

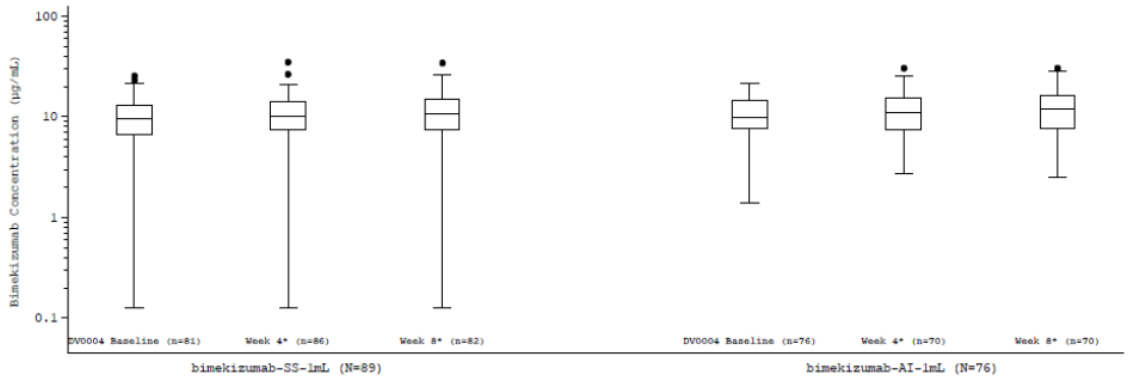
Data supporting self-injection

The GeoMean trough concentrations at Week 4 and Week 8 (associated with self-injection at the previous visits using the bimekizumab-SS-1mL and bimekizumab-AI-1m device presentations) were similar to those at Baseline (associated with the last injection by study personnel in the feeder study using the 1mL PFS). Summary statistics and boxplots of trough bimekizumab concentrations by visit and by device presentation are presented below:

Table 7: Trough bimekizumab plasma concentration (µg/mL) by visit and device presentation (PK-PPS-s and PK-PPS-a)

Visit	Statistic	BKZ-SS-1mL BKZ 160mg Q4W N=89	BKZ-AI-1mL BKZ 160mg Q4W N=76
Baseline	n	81	76
	GeoMean	9.028	9.863
	GeoCV (%)	78.2	49.9
Week 4 [a]	n	86	70
	GeoMean	9.123	10.376
	GeoCV (%)	87.6	54.9
Week 8 [a]	n	82	70
	GeoMean	9.924	10.889
	GeoCV (%)	77.5	56.1

BKZ=bimekizumab; BKZ-AI-1mL=1mL bimekizumab auto-injector; BKZ-SS-1mL=1mL bimekizumab safety syringe; BLQ=below limit of quantification; CV=coefficient of variation; GeoCV=geometric CV; GeoMean=geometric mean; LLOQ=lower limit of quantification; PK PPS-a=BKZ-AI-1mL Pharmacokinetic Per Protocol Set; PK-PPS-s=BKZ-SS-1mL Pharmacokinetics Per Protocol Set; Q4W=every 4 weeks



BKZ=bimekizumab; BKZ-SS-1mL=1mL bimekizumab safety syringe; BLQ=below limit of quantification; CV=coefficient of variation; LLOQ=lower limit of quantification; PK-PPS-a=BKZ-AI-1mL Pharmacokinetic Per Protocol Set; PK-PPS-s=BKZ-SS-1mL Pharmacokinetic Per Protocol Set; Q4W=every 4 weeks; SD=standard deviation

Figure 4: Boxplot of bimekizumab plasma concentration by visit and device for the bimekizumab-SS-1mL group and the bimekizumab-AI-1mL group (PK-PPS-s and PK-PPS-a)

Data supporting sites of injection

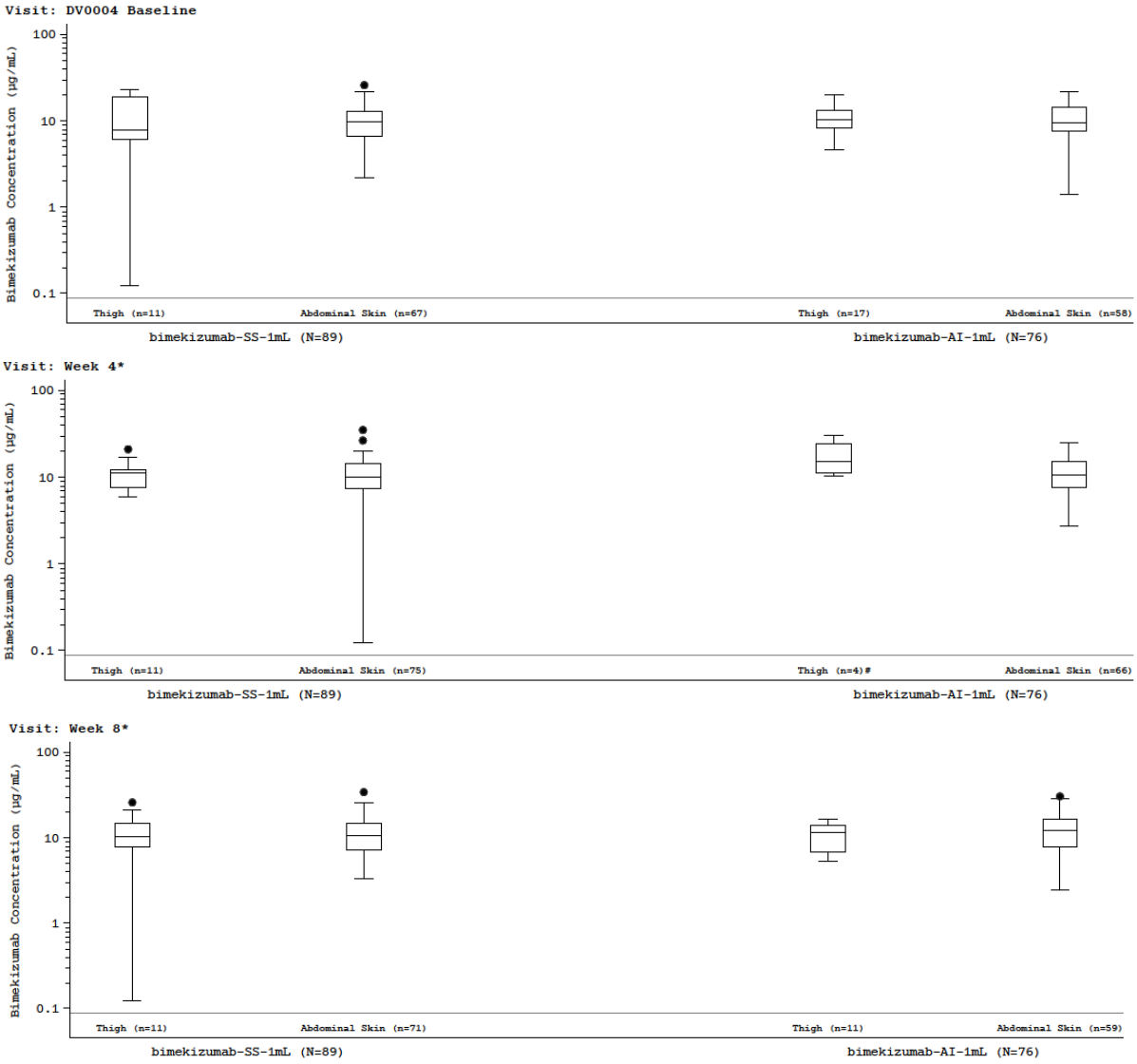
Within both the bimekizumab-SS-1mL and bimekizumab-AI-1mL groups, the trough bimekizumab concentrations between injection sites tended to be similar and the ranges overlapped across all 3 visits, regardless of whether the previous dose had been self-administered or given by study personnel.

However, the low number of study participants who had injections in the thigh limits interpretation. Summary statistics and boxplots of trough bimekizumab concentration by injection site after self-injection or injection by study personnel are provided below:

Table 8: Trough bimekizumab plasma concentration (µg/mL) by injection site after self-injection or injection by study personnel (PK-PPS-s and PK-PPS-a)

Visit	Injection site [a]	Statistic	BKZ-SS-1mL BKZ 160mg Q4W N=89	BKZ-AI-1mL BKZ 160mg Q4W N=76
Baseline (after injection by study personnel from feeder study) [b]	Abdomen	n	67	58
		GeoMean	9.437	9.728
		GeoCV (%)	52.0	53.1
	Thigh	n	11	17
		GeoMean	7.376	10.255
		GeoCV (%)	272.0	41.0
Week 4 (after self-injection at Baseline)	Abdomen	n	75	66
		GeoMean	8.918	10.099
		GeoCV (%)	93.7	54.0
	Thigh	n	11	4
		GeoMean	10.654	16.233
		GeoCV (%)	39.6	51.5
Week 8 (after self-injection at Week 4)	Abdomen	n	71	59
		GeoMean	10.335	11.020
		GeoCV (%)	52.4	58.6
	Thigh	n	11	11
		GeoMean	7.639	10.213
		GeoCV (%)	257.2	43.5

BKZ=bimekizumab; BKZ-AI-1mL=1mL bimekizumab auto-injector; BKZ-SS-1mL=1mL bimekizumab safety syringe; BLQ=below limit of quantification; CV=coefficient of variation; GeoCV=geometric CV; GeoMean=geometric mean; LLOQ=lower limit of quantification; PK-PPS-a=BKZ-AI-1mL Pharmacokinetic Per Protocol Set; PK-PPS-s=BKZ-SS-1mL Pharmacokinetics Per Protocol Set; Q4W=every 4 weeks



bimekizumab-AI-1mL=1mL bimekizumab auto-injector. bimekizumab-SS-1mL=1mL bimekizumab safety syringe, BKZ=bimekizumab, BLQ=below level of quantification, CV=coefficient of variation, LLOQ=lower level of quantification, SD=standard deviation.
Note: The length of the box represents the interquartile range (the distance between the 25th and 75th percentiles). The symbol in the box interior represents the group mean. The horizontal line in the box interior represents the group median. The vertical lines
(called whiskers) issuing from the box extend to the group minimum and maximum values Values BLQ are replaced by the value of LLOQ/2=0.125µg/ml in the calculations of means, SDs and CVs.

Figure 5: Boxplot of plasma concentration (µg/mL) by visit and injection site analysis set (PK-PPS)

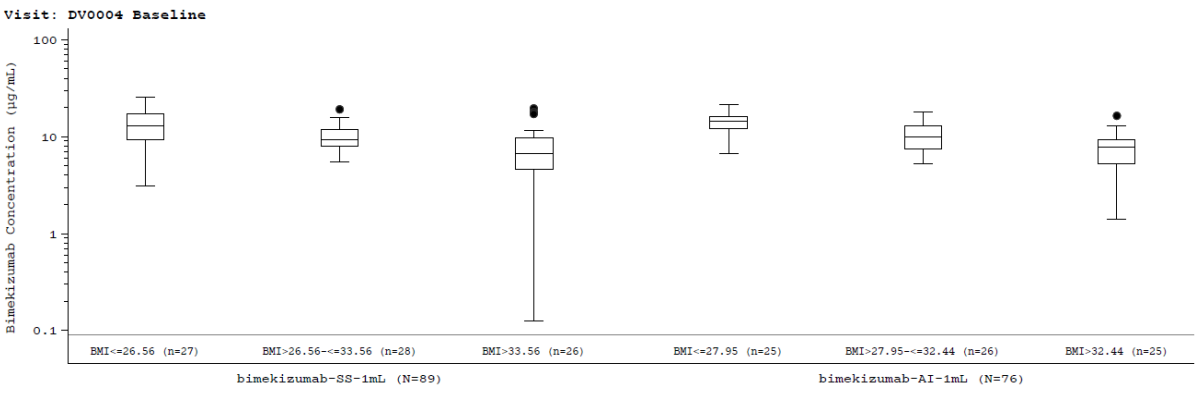
Data supporting use across different BMI tertiles

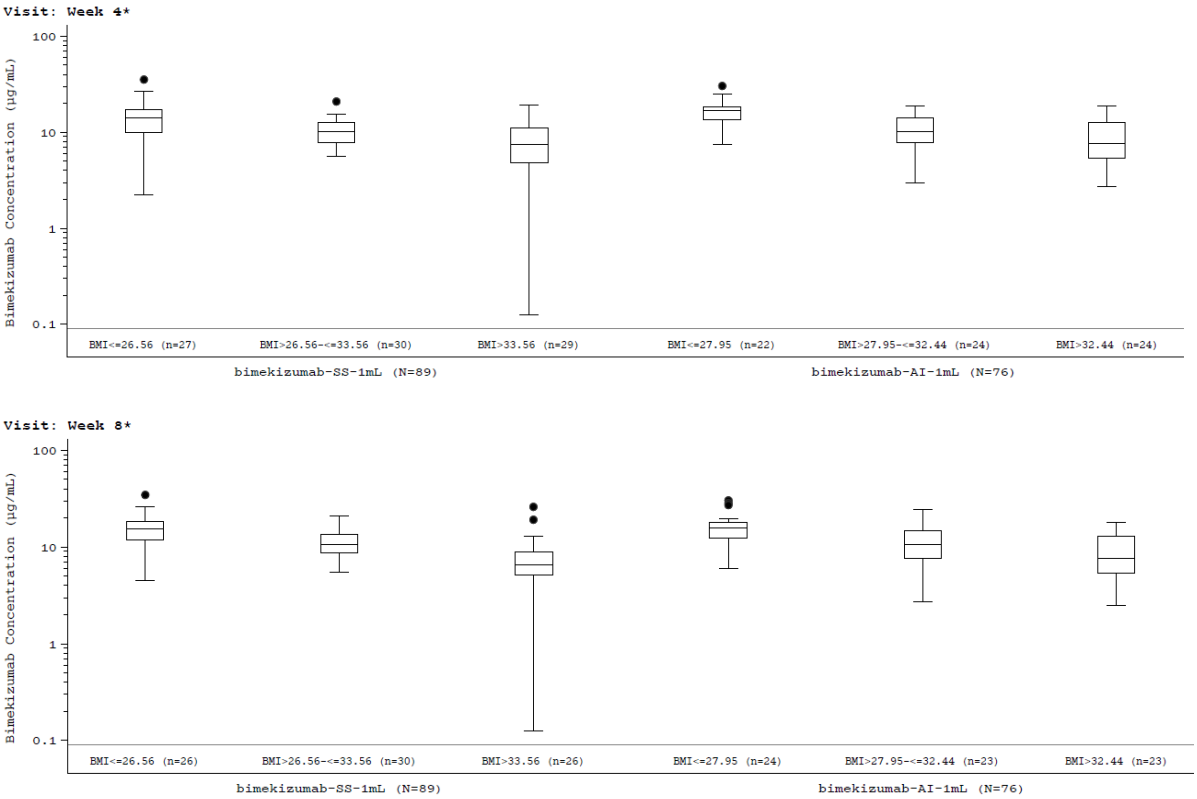
In both the bimekizumab-SS-1mL and bimekizumab-AI-1mL groups, trough concentrations decreased as BMI increased with the lowest geometric mean trough bimekizumab plasma concentrations generally observed for study participants in the highest BMI tertile. Within each tertile, the trough bimekizumab concentrations were reasonably similar regardless of whether the previous dose was self-administered or administered by the study personnel. Summary statistics and boxplots of bimekizumab plasma concentration by BMI tertile after self-injection or injection by study personnel are presented for each device presentation below:

Table 9: Trough bimekizumab plasma concentration (µg/mL) by BMI tertile after self-injection or injection by study personnel (PK-PPS-s and PK-PPS-a)

Visit	BMI (kg/m^2)	Statistic	BKZ-SS-1mL BKZ 160mg Q4W N=89	BKZ-AI-1mL BKZ 160mg Q4W N=76
Baseline (after injection by study personnel from feeder study)	BMI≤t1	n	27	25
		GeoMean	12.382	13.714
		GeoCV (%)	53.6	29.9
	t1<BMI≤t2	n	28	26
		GeoMean	9.574	9.977
		GeoCV (%)	33.4	33.7
	BMI>t2	n	26	25
		GeoMean	6.105	7.008
		GeoCV (%)	118.8	54.9
Week 4 (after self-injection at Baseline)	BMI≤t1	n	27	22
		GeoMean	12.915	15.387
		GeoCV (%)	57.0	33.3
	t1<BMI≤t2	n	30	24
		GeoMean	10.053	9.613
		GeoCV (%)	32.1	46.5
	BMI>t2	n	29	24
		GeoMean	5.970	7.805
		GeoCV (%)	136.6	54.6
Week 8 (after self-injection at Week 4)	BMI≤t1	n	26	24
		GeoMean	14.456	15.169
		GeoCV (%)	43.9	38.6
	t1<BMI≤t2	n	30	23
		GeoMean	10.704	10.211
		GeoCV (%)	31.7	52.3
	BMI>t2	n	26	23
		GeoMean	6.243	8.216
		GeoCV (%)	116.8	55.0

BKZ=bimekizumab; BKZ-AI-1mL=1mL bimekizumab auto-injector; BKZ-SS-1mL=1mL bimekizumab safety syringe; BLQ=below limit of quantification; BMI=body mass index; CV=coefficient of variation; GeoCV=geometric CV; GeoMean=geometric mean; LLOQ=lower limit of quantification; PK-PPS-s=BKZ-SS-1mL Pharmacokinetics Per Protocol Set; Q4W=every 4 weeks





bimekizumab-AI-1mL=1mL bimekizumab auto-injector. bimekizumab-SS-1mL=1mL bimekizumab safety syringe, BKZ=bimekizumab, BLQ=below level of quantification, CV=coefficient of variation, LLOQ=lower level of quantification, SD=standard deviation.
Note: The length of the box represents the interquartile range (the distance between the 25th and 75th percentiles). The symbol in the box interior represents the group mean. The horizontal line in the box interior represents the group median. The vertical lines (called whiskers) issuing from the box extend to the group minimum and maximum values Values BLQ are replaced by the value of LLOQ/2=0.125µg/ml in the calculations of means, SDs and CVs.

Figure 6: Boxplot of plasma concentration (µg/mL) by visit and BMI tertile (PK-PPS)

Pharmacokinetics in Target Population

Phase 2 Studies

Study AS0008

AS0008 was a Phase 2b, multicenter, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy, PK, PD, and safety of bimekizumab in adult study participants with active axSpA. The inclusion criteria were designed to ensure all study participants had moderate-to-severe active axSpA. This study included 4 periods: a Screening Period (4 weeks), a Double-blind Period (12 weeks), a Dose-blind Period (36 weeks), and a Safety Follow-up (SFU) Visit (20 weeks after the last dose).

During the Double-blind Period, a total of 303 study participants were randomised 1:1:1:1:1 (stratified by region and prior tumor necrosis factor [TNF] inhibitor exposure) to five groups: placebo (n=60), or to receive bimekizumab subcutaneously every 4 weeks (Q4W) at doses of 16mg (n=61), 64mg (n=61) 160mg (n=60), or 320mg (n=61). Blood samples for bimekizumab plasma concentrations were taken at Baseline, and Weeks 1, 2, 4, 8, and 12.

After the 12-week Double-blind Period, 296 study participants entered the 36-week Dose-blind Period. At the Week 12 Visit, study participants were allocated to bimekizumab treatment regimens as follows; Study participants in the placebo and bimekizumab 16mg or 64mg groups were re-randomised in a 1:1 fashion to bimekizumab 160mg or bimekizumab 320mg Q4W and study participants in the bimekizumab 160mg or bimekizumab 320mg groups continued to receive their respective treatments. Blood samples

for bimekizumab plasma concentrations were taken at Baseline, and Weeks 16, 20, 24, 36, 48, and during the Safety Follow-up.

Patients may have received 1 prior TNF inhibitor.

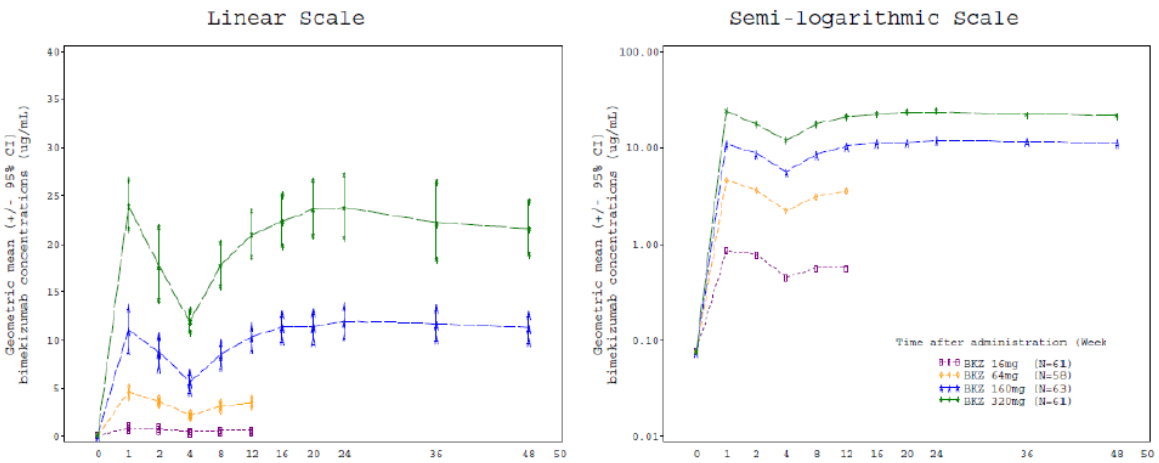
The following restrictions were applied for the biological DMARDs:

Table 10: prohibited or restricted medications and required wash-out periods prior to Baseline

Drug class	Dose	Exclusion criteria
TNF inhibitor: IFX ADA ETN GOL CZP	Any dose	For IFX, ADA, GOL, and CZP any use within the 3 months prior to the Baseline Visit. For ETN, use within the 28 days prior to the Baseline Visit. This applied to biosimilar versions of any TNF inhibitor
Any non-TNF biologic medications	Any dose	Any exposure history.

ADA=adalimumab; COX-2=cyclooxygenase-2; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; LEF=leflunomide; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; SSZ=sulfasalazine; TNF=tumor necrosis factor

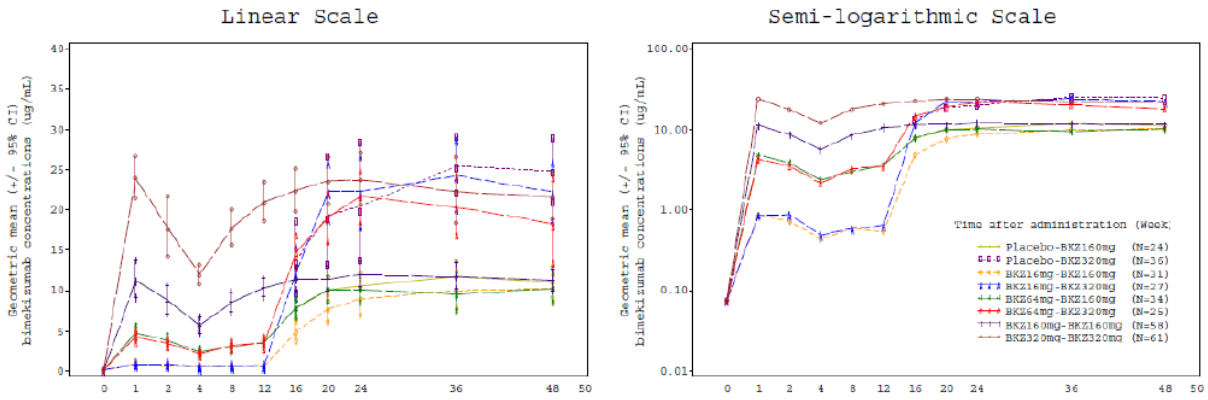
Figure 7 shows a summary of bimekizumab plasma concentrations by visit and by treatment group for the PK-PPS. Trough samples collected from Week 4 onwards are not comparable to Weeks 1 and 2, which were post-dose samples. Geometric mean plasma bimekizumab concentrations increased in a dose proportional manner and the placebo group levels were BLQ for all samples up to Week 12. For the 160mg and 320mg groups (who continued on the same dose after week 12), steady state was achieved between Week 16 and Week 20.



BKZ=bimekizumab; CI=confidence interval; PK-PPS=Pharmacokinetic Per-Protocol Set

Figure 7: Bimekizumab concentrations (µg/mL) by visit (PK-PPS)

Figure 8 shows a summary plasma concentrations of bimekizumab by visit for the overall study and by treatment group for the subset of study participants in the Double Blind Set (DBS) who were part of the PK-PPS. For study participants initially randomised to placebo, bimekizumab 16mg, or bimekizumab 64mg, after being rerandomised to bimekizumab 160mg or 320mg at Week 12, geometric mean plasma bimekizumab concentrations increased and were similar at Week 20 to those of study participants initially randomised to bimekizumab 160mg or bimekizumab 320mg, and remained similar through Week 48.



BKZ=bimekizumab; BLQ=below the level of quantification; CI=confidence interval; CV=coefficient of variation; DBS=Dose-blind Set; LLOQ=lower limit of quantification; max=maxium; min=minimum; PK-PPS=Pharmacokinetics Per-Protocol Set; SD=standard deviation

Figure 8: Bimekizumab concentrations (µg/mL) by week (DBS*)

Study AS0009

AS0009 is a multicenter Open-Label Extension (OLE) study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult study participants with axSpA who completed the Phase 2b study AS0008. The OLE study assessed the safety, tolerability, and efficacy of bimekizumab for a period of up to 208 weeks (~4 years). The data available for this assessment is based on an interim analysis after the final study participant had reached Week 108.

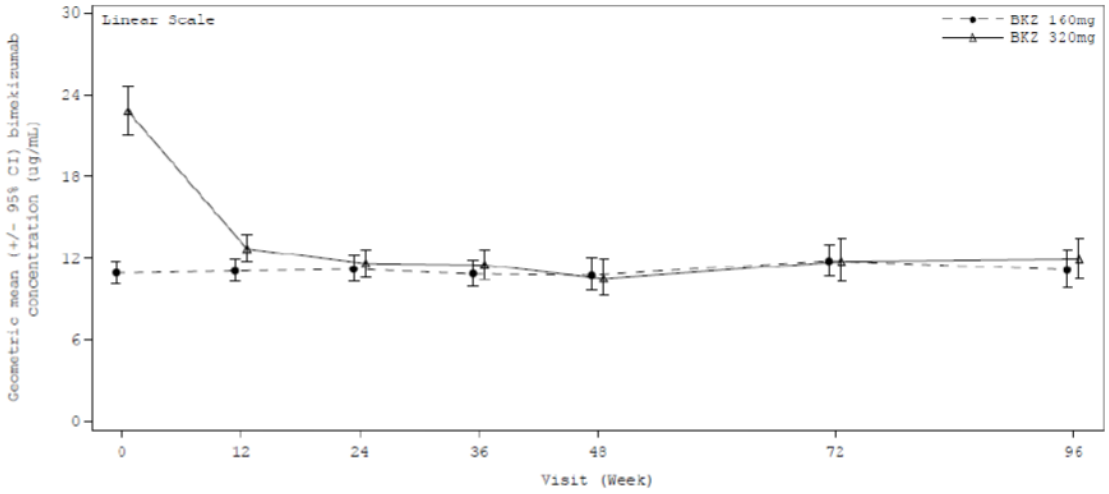
At the time of completion of AS0008, participants were receiving 1 of 2 doses of bimekizumab; 160mg Q4W or 320mg Q4W. All participants in the AS0009 OLE study received bimekizumab 160mg Q4W, giving two groups Bimekizumab 160mg→160mg and Bimekizumab 320mg→160mg. A total of 255 participants started the study and 31 participants were discontinued on or before Week 108. Blood samples for bimekizumab plasma concentrations were taken at the Entry Visit (EV) (this was also the final visit of AS0008), and Weeks 12, 24, 36, 48, 72, and 96.

The following restrictions were applied for the biological DMARDs:

Table 11: prohibited or restricted medications

Drug class	Dose	Comments
TNF inhibitors -infliximab -adalimumab -etanercept -golimumab -certolizumab pegol	Any dose	This applies to biosimilar versions of any TNF inhibitor.
Any nonTNF biologic medications	Any dose	Any exposure history is prohibited.

A summary of the plasma concentrations of bimekizumab by visit is presented in Figure 9 below. Overall, the geometric mean plasma bimekizumab concentration remained relatively constant throughout AS0009 for participants who had received Bimekizumab 160mg in the AS008 study, indicating steady state had been achieved. Participants who received Bimekizumab 320mg in AS0008 showed plasma concentrations of bimekizumab approximately 2 times higher than the 160mg group at the EV, which decreased to steady state levels by Week 24.



BKZ=bimekizumab; BLQ=below limit of quantification; CI=confidence interval; LLOQ=lower limit of quantification; SS=Safety Set

Figure 9: Bimekizumab plasma concentration (SS)

Study AS0013

AS0013 was a multicenter, Phase 2a, randomised, study participant-blind, and investigator-blind, parallel-group study to evaluate the efficacy and safety of bimekizumab compared to certolizumab pegol in adult study participants with active adult-onset axSpA. The study period included a Screening Period, a Treatment Period (Week 0 to Week 12) and a Treatment Extension Period (Week 12 to 48).

Eligible study participants were randomised in a 2:1 ratio to receive 1 of 2 investigational medicinal products (IMP), either bimekizumab or certolizumab pegol. During the Treatment Period, study participants received Bimekizumab 160mg SC Q2W from Week 0 through Week 10 (in addition the participants received 1 placebo injection at Baseline (Visit 2), Week 2 (Visit 3), and Week 4 (Visit 4) in order to have maintained the blind for the certolizumab pegol), or Certolizumab pegol 400mg sc Q2W at Weeks 0, 2, and 4 (loading dose) followed by certolizumab pegol 200mg sc Q2W in Weeks 6 to 10. For the 36 Week Treatment Extension Period participants remained on the same IMP at a Q4W dosing schedule; bimekizumab 320mg sc every 4 weeks (Q4W) from Week 12 to Week 44 or certolizumab pegol 400mg Q4W from Week 12 to Week 44. Blood samples for PK were collected at Baseline, Week 4, Week 12, Week 24, Week 36, Week 48, and during the Safety Follow-up at Week 64.

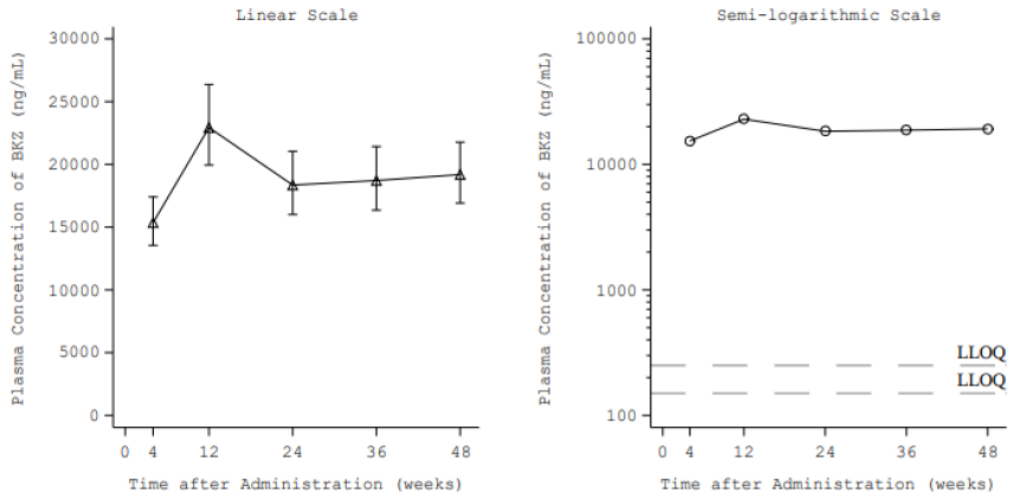
Patients may have received 1 prior TNF antagonist.

The following restrictions were applied for the biological DMARDs:

Drug class	Dose	Exclusion criteria
TNFα antagonists -infliximab -adalimumab -etanercept -golimumab -certolizumab pegol	Any dose	For IFX, ADA, and GOL, any use within the 12 weeks prior to the Baseline Visit. For ETN, use within the 28 days prior to the Baseline Visit. For CZP, any previous use. This applied to biosimilar versions of any TNF inhibitors.
Any non-TNF biologic medications	Any dose	Any exposure history.

ADA=adalimumab; COX-2=cyclooxygenase 2; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; im=intramuscular; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; sc=subcutaneous; SSZ=sulfasalazine; TNF=tumor necrosis factor

A summary of bimekizumab plasma concentrations for those who received bimekizumab is presented in Figure 10. During the Treatment Period, when bimekizumab 160mg was administered Q2W from Week 0 to Week 10, the geometric mean trough concentration increased from Week 4 to Week 12. During the Treatment Extension Period, when bimekizumab 320mg was administered Q4W from Week 12 to Week 44, the trough concentration of bimekizumab decreased through Week 24 and then remained relatively stable at Week 36 and Week 48.



BKZ=bimekizumab; CI=confidence interval; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set

Figure 10: Geometric mean (95% CI) plasma concentrations of bimekizumab by scheduled time (PK-PPS)

Phase 3 Studies

Study AS0010

AS0010 is a Phase 3 randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab compared with placebo in participants with active nonradiographic axial spondyloarthritis. The study period for this report includes up to a 5-week Screening period, through Week 24 of the treatment period, with placebo participants switching to bimekizumab at the end of Week 16 of the treatment period.

Eligible study participants were randomised 1:1 to receive 1 of 2 treatments (bimekizumab 160mg sc Q4W or placebo sc Q4W), and remain on allowable background medication, until Week 16. Thereafter, study participants randomised to bimekizumab 160mg Q4W remained on their randomised dose and study participants randomised to placebo were reallocated to receive bimekizumab 160mg Q4W after all Week 16 assessments had been completed. Blood samples for bimekizumab plasma concentrations were taken at Baseline, and Weeks 2, 4, 8, 12, 16, 20, 24 for the study period in this report.

Patients may have received 1 prior TNF antagonist.

The applicant has planned to further collect PK samples at weeks 36, 52 and at the end of SFU period.

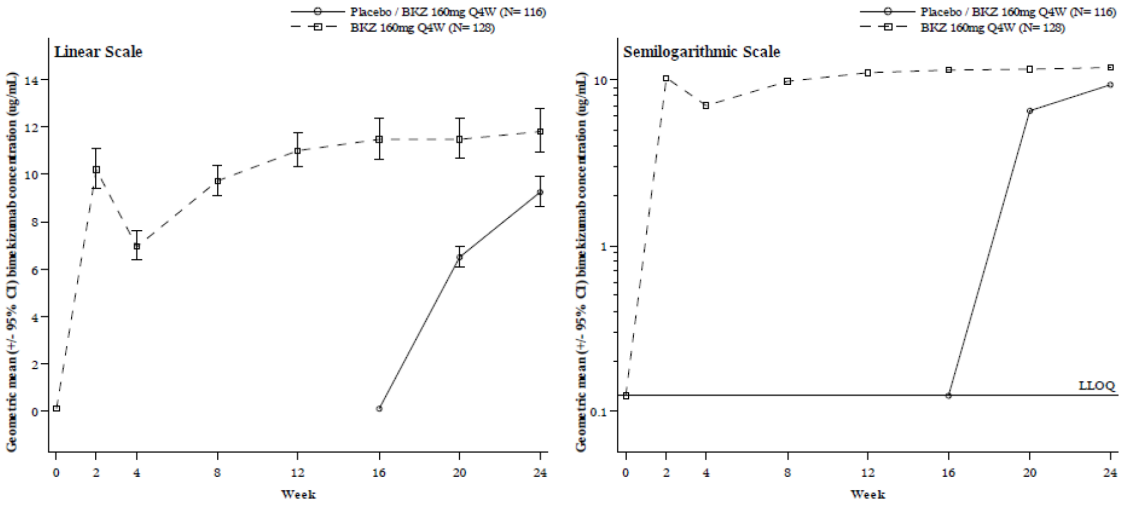
The following restrictions were applied for the biological DMARDs:

Drug class/dose	Exclusion criteria	Study visits/during the study	Nonbiologic rescue therapy as add-on therapy to bimekizumab from Week 20 or later[a]
Biologic DMARDs			
TNFα inhibitors: • IFX • GOL • CZP • ADA • ETN • Biosimilar versions of any TNFα inhibitor	For IFX, ADA, GOL, and CZP, any use within the 12 weeks prior to the BL Visit For ETN, used within the 28 days prior to the BL Visit Any use of >1 TNFα in the history Study participants not meeting Inclusion Criterion #12	**Prohibited**	Not applicable
Other biologics: • Abatacept • Alefacept • Efalizumab • Guselkumab • Sarilumab • Sirukumab • Tocilizumab • Others in development targeting IL-6 or IL-6R	Any use within 12 weeks prior to BL	**Prohibited**	Not applicable
• Ustekinumab	Any use within 24 weeks prior to BL	**Prohibited**	Not applicable
• Tildrakizumab	Any use within 4 months prior to BL	**Prohibited**	Not applicable
• Risankizumab	Any use within 5 months prior to BL	**Prohibited**	Not applicable
• Briakinumab	Any use within 6 months prior to BL	**Prohibited**	Not applicable
• Rituximab (incl. biosimilars), ocrelizumab	Any use within 12 months prior to BL	**Prohibited**	Not applicable
Anti-IL-17 therapy: • Bimekizumab • Secukinumab • Ixekizumab • Brodalumab • Others in development	Any exposure history	**Prohibited**	Not applicable

ADA=adalimumab; BL=Baseline; COX-2=cyclooxygenase 2; CRO=contract research organization; csARD=conventional synthetic antirheumatic drug; CZP=certolizumab pegol; DMARD=disease-modifying antirheumatic drug; ETN=etanercept; GOL=golimumab; h=hour; HCQ=hydroxychloroquine; incl=including; IFX=infliximab; IL=interleukin; JAK=Janus kinase; LEF=leflunomide; MTX=methotrexate; NSAID=nonsteroidal anti-inflammatory drug; PRN=as needed; sc=subcutaneous; SSZ=sulfasalazine; TNFα=tumor necrosis factor alpha

[a] Note: any medication not listed here for rescue therapy must have been approved by the CRO Medical Monitor prior to starting that medication.

A summary of bimekizumab plasma concentrations for the bimekizumab 160mg Q4W group and placebo by visit is presented in Figure 11. Overall, geometric mean plasma bimekizumab trough concentrations increased over time and steady state was achieved by Week 16 of dosing with bimekizumab 160mg Q4W. There was a 1.65-fold increase in geometric mean trough plasma bimekizumab concentration between Week 4 and Week 16 when steady state was reached. In the placebo/bimekizumab 160mg Q4W group, once study participants switched to bimekizumab treatment, the PK of bimekizumab followed similar trends to study participants randomized to bimekizumab 160mg Q4W at Baseline.



BKZ=bimekizumab; BLQ=below the limit of quantification; CI=confidence interval; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set; Q4W=every 4 weeks

Figure 11: Geometric mean of bimekizumab plasma concentration over time (PK-PPS)

A summary of bimekizumab plasma concentrations for the bimekizumab 160mg Q4W group at Week 16 and Week 24 is presented for the PK-PPS in the Table 12 below:

Table 12: Bimekizumab plasma concentration for the BKZ 160mg Q4W group at week 16 and week 24 (PK-PPS)

Visit (Week)	n	Geometric Mean (Geometric CV%) [Geometric 95% CI]
Visit 8 (Week 16)	123	11.4604 (43.6) [10.6380, 12.3465]
Visit 10 (Week 24)	121	11.8029 (44.8) [10.9277, 12.7482]

BKZ=bimekizumab; BLQ=below the limit of quantification; CI=confidence interval; CV=coefficient of variation; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set; Q4W=every 4 weeks
Note: Values BLQ were replaced by the value of LLOQ/2=0.125µg/mL in the calculations of CVs.
Note: CVs were only calculated if at least two-thirds of the concentrations were quantified at the respective time point and n ≥3.

The bimekizumab trough plasma concentrations observed in the Japanese study population were consistent with those in the global study population following bimekizumab 160mg Q4W treatment, and steady state bimekizumab trough concentrations were reached by Week 16 (Table 13).

Table 13: Bimekizumab plasma concentration for Japanese participants in the BKZ 160mg Q4W group at week 16 and week 24 (PK-PPS)

Visit (Week)	n	Geometric Mean (Geometric CV%) [Geometric 95% CI]
Visit 8 (Week 16)	6	14.7636 (20.0) [11.9901, 18.1785]
Visit 10 (Week 24)	6	15.6952 (17.5) [13.0853, 18.8256]

BKZ=bimekizumab; BLQ=below the limit of quantification; CI=confidence interval; CV=coefficient of variation; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set; Q4W=every 4 weeks

Study AS0011

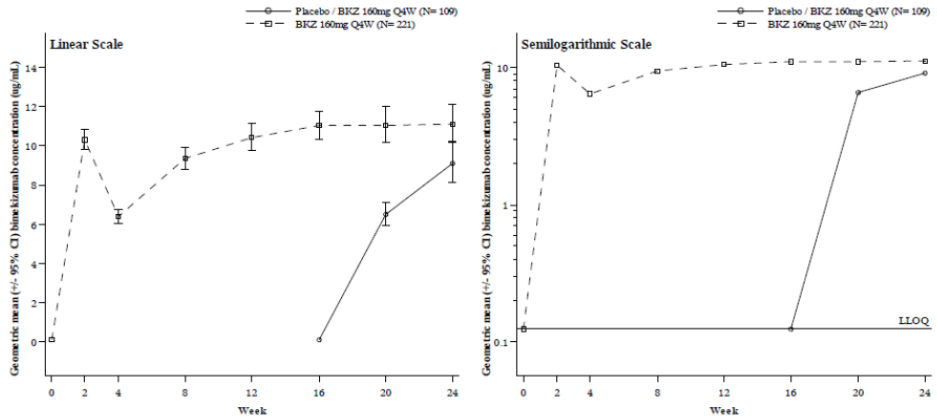
AS0011 is a multicenter, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in study participants with active ankylosing spondylitis with radiographic sacroiliitis (r-axSpA).

This study includes the following 3 periods: a Screening Period, a Treatment Period (52 weeks) consisting of a 16-week Double-Blind Treatment and subsequent Maintenance period. Eligible study participants were randomised 2:1 to receive 1 of 2 treatments (bimekizumab 160mg sc Q4W or placebo sc Q4W) and remain on their allowable background medication. At the end of the 16-week Double-Blind Treatment Period, study participants receiving placebo were re-allocated to bimekizumab treatment at Week 16 after all assessments had been completed. Blood samples for bimekizumab plasma concentrations were taken at Baseline, and Weeks 2, 4, 8, 12, 16, 20, and 24.

Patients may have received 1 prior TNF antagonist.

The MAH has planned to further collect PK samples at weeks 36, 52 and at the end of SFU period.

A summary of bimekizumab plasma concentrations for the bimekizumab 160mg Q4W group and placebo by visit is presented in Figure 12. There was a 1.72-fold increase in geometric mean trough bimekizumab concentration between Week 4 and Week 16 when steady state was reached in the bimekizumab 160mg Q4W group. In the placebo/bimekizumab 160mg Q4W group, once study participants switched to bimekizumab treatment, the PK of bimekizumab followed similar trends to study participants randomized to bimekizumab 160mg Q4W at Baseline.



BKZ=bimekizumab; BLQ=Below the limit of quantification; CI=confidence interval; LLOQ=lower limit of quantification

Figure 12: Geometric mean of BKZ plasma concentration over time (PK-PPS)

A summary of bimekizumab plasma concentrations for the bimekizumab 160mg Q4W group at Week 16 and Week 24 is presented for the PK-PPS in the Table 14 below:

Table 14: Bimekizumab plasma concentration for the BKZ 160mg Q4W group at week 16 and week 24 (PK-PPS)

Visit (Week)	n	GeoMean (GeoCV%) [95% CI]
Visit 8 (Week 16)	206	11.0208 (49.6) [10.3332, 11.7542]
Visit 10 (Week 24)	194	11.1164 (65.3) [10.2171, 12.0947]

BKZ=bimekizumab; BLQ=Below the limit of quantification; CI=confidence interval; CV=coefficient of variation; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set

Note: Values BLQ were replaced by the value of LLOQ/2=0.125µg/mL in the calculations of CVs.

Note: CVs were only calculated if at least 2/3 of the concentrations were quantified at the respective time point and n ≥3.

The bimekizumab trough plasma concentrations observed in the Japanese study population were consistent with those in the global study population following bimekizumab 160mg Q4W treatment, and steady state bimekizumab trough concentrations were reached by Week 16 (Table 15).

Table 15: Bimekizumab plasma concentration for Japanese participants in the BKZ 160mg Q4W group at week 16 and week 24 (PK-PPS)

Visit (Week)	n	GeoMean (GeoCV%) [95% CI]
Visit 8 (Week 16)	8	11.1310 (36.1) [8.3085, 14.9125]
Visit 10 (Week 24)	7	11.7537 (48.0) [7.7116, 17.9145]

BKZ=bimekizumab; BLQ=Below the limit of quantification; CI=confidence interval; CV=coefficient of variation; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set

Population PK modelling

The data for the present analysis originated from fifteen different Phase 2 and Phase 3 studies: PS0010, PS0011, PS0016, PS0008, PS0009, PS0013, PS0015, PA0008, PA0010, PA0011, PA0012, AS0008, AS0013, AS0010 and AS0011. In these studies, patients with PSO, PsA or axSpA had subcutaneous (SC) administrations of bimekizumab with various dosing regimens. Studies PS0015, PA0010, PA0011, PA0012, AS0010 and AS0011 were still ongoing at the time of the analysis and consequently interim data was used for these studies. The population PK analysis included all data available at Week 24 cut-off for studies PA0010, AS0010, and AS0011, and all data available at Week 16 cut-off for study PA0011, as well as the available data from study PA0012 at the time of the PA0011 data cut. For study PS0015, data up to week 48 (end of second treatment period) was included.

The population PK analyses were performed in the non-linear mixed effect modeling software NONMEM version 7.4 or higher using the first-order conditional estimation method with interaction (FOCEI) estimation. Covariate-parameter relationships were assessed using the stepwise covariate model building procedure (SCM) with adaptive scope reduction (ASR). The evaluated covariates were: body weight (WT), age, sex, race/region, disease indication, disease duration, methotrexate (MTX) use at Baseline, corticosteroids use at Baseline, conventional synthetic disease modifying anti-rheumatic drug (csDMARD) use at Baseline, prior anti-TNF therapy, prior use of biologics, ADAb and neutralizing antibodies (NAb) status, anti-drug-antibodies (ADAb) titer, high sensitivity C-reactive protein (hs-CRP) at Baseline, and liver function at Baseline.

The dataset included 33,996 bimekizumab PK observations with multiple SC administrations across doses ranging from 16mg to 480mg and a total of 4010 patients (1809 with moderate to severe PSO, 1274 with PsA, and 927 with axSpA). The following observations were excluded: 1331 (3.8%) below LLOQ, 5 above LLOQ before the first active dose, 16 observations with duplicated records, and 1 observation associated with a double dose.

Study participant characteristics for the PK analysis data set were presented by disease indication for: baseline continuous covariates (Table 16), baseline categorical covariates (Table 17), and combined ADAb and neutralising antibodies (NAb) status (Table 18).

Table 16: Baseline characteristics for the participants in the PK analysis data set: covariates, presented by disease indication

	PSO N=1809	PsA N=1274	axSpA N=927	Overall N=4010
Age (year)				
Mean (SD)	45.0 (13.6)	49.3 (12.4)	40.8 (11.9)	45.4 (13.2)
Median (min, max)	44.0 (18.0, 83.0)	49.5 (20.0, 85.0)	39.0 (18.0, 80.0)	45.0 (18.0, 85.0)
Body weight (kg)				
Mean (SD)	89.7 (22.0)	85.4 (19.5)	80.6 (17.7)	86.2 (20.6)
Median (min, max)	87.2 (40.1, 237)	84.0 (40.0, 170)	79.0 (37.0, 159)	84.0 (37.0, 237)
Disease duration (years)				
Mean (SD)	18.0 (12.6)	7.14 (8.17)	6.22 (7.81)	11.9 (11.8)
Median (min, max)	15.6 (0, 68.8)	4.50 (0, 55.9)	2.86 (0, 41.0)	8.00 (0, 68.8)
Missing (N (%))	0 (0%)	13 (1.0%)	0 (0%)	13 (0.32%)
hs-CRP (mg/L)				
Mean (SD)	-	10.8 (17.4)	15.5 (19.0)	12.7 (18.2)
Median (min, max)	-	4.49 (0.0500, 204)	9.06 (0.0500, 175)	6.04 (0.0500, 204)
Missing (N (%))	1809 (100%)	0 (0%)	2 (0.22%)	1811 (45%)
ALT (U/L)				
Mean (SD)	29.6 (31.5)	27.7 (19.8)	25.2 (17.8)	28.0 (25.4)
Median (min, max)	24.0 (3.00, 1100)	23.0 (3.00, 285)	21.0 (3.00, 249)	23.0 (3.00, 1100)
AST (U/L)				
Mean (SD)	24.5 (18.4)	23.3 (11.9)	22.0 (13.6)	23.6 (15.5)
Median (min, max)	21.0 (9.00, 645)	21.0 (6.00, 199)	20.0 (7.00, 341)	21.0 (6.00, 645)
Total bilirubin (µmol/L)				
Mean (SD)	10.4 (5.03)	9.51 (4.26)	8.63 (3.85)	9.69 (4.59)
Median (min, max)	9.20 (1.70, 46.7)	8.60 (2.10, 38.1)	7.80 (2.80, 31.1)	8.70 (1.70, 46.7)

Table 17: Baseline characteristics for the participants in the PK analysis data set: covariates, presented by disease indication

	PSO N=1809	PsA N=1274	axSpA N=927	Overall N=4010
Sex				
Male	1244 (69%)	606 (48%)	671 (72%)	2521 (63%)
Female	565 (31%)	668 (52%)	256 (28%)	1489 (37%)
Disease indication				
Psoriasis	1809 (100%)	0 (0%)	0 (0%)	1809 (45%)
Psoriatic arthritis	0 (0%)	1274 (100%)	0 (0%)	1274 (32%)
Axial spondyloarthritis	0 (0%)	0 (0%)	927 (100%)	927 (23%)
Race[a]				
American Indian	3 (0.17%)	1 (0.078%)	1 (0.11%)	5 (0.12%)
Chinese	3 (0.17%)	0 (0%)	60 (6.5%)	63 (1.6%)
Japanese	89 (4.9%)	30 (2.4%)	23 (2.5%)	142 (3.5%)
Other Asian	74 (4.1%)	7 (0.55%)	1 (0.11%)	82 (2.0%)
Black	29 (1.6%)	6 (0.47%)	3 (0.32%)	38 (0.95%)
Pacific Islander	7 (0.39%)	0 (0%)	0 (0%)	7 (0.17%)
Caucasian	1578 (87%)	1221 (96%)	824 (89%)	3623 (90%)
Other	26 (1.4%)	8 (0.63%)	9 (0.97%)	43 (1.1%)
(Missing)	0 (0%)	1 (0.078%)	6 (0.65%)	7 (0.17%)
Methotrexate use				
No	1808 (100%)	575 (45%)	859 (93%)	3242 (81%)
Yes	1 (0.055%)	699 (55%)	68 (7.3%)	768 (19%)
Corticosteroids use				
No	1806 (100%)	1073 (84%)	853 (92%)	3732 (93%)
Yes	3 (0.17%)	201 (16%)	74 (8.0%)	278 (6.9%)
csDMARDs use				
No	1807 (100%)	460 (36%)	714 (77%)	2981 (74%)
Yes	2 (0.11%)	814 (64%)	213 (23%)	1029 (26%)
Prior anti-TNFs use				
No	1546 (85%)	862 (68%)	807 (87%)	3215 (80%)
Yes	263 (15%)	412 (32%)	120 (13%)	795 (20%)
Prior biologics use				
No	1181 (65%)	862 (68%)	791 (85%)	2834 (71%)
Yes	628 (35%)	412 (32%)	136 (15%)	1176 (29%)
Body weight (kg)				
<120	1651 (91%)	1210 (95%)	908 (98%)	3769 (94%)
≥120	158 (8.7%)	64 (5.0%)	19 (2.0%)	241 (6.0%)
Age (year)				
<65	1657 (92%)	1122 (88%)	894 (96%)	3673 (92%)
≥65	152 (8.4%)	152 (12%)	33 (3.6%)	337 (8.4%)
Age (year)				
<75	1784 (99%)	1260 (99%)	921 (99%)	3965 (99%)
≥75	25 (1.4%)	14 (1.1%)	6 (0.65%)	45 (1.1%)

[a]Asian race was defined as followed: Japanese (Asian participants living in Japan), Chinese (Asian participants living in China, Hong Kong or Taiwan) and other Asian (other Asian participants, excluding Japanese and Chinese).
Numbers represent the number of subjects in each category; percentages represent the corresponding percentage of total number of subjects, specified in the column header.

Table 18: Combined ADAb/Nab status categorical covariates statistics in the PK analysis data set, presented by disease indication

	PSO N=1809	PsA N=1274	axSpA N=927	Overall N=4010
Combined ADAb/NAb status				
ADAb negative or missing	1169 (65%)	652 (51%)	614 (66%)	2435 (61%)
ADAb positive and NAb missing	46 (2.5%)	45 (3.5%)	87 (9.4%)	178 (4.4%)
ADAb positive and NAb negative	350 (19%)	361 (28%)	128 (14%)	839 (21%)
ADAb positive and NAb positive	244 (13%)	216 (17%)	98 (11%)	558 (14%)

ADAb and NAb status effects were tested in the model using this combined covariate, as defined in the analysis plan.
All participants included in Phase 2 trials had missing NAb status.

The starting point of model development was based on the previous popPK model for bimekizumab in patients with PSO: a one-compartment model with first order absorption and first order elimination, including a covariate effect of WT on CL/F and V/F. A parameter for Frel was included, with a typical value fixed to 1. A two-compartment model was explored but did not provide a better fit of the PK data. Thus, the two-compartment model was not retained.

The covariate testing identified the following statistically significant covariate-parameter relationships: WT, ADAb/NAb status, ADAb titer, hs-CRP, prior use of biologics, age, race, sex and total bilirubin on CL/F, WT on V/F, as well as age and disease indication on Frel.

The final popPK model was a one compartment model with first-order absorption and elimination. IIV terms were supported on CL/F, V/F and Frel. The RUV for bimekizumab was described by a proportional model and was associated with an exponential IIV term. Covariate effects included in the final model were WT on CL/F and V/F and race on CL/F. In the final model, the estimated exponent of WT effect on CL/F and V/F was 0.996 and 0.733, respectively. The impacts of other significant covariates identified in the covariate testing on PK parameters and steady-state exposures were small and not retained in the final model. There was no evidence of a statistically significant difference in CL/F or V/F between patients with PSO, PsA or axSpA and no evidence of statistically significant effects for concomitant use of MTX, csDMARDs or corticosteroids at Baseline on CL/F.

The parameter estimates of the final bimekizumab population PK model, compared to the base model, are presented in Table 19. GOF plots are presented in Figure 13 (observed versus predicted concentrations) and Figure 14 (CWRES versus predicted concentrations and time). The GOF plots do not show any unacceptable trends overall. Figure 15 and Figure 16 present pcVPC plots for bimekizumab, stratified by phase of development and study, respectively. The figures show that the final bimekizumab model provides a good description of both the general trend and the variability in all studies.

Table 19: Parameter estimates of the final bimekizumab population PK model, compared to the base bimekizumab population PK model

		Final model			Base model		
OFV		99385.5			99498.90		
Condition number		7.6			7.14		
		Final model			**Base model**		
	Unit	**Value**	**RSE (%)**	**SHR (%)**	**Value**	**RSE (%)**	**SHR (%)**
CL/F	L/day	0.343	0.599		0.347	0.593	
V/F	L	11.2	0.586		11.2	0.585	
k_a	/day	0.693	4.78		0.696	4.83	
F_{rel}		1.00	(FIX)		1.00	(FIX)	
CL/F: allometric exponent for WT		0.996	2.23		0.963	2.32	
V/F: allometric exponent for WT		0.733	3.33		0.731	3.33	
CL/F: Japanese		0.235	12.0				
CL/F: Chinese or other Asian		0.133	22.3				
IIV CL/F	CV	0.198	1.97	21.9	0.202	1.92	21.3
IIV V/F	CV	0.170	2.77	34.2	0.172	2.77	34.2
IIV F_{rel}	CV	0.257	1.50	14.6	0.256	1.51	15.0
IIV RUV	CV	0.402	1.23	5.44	0.402	1.23	5.42
RUV	CV	0.139		3.58	0.139		3.58

The AIC for the final model is 99409.52 and the AIC for the base model is 99518.9
The equations for the typical values of CL/F and V/F are $CL/F = 0.343 \cdot (\frac{WT}{84})^{0.996}$; $V/F = 11.2 \cdot (\frac{WT}{84})^{0.733}$
The effect of race on CL/F is calculated as a proportional change (1+ final model value), compared to Caucasian, Black or others.
The RSE for IIV and RUV parameters are reported on the approximate SD scale.
OFV: objective function value; AIC: Akaike information criterion; CL/F: apparent clearance; V/F: apparent volume of distribution; k_a: first-order absorption rate constant; F_{rel}: relative bioavailability; WT: body weight; IIV: interindividual variability; RUV: residual unexplained variability; CV: coefficient of variation; RSE: relative standard error; SHR: shrinkage; SD: standard deviation

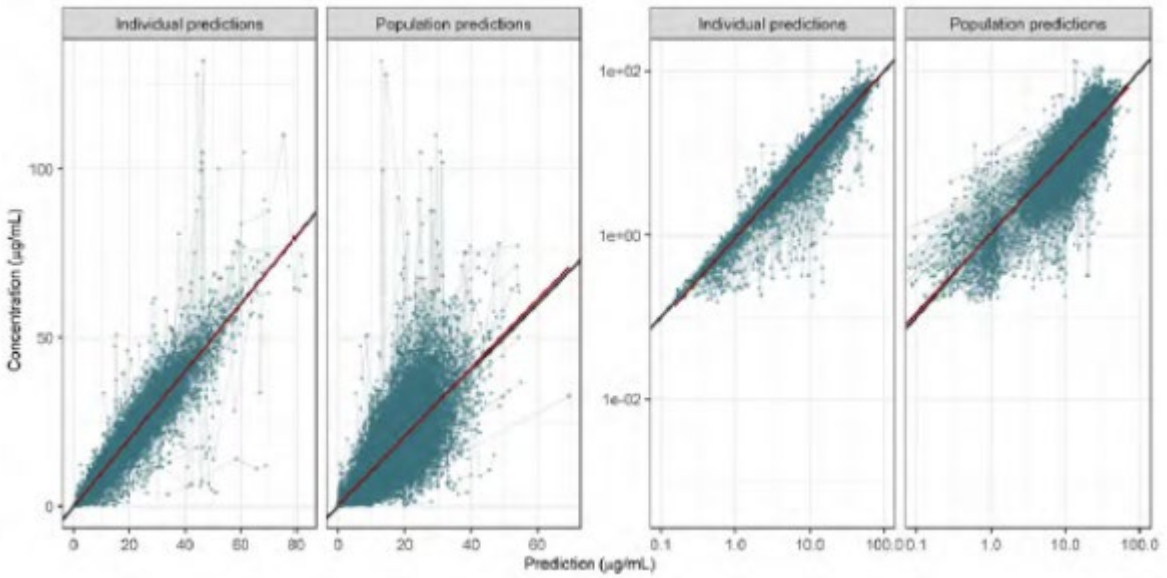


Figure 13: Observed concentrations versus PRED and IPRED for the final population PK model for bimekizumab concentrations. The left panel shows the data on a linear scale and the right panel shows the same plot with logarithmic scales. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The diagonal black line is the line of identity and the red line is a smooth (span 0.75)

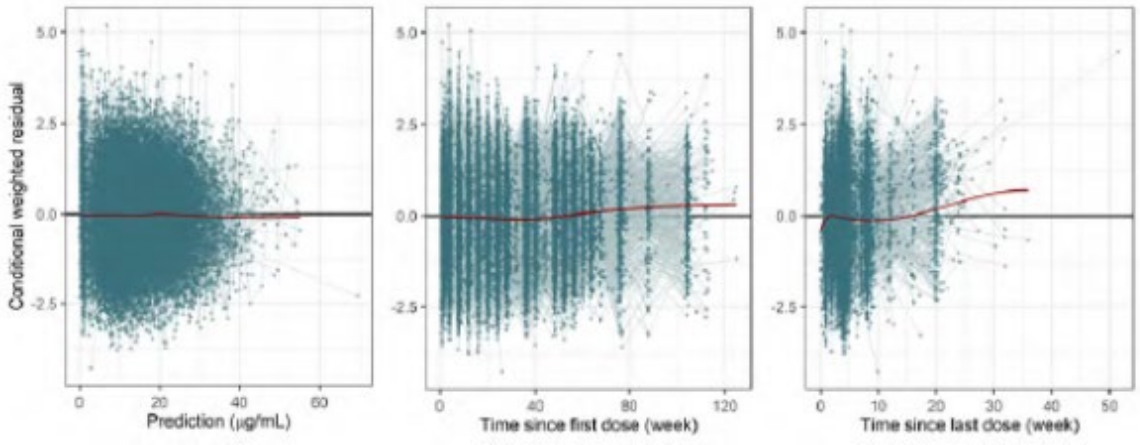


Figure 14: CWRES versus PRED (left panel), time since first dose (middle panel) and time since last dose (right panel) of bimekizumab concentrations for the final population PK model. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The horizontal black line is the zero line and the red line is a smooth. Observations associated with population prediction greater than 60 or time since last dose greater than 50 are excluded from the smooths (span 0.75)

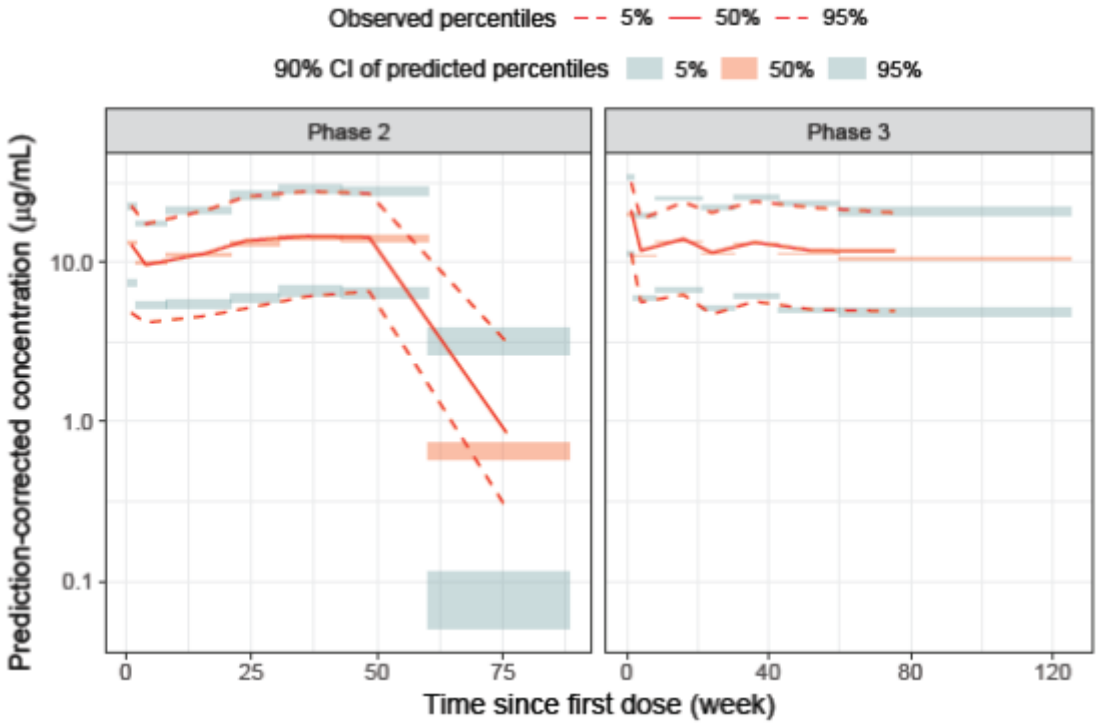


Figure 15: Prediction corrected visual predictive check of bimekizumab concentrations, for the final bimekizumab population PK model. Bimekizumab concentrations are displayed versus time after first dose on a semi-logarithmic scale. The solid and dashed red lines represent the median 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 90% confidence interval of the median, 5th and 95th percentiles predicted by the model

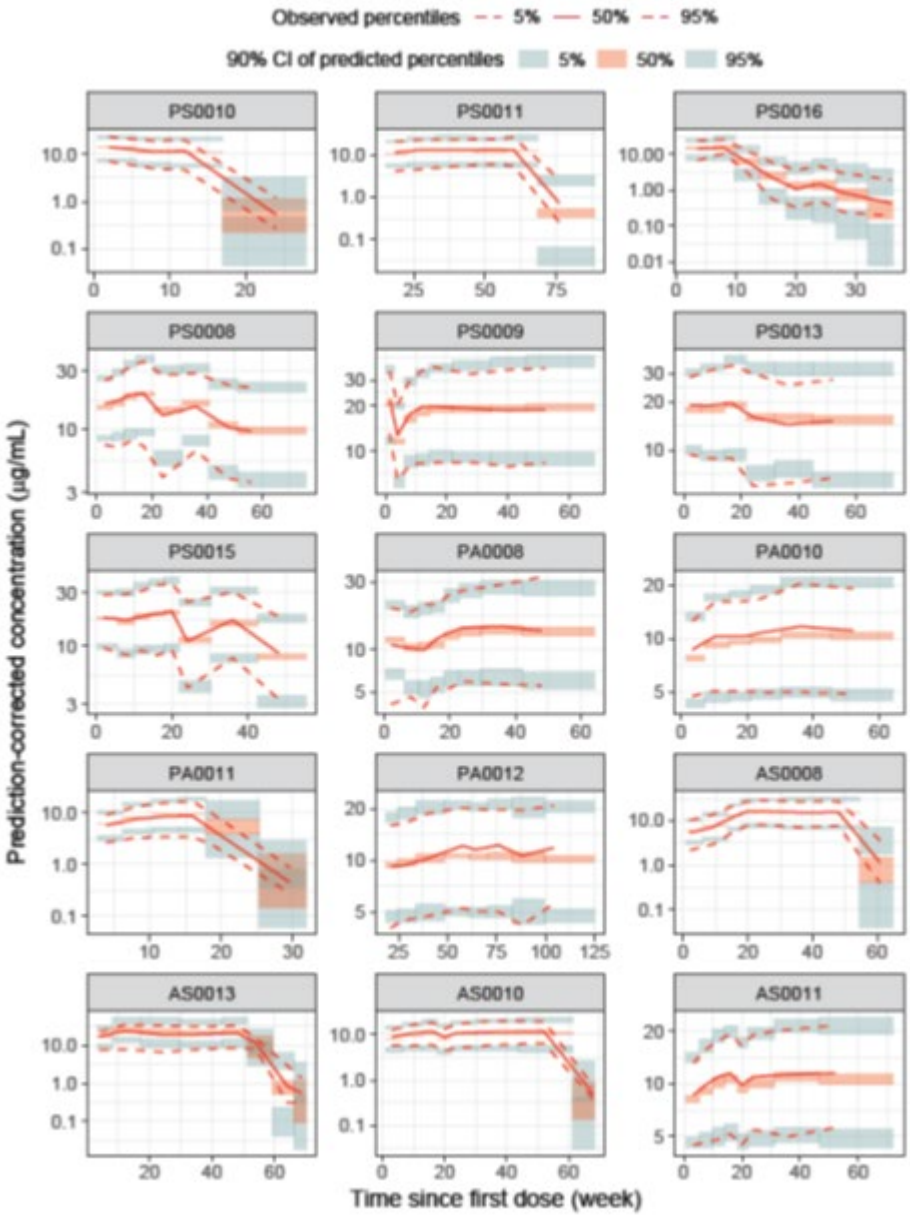


Figure 16: Prediction corrected visual predictive check of bimekizumab concentrations, stratified by study, for the final bimekizumab population PK model. Bimekizumab concentrations are displayed versus time after first dose on a semi-logarithmic scale. The solid and dashed red lines represent the median 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 90% interval of the median, 5th and 95th percentiles predicted by the model

Forest plots showing the covariate-parameter relationships of the final bimekizumab population PK model are presented in Figure 17 and Figure 18, for primary PK parameters (CL/F, V/F and Frel) and exposure

metrics (Cmax, Ctrough, AUC and t1/2), respectively. For race, the Forest plots show the impact of each race subgroup, compared to the reference group (Caucasian, Black and others). For WT, the Forest plots show the impact of the 5%, 25%, 75% and 95% percentiles, compared to the median. The effect of Japanese race was outside of the 0.8-1.25 boundaries for all PK parameters except Cmax. The effect of Chinese/other Asian race was included in the 0.8-1.25 boundaries for all PK parameters except Ctrough.

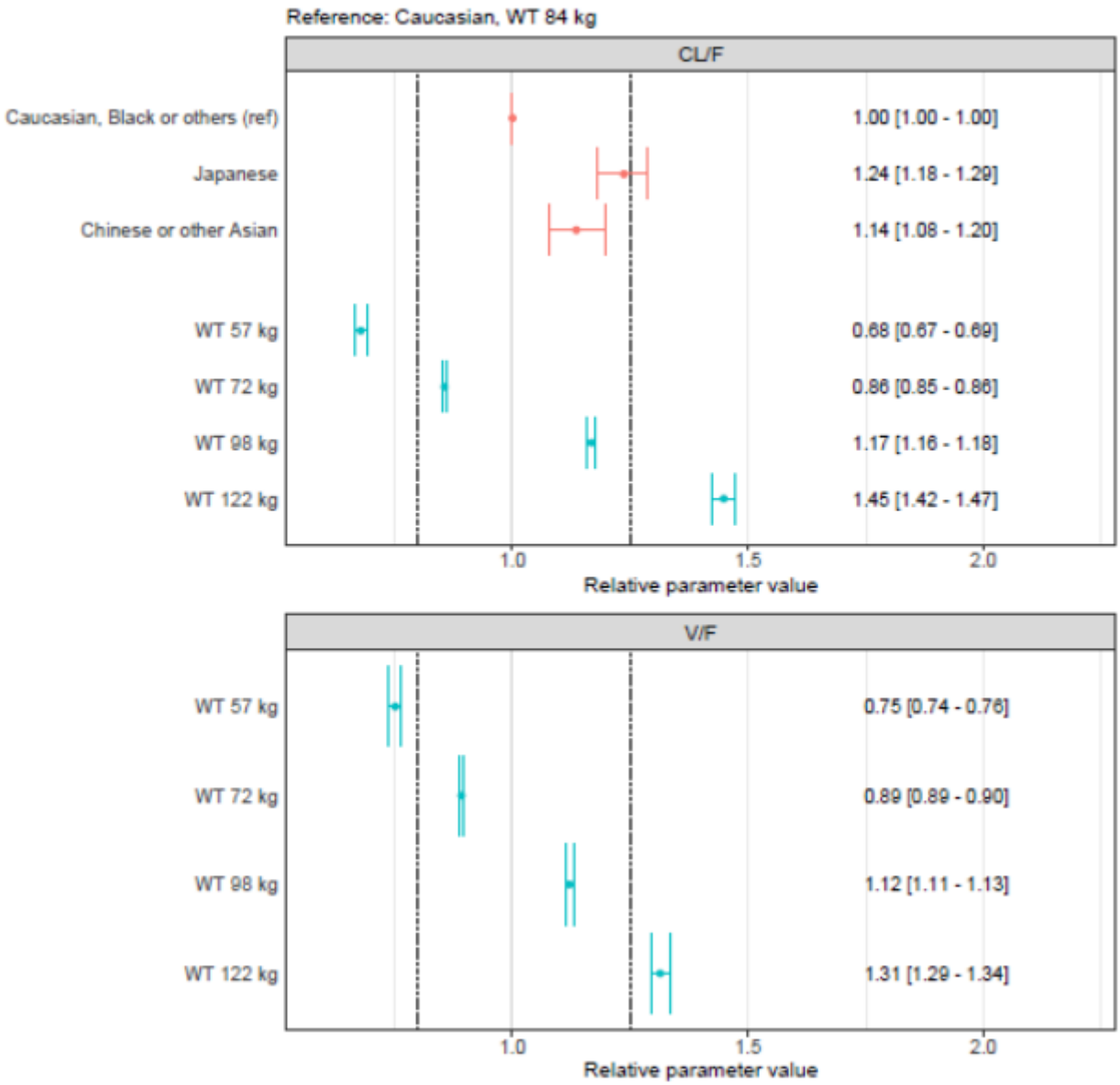


Figure 17: Forest plots illustrating the effects of covariates on bimekizumab PK parameters CL/F and V/F, conditioned on a typical study participant, based on the final bimekizumab model. Closed dots are error bars, together with their specific values, represent the median of the predicted relative change from the reference participant and its associated 95% CIs; these values are calculated based on 250 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference participant (for whom covariate characteristics are provided above the plot) are shown by the solid vertical lines; the dashed vertical lines indicate the 80%-125% margins relative to the reference participant. For race, the impact of each race subgroup is shown, compared to the reference group (Caucasian, Black and others). For WT, the impact of the 5%, 25%, 75% and 95% percentiles is shown, compared to the medium

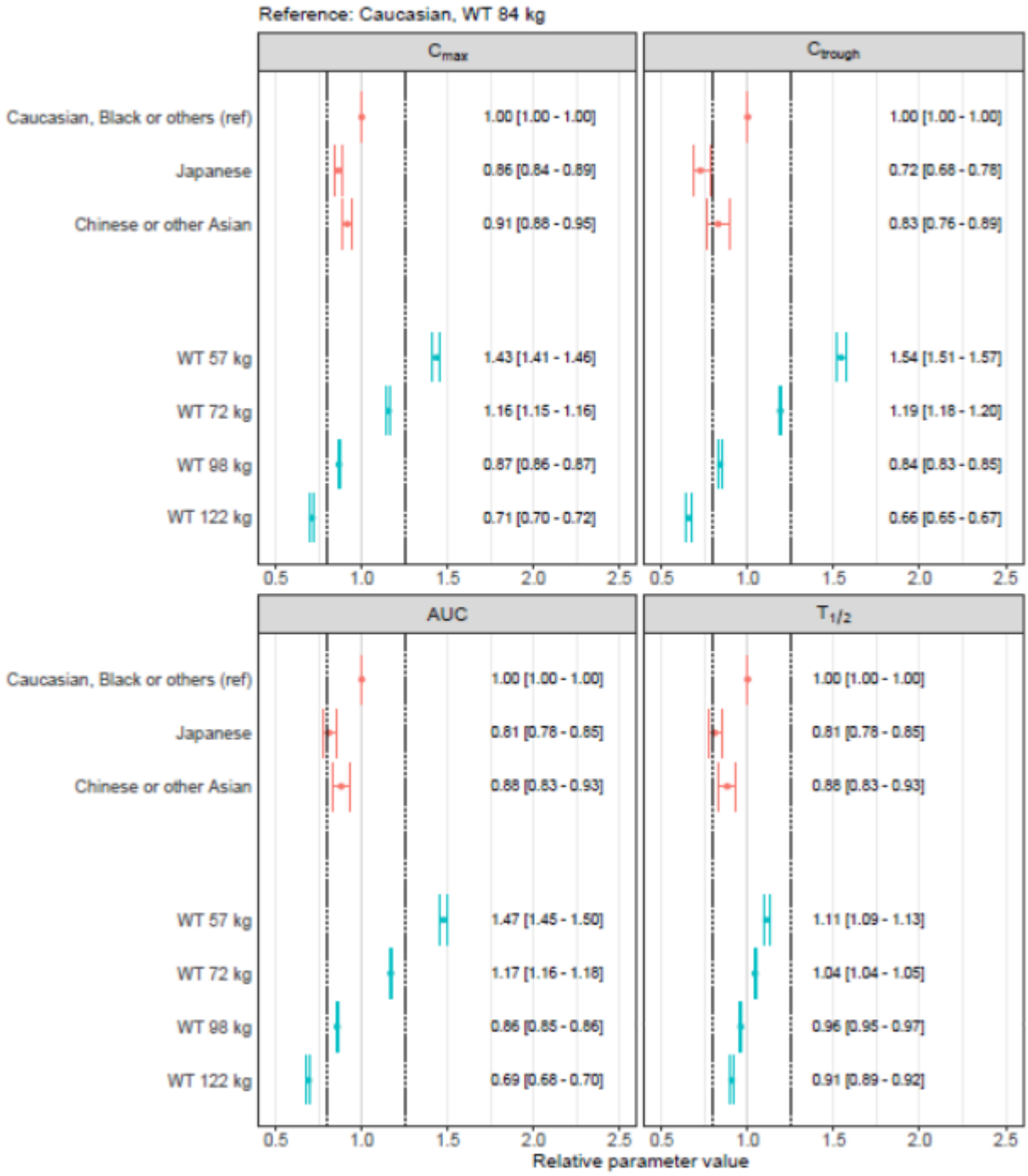


Figure 18: Forest plots illustrating the effects of covariates on bimekizumab PK parameters Cmax, Ctrough, AUC, and t1/2, conditioned on a typical study participant, for a 160 mg Q4W dosing regimen, based on the final bimekizumab model. Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference participant and its associated 95% CIs; these values are calculated based on 250 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference participant (for whom covariate characteristics are provided above the plot) are shown by the solid vertical lines; the dashed vertical lines indicate the 80%-125% margins relative to the reference participant. For race, the impact of each race subgroup is shown, compared to the reference group (Caucasian, Black and others). For WT, the impact of the 5%, 25%, 75% and 95% percentiles is shown, compared to the median

Based on the final bimekizumab popPK model, simulations were performed to predict bimekizumab PK at steady-state when receiving 160 mg Q4W, 320 mg Q8W or 320 mg Q4W. The resulting AUCss, Cmax,ss, Ctrough,ss, Tmax, t1/2 and accumulation ratio (AR) are presented in Table 20.

Table 20: Median and 2.5th-97.5th percentiles of AUC_{SS}, $C_{max,SS}$ and $C_{trough,SS}$ over 8 weeks and Tmax, $t_{1/2}$ and AR stratified by dosing regimen

Dosing regimen	AUC_{ss}[a,b] (µg · day/mL)	$C_{max,ss}$[a] (µg/mL)	$C_{trough,ss}$[a] (µg/mL)	T_{max}[a] (days)	$t_{1/2}$[a] (days)	AR[a]
160 mg Q4W	922 [424 - 2010]	22.0 [10.8 - 45.3]	10.7 [4.09 - 26.2]	3.87 [3.62 - 4.03]	22.5 [13.2 - 38.1]	1.73 [1.30 - 2.51]
320 mg Q8W	922 [424 - 2010]	30.6 [15.4 - 60.8]	6.34 [1.68 - 18.5]	4.40 [3.94 - 4.73]	22.5 [13.2 - 38.1]	1.22 [1.06 - 1.56]
320 mg Q4W	1840 [848 - 4010]	44.0 [21.5 - 90.6]	21.5 [8.19 - 52.5]	3.87 [3.62 - 4.03]	22.5 [13.2 - 38.1]	1.73 [1.30 - 2.51]

[a]: Median [2.5th-97.5th percentiles]
[b]: For Q4W dosing regimens, the AUC_{ss} was multiplied by 2 to obtain AUC_{ss} over 8 weeks.

Immunogenicity

Phase 1

Study UP0067

UP0067 was a Phase 1, randomised, double-blind, placebo-controlled single dose study to evaluate the PK, safety, and tolerability of bimekizumab in healthy Chinese volunteers. Blood samples were taken for anti-bimekizumab antibodies at Day 1 (Predose), and Days 14, 28, 56, 84, 112, and at the Day 140 Safety follow-up.

Anti-bimekizumab antibody status by visit is summarised in Table 21. Overall, the incidence of ADAb positivity was similar between the bimekizumab 160mg group (71.4%) and the bimekizumab 320mg group (81.18%). Five study participants (27.8%) had ADAb-positive results on Day 1 (predose). All ADAb-positive study participants had titers at the LLOQ or a level not significantly higher than LLOQ (0.25µg/mL), with the exception of one study participant at Day 84 who received bimekizumab 320mg. There was no impact of ADAb status on the PK of bimekizumab after a single dose (160mg or 320mg).

Table 21: ADAb status by visit (SS)

Visit	Status	BKZ 160mg N=7 n/Nsub (%)	BKZ 320mg N=11 n/Nsub (%)	BKZ Total N=18 n/Nsub (%)
Day 1, Predose	Positive	3/7 (42.9)	2/11 (18.2)	5/18 (27.8)
	Negative	4/7 (57.1)	9/11 (81.8)	13/18 (72.2)
	Missing	0	0	0
Day 14	Positive	3/7 (42.9)	4/11 (36.4)	7/18 (38.9)
	Negative	4/7 (57.1)	7/11 (63.6)	11/18 (61.1)
	Missing	0	0	0
Day 28	Positive	5/7 (71.4)	7/11 (63.6)	12/18 (66.7)
	Negative	2/7 (28.6)	4/11 (36.4)	6/18 (33.3)
	Missing	0	0	0
Day 56	Positive	4/7 (57.1)	5/11 (45.5)	9/18 (50.0)
	Negative	3/7 (42.9)	6/11 (54.5)	9/18 (50.0)
	Missing	0	0	0
Day 84	Positive	3/7 (42.9)	7/11 (63.6)	10/18 (55.6)
	Negative	4/7 (57.1)	4/11 (36.4)	8/18 (44.4)
	Missing	0	0	0
Day 112	Positive	3/7 (42.9)	4/11 (36.4)	7/18 (38.9)
	Negative	4/7 (57.1)	7/11 (63.6)	11/18 (61.1)
	Missing	0	0	0
Day 140, SFU	Positive	3/7 (42.9)	4/11 (36.4)	7/18 (38.9)
	Negative	4/7 (57.1)	7/11 (63.6)	11/18 (61.1)
	Missing	0	0	0
Visit	**Status**	**BKZ 160mg N=7 n/Nsub (%)**	**BKZ 320mg N=11 n/Nsub (%)**	**BKZ Total N=18 n/Nsub (%)**
Overall	Positive	5/7 (71.4)	9/11 (81.8)	14/18 (77.8)
	Negative	2/7 (28.6)	2/11 (18.2)	4/18 (22.2)
	Missing	0	0	0

ACP=above cut point; ADAb=anti-bimekizumab antibody; BKZ=bimekizumab; CP=confirmed positive; SFU=Safety Follow-up; SS=Safety Set

Phase 2

Study AS0008

AS0008 was a Phase 2b, multicenter, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the efficacy, PK, PD, and safety of bimekizumab in adult study participants with active Ankylosing Spondyloarthritis (AS). Blood samples for ADAb detection were taken at Baseline, and at Weeks 4, 8, 12, 16, 20, 24, 36, and Week 48.

A summary of ADAb status by visit for the Pharmacodynamic Per-Protocol Set (PD-PPS) is presented in Table 22. Overall, the percentage of study participants who were ADAb positive at any point up to Week

48 in the bimekizumab 160mg group and bimekizumab 320mg group were low and similar. Overall, no trends in the status of ADAb positivity and the efficacy of bimekizumab (measured by ASAS40) in treating the signs and symptoms of AS were observed.

Table 22: ADAb status by visit (Overall; PD-PPS)

Visit	ADAb status	Placebo N=60 n (%)	BKZ 16mg N=61 n (%)	BKZ 64mg N=58 n (%)	BKZ 160mg N=63 n (%)	BKZ 320mg N=61 n (%)
Overall [a]	ADAb+	2 (3.3)	13 (21.3)	14 (24.1)	15 (23.8)	14 (23.0)
	ADAb-	58 (96.7)	48 (78.7)	43 (74.1)	47 (74.6)	47 (77.0)
	Total	60 (100)	61 (100)	57 (98.3)	62 (98.4)	61 (100)
Day 1, Baseline [b]	ADAb+	2 (3.3)	1 (1.6)	3 (5.2)	1 (1.6)	2 (3.3)
	ADAb-	58 (96.7)	60 (98.4)	55 (94.8)	62 (98.4)	58 (95.1)
	Total	60 (100)	61 (100)	58 (100)	63 (100)	60 (98.4)
Week 4 [b]	ADAb+	1 (1.7)	5 (8.2)	10 (17.2)	8 (12.7)	11 (18.0)
	ADAb-	59 (98.3)	54 (88.5)	47 (81.0)	54 (85.7)	50 (82.0)
	Total	60 (100)	59 (96.7)	57 (98.3)	62 (98.4)	61 (100)
Week 8 [b]	ADAb+	1 (1.7)	9 (14.8)	7 (12.1)	7 (11.1)	5 (8.2)
	ADAb-	58 (96.7)	52 (85.2)	49 (84.5)	54 (85.7)	55 (90.2)
	Total	59 (98.3)	61 (100)	56 (96.6)	61 (96.8)	60 (98.4)
Week 12 [b]	ADAb+	2 (3.3)	12 (19.7)	7 (12.1)	7 (11.1)	3 (4.9)
	ADAb-	58 (96.7)	48 (78.7)	49 (84.5)	54 (85.7)	58 (95.1)
	Total	60 (100)	60 (98.4)	56 (96.6)	61 (96.8)	61 (100)
Week 16 [b]	ADAb+	-	-	-	6 (9.5)	2 (3.3)
	ADAb-	-	-	-	53 (84.1)	59 (96.7)
	Total	-	-	-	59 (93.7)	61 (100)
Week 20 [b]	ADAb+	-	-	-	4 (6.3)	3 (4.9)
	ADAb-	-	-	-	56 (88.9)	56 (91.8)
	Total	-	-	-	60 (95.2)	59 (96.7)
Week 24 [b]	ADAb+	-	-	-	3 (4.8)	1 (1.6)
	ADAb-	-	-	-	57 (90.5)	57 (93.4)
	Total	-	-	-	60 (95.2)	58 (95.1)
Week 36 [b]	ADAb+	-	-	-	0	0
	ADAb-	-	-	-	60 (95.2)	58 (95.1)
	Total	-	-	-	60 (95.2)	58 (95.1)
Week 48 [b]	ADAb+	-	-	-	3 (4.8)	0
	ADAb-	-	-	-	56 (88.9)	56 (91.8)
	Total	-	-	-	59 (93.7)	56 (91.8)

ADAb=anti-drug antibody; BKZ=bimekizumab; PD-PPS=Pharmacodynamic Per-Protocol Set
Note: At Week 12, Placebo, BKZ 16mg, and BKZ 64mg study participants were re-randomized to either BKZ

AS0009

AS0009 is a multicenter Open-Label Extension (OLE) study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult study participants with ankylosing spondylitis who completed the Phase 2b study AS0008. The data available for this assessment is based on an interim analysis after the final study participant had reached Week 108. Blood samples for anti-bimekizumab antibodies were taken at the Entry Visit, and at Weeks 12, 24, 36, 48, 72, and Week 96.

A summary of ADAb status in AS0009 is presented for the Safety Set (SS) in Table 23. In AS0009 (~2 years of treatment), the incidence of ADAb positivity was 11.6% and 17.5% for participants who received bimekizumab 160 mg and 320 mg Q4W in the AS0008 study, respectively. For the study participants who received bimekizumab 160 mg and 320 mg Q4W in the AS0008 and subsequently continued treatment in AS0009, the incidence of ADAb positivity was 24% and 33% respectively. The ADAb positivity did not appear to have an effect on bimekizumab concentrations or an impact on efficacy.

Table 23: ADAb status in AS0009 (SS)

		BKZ dose at AS0008 completion→BKZ dose in AS0009	
AS0009 Visit (Week)	**ADAb status**	*BKZ 160mg→160mg N=129[a] n (%)[a]*	*BKZ 320mg→160mg N=126[a] n (%)[a]*
Overall [b]	ADAb+	15 (11.6)	22 (17.5)
	ADAb-	114 (88.4)	103 (81.7)
	Total	129 (100)	125 (99.2)
Overall including SFU [c]	ADAb+	16 (12.4)	22 (17.5)
	ADAb-	113 (87.6)	103 (81.7)
	Total	129 (100)	125 (99.2)
Visit 1 (EV)	ADAb+	4 (3.1)	2 (1.6)
	ADAb-	125 (96.9)	124 (98.4)
	Total	129 (100)	126 (100)
Visit 4 (Week 12)	ADAb+	7 (5.4)	9 (7.1)
	ADAb-	122 (94.6)	116 (92.1)
	Total	129 (100)	125 (99.2)
Visit 5 (Week 24)	ADAb+	5 (3.9)	8 (6.3)
	ADAb-	119 (92.2)	113 (89.7)
	Total	124 (96.1)	121 (96.0)
Visit 6 (Week 36)	ADAb+	7 (5.4)	7 (5.6)
	ADAb-	113 (87.6)	110 (87.3)
	Total	120 (93.0)	117 (92.9)
Visit 7 (Week 48)	ADAb+	2 (1.6)	10 (7.9)
	ADAb-	118 (91.5)	107 (84.9)
	Total	120 (93.0)	117 (92.9)
Visit 9 (Week 72)	ADAb+	4 (3.1)	5 (4.0)
	ADAb-	116 (89.9)	107 (84.9)
	Total	120 (93.0)	112 (88.9)
Visit 11 (Week 96)	ADAb+	2 (1.6)	2 (1.6)
	ADAb-	112 (86.8)	105 (83.3)
	Total	114 (88.4)	107 (84.9)
SFU	ADAb+	1 (0.8)	0
	ADAb-	8 (6.2)	10 (7.9)
	Total	9 (7.0)	10 (7.9)

ADAb=anti-bimekizumab antibody; BKZ=bimekizumab; EV=Entry Visit; SFU=Safety Follow-Up; SS=Safety Set

Study AS0013

AS0013 was a multicenter, Phase 2a, randomised, study participant-blind, and Investigator-blind, parallel-group study to evaluate the efficacy and safety of bimekizumab compared to certolizumab pegol in adult study participants with active adult-onset axSpA. Blood samples for bimekizumab antibody detection were taken at Baseline, and Weeks 4, 12, 24, 36, and Week 48.

At Baseline, the prevalence of ADAb positivity was ~4% in the bimekizumab group. Over time, the cumulative number of study participants with treatment-induced anti-bimekizumab antibodies (23.5%) reached a maximum by Week 36. These results align with previous studies of the bimekizumab Q4W treatment regimen.

Phase 3

Study AS0010

AS0010 is a Phase 3 randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab compared with placebo in participants with active nonradiographic axial spondyloarthritis. The study period for the interim study report includes up to a 5-week Screening, through Week 24 of the treatment period, with placebo participants switching to bimekizumab at the end of Week 16 of the treatment period. Blood samples for anti-bimekizumab antibody detection were taken at Baseline, and Weeks 4, 8, 12, 16, 20, and 24 for the study period in the report.

A summary of ADAb status up to Week 16 and up to Week 24 and the number and percentage of study participants in each ADAb subcategory up to Week 24 is presented for the Immunogenicity SS in Table 24. Exportation of all samples from China was not possible. Therefore, the Immunogenicity SS used for ADAb and NAb analyses in this Week 24 report only includes available samples from non-Chinese study participants.

By Week 16 and Week 24, 42.0% and 51.3%, respectively, of study participants in the bimekizumab 160mg Q4W group were ADAb positive, with low (4.2%) Baseline ADAb positivity rates and most of the ADAb positivity developed after bimekizumab treatment initiation (47.9% of study participants had a total treatment-emergent ADAb positive result in the bimekizumab 160mg Q4W group by Week 24). The ADAb titers were generally low, close to the lower limit of assay detection with no apparent trend of increased titers over study visits in the 24-week treatment period. The incidence of boosted ADAb titers was low after treatment up to 24 weeks (0.8%) in the bimekizumab 160mg Q4W group. The plasma concentrations of bimekizumab 160mg Q4W were similar in ADAb positive and ADAb negative study participants up to Week 24.

Table 24: ADAb status overall and in each ADAb subcategory by treatment group (Immunogenicity SS)

Period/ADAb status	Placebo/BKZ 160mg Q4W N=119 n (%)	BKZ 160mg Q4W N=119 n (%)
Overall up to Week 16 [a]		
ADAb positive	–	50 (42.0)
ADAb negative	–	69 (58.0)
Total	–	119 (100)
Missing	–	0
Overall up to Week 16- efficacy subgroup analysis [b]		
ADAb positive	–	18 (15.1)
ADAb negative	–	101 (84.9)
Total	–	119 (100)
Missing	–	0
Overall up to Week 24 [a]		
ADAb positive	27 (22.7)	61 (51.3)
ADAb negative	82 (68.9)	57 (47.9)
Total	109 (91.6)	118 (99.2)
Missing	10 (8.4)	1 (0.8)
Overall up to Week 24- efficacy subgroup analysis [b]		
ADAb positive	11 (9.2)	39 (32.8)
ADAb negative	98 (82.4)	79 (66.4)
Total	109 (91.6)	118 (99.2)
Missing	10 (8.4)	1 (0.8)
Incidence by ADAb subcategory [c, d]		
1 - Pre-ADAb negative – TE-ADAb negative	82 (68.9)	57 (47.9)
2 - Pre-ADAb negative – TE-ADAb positive	16 (13.4)	56 (47.1)
3 - Pre-ADAb positive – TE-reduced ADAb	3 (2.5)	1 (0.8)
4 - Pre-ADAb positive – TE-unaffected ADAb positive	7 (5.9)	3 (2.5)
5 - Pre-ADAb positive – TE-ADAb boosted positive	0	1 (0.8)
6 - ADAb inconclusive	1 (0.8)	0
7 - Total treatment-emergent (combination of 2 and 5)	16 (13.4)	57 (47.9)
8 - Pre-ADAb positive	11 (9.2)	5 (4.2)
9 - Missing	10 (8.4)	1 (0.8)

ADAb=anti-BKZ antibody; BKZ=bimekizumab; Q4W=every 4 weeks; SS=Safety Set; TE=treatment-emergent

AS0011

AS0011 is an ongoing multicenter, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in study participants with active ankylosing spondylitis with radiographic sacroiliitis (r-axSpA). Blood samples for anti-bimekizumab antibodies were taken at Baseline, and at Weeks 4, 8, 12, 16, 20, and 24 for this study period.

A summary of ADAb status up to Week 16 and up to Week 24 and the number and percentage of study participants for each ADAb subcategory up to Week 24 is presented for the Immunogenicity SS in Table 25. By Week 16 and Week 24, 31.4% and 37.1% respectively, of study participants in the bimekizumab 160mg Q4W group were ADAb positive, with low (5.2%) baseline ADAb positivity rates and most ADAb positivity developed after bimekizumab treatment initiation (33.0% of study participants had a total treatment-emergent ADAb positive result in the bimekizumab 160mg Q4W group by Week 24). The ADAb titers were generally low, close to the lower limit of assay detection with no apparent trend of increased

titers over study visits in the 24-week treatment period. The incidence of boosted ADAb titers was low (1.0% of study participants in the bimekizumab 160mg Q4W group by Week 24).

Table 25: ADAb status overall and in each ADAb subcategory by treatment group (Immunogenicity SS)

	PBO/BKZ 160mg Q4W N=94 n (%)	BKZ 160mg Q4W N=194 n (%)
Overall up to Week 16 [a]		
ADAb positive	-	61 (31.4)
ADAb negative	-	130 (67.0)
Total	-	191 (98.5)
Missing	-	3 (1.5)
Overall up to Week 16- efficacy subgroup analysis [b]		
ADAb positive	-	28 (14.4)
ADAb negative	-	163 (84.0)
Total	-	191 (98.5)
Missing	-	3 (1.5)
Overall up to Week 24 [a]		
ADAb positive	9 (9.6)	72 (37.1)
ADAb negative	82 (87.2)	117 (60.3)
Total	91 (96.8)	189 (97.4)
Missing	3 (3.2)	5 (2.6)
Overall up to Week 24- efficacy subgroup analysis [b]		
ADAb positive	3 (3.2)	52 (26.8)
ADAb negative	88 (93.6)	137 (70.6)
Total	91 (96.8)	189 (97.4)
Missing	3 (3.2)	5 (2.6)
Incidence by ADAb subcategory [c, d, e]		
1 - Pre-ADAb negative – TE-ADAb negative	82 (87.2)	117 (60.3)
2 - Pre-ADAb negative – TE-ADAb positive	5 (5.3)	62 (32.0)
3 - Pre-ADAb positive – TE-reduced ADAb	2 (2.1)	1 (0.5)
4 - Pre-ADAb positive – TE-unaffected ADAb positive	2 (2.1)	6 (3.1)
5 - Pre-ADAb positive – TE-ADAb boosted positive	0	2 (1.0)
6 - ADAb inconclusive	0	1 (0.5)
7 - Total treatment-emergent (combination of 2 and 5)	5 (5.3)	64 (33.0)
8 – Pre-ADAb positive	4 (4.3)	10 (5.2)
9 – Missing	3 (3.2)	5 (2.6)

ADAb=antidrug antibody; BKZ=bimekizumab; IMP=investigational medicinal product; PBO=placebo; Q4W=every 4 weeks; SFU=Safety Follow-up; SS=Safety Set; TE=treatment-emergent

Population PK and PK/PD modelling

In the integrated popPK analysis, patients who were ADAb+/NAb+ were predicted to have 7% (95% CI 5%–10%) faster CL/F than ADAb- patients. Therefore, steady-state AUC and Ctrough exposures were predicted to be 7% and 9% lower, respectively, in ADAb+/NAb+ patients, compared to ADAb- patients. Patients who were ADAb+/NAb- were predicted to have similar CL/F to those who were ADAb-. Patients with ADAb titer value of 788 (95th percentile of strictly positive ADAb titer values) were predicted to have 9% (95% CI 9%–10%) faster CL/F compared to ADAb- patients.

Simulations based on the final popPK/PD model indicated that ADAb positivity was not associated with a clinically meaningful impact on efficacy as assessed by ASAS responses at Week 16.

Special populations

Renal and hepatic impairment

No specific studies have been conducted in study participants to determine the effect of renal or hepatic impairment on the PK of bimekizumab. The renal elimination of intact bimekizumab, an IgG mAb, is expected to be low and of minor importance. Further, as a mAb, bimekizumab is not expected to be metabolized in the liver. Thus, no dose adjustment is proposed, by the MAH, in these patient populations.

Age

In the integrated popPK analysis (age range of 18.0◦years to 85.0◦years), compared to the reference value of 45 years old, patients aged 24 years old (5th percentile) were predicted to have 4% (95% CI 3%-5%) faster CL/F and 7% (95% CI 5%–9%) higher Frel, while patients aged 68 years old (95th percentile) were predicted to have 4% (95% CI 3%–6%) slower CL/F and 7% (95% CI 5%–8%) lower Frel. Thus, the PK parameters were similar in the different age subgroups. A table with predicted bimekizumab exposures stratified by different age categories (< 65 years and ≥65 years and < 75 years and ≥75 years) is presented in Table 26.

Table 26: Simulated AUCSS, Cmax,SS, Ctrough,SS, Tmax,SS, AR and t1/2 stratified by different age categories assuming a 160 mg Q4W dosing regimen

Age group	n[a]	AUC_{ss}[b] (µg · day/mL)	$C_{max,ss}$[b] (µg/mL)	$C_{trough,ss}$[b] (µg/mL)	$T_{max,ss}$[b] (day)	AR[b]	$t_{1/2}$[b] (day)
<65 y	3673	461 [212 - 1010]	22.0 [10.8 - 45.4]	10.7 [4.09 - 26.3]	3.87 [3.62 - 4.03]	1.73 [1.30 - 2.51]	22.5 [13.2 - 38.1]
>=65 y	337	464 [212 - 986]	22.2 [10.7 - 44.5]	10.8 [4.08 - 25.7]	3.87 [3.62 - 4.03]	1.72 [1.30 - 2.50]	22.4 [13.2 - 37.9]
<75 y	3965	461 [212 - 1000]	22.0 [10.8 - 45.3]	10.7 [4.09 - 26.3]	3.87 [3.62 - 4.03]	1.73 [1.30 - 2.51]	22.5 [13.2 - 38.1]
>=75 y	45	479 [229 - 994]	22.8 [11.6 - 45.2]	11.2 [4.47 - 25.7]	3.87 [3.63 - 4.03]	1.73 [1.31 - 2.49]	22.6 [13.4 - 37.8]

[a]: n corresponds to the number of study participants in the analysis data set.
[b]: Median [2.5th - 97.5th percentile].

In the PK/PD model of ASAS response, age was a statistically significant covariate on Emax; ASAS response increased with decreasing age. Following bimekizumab 160mg Q4W dosing, in participants at the 5th and 95th age percentile (23 years and 61 years, respectively), the median predicted ASAS40 response rate was 70.3% and 34.3%, respectively (Figure 19). In study participants at the higher end of the age range, a bimekizumab dose of 320mg Q4W was predicted to result in a similar median ASAS response compared to a 160mg Q4W dose. Thus, no dose adjustment for age is warranted according to the MAH.

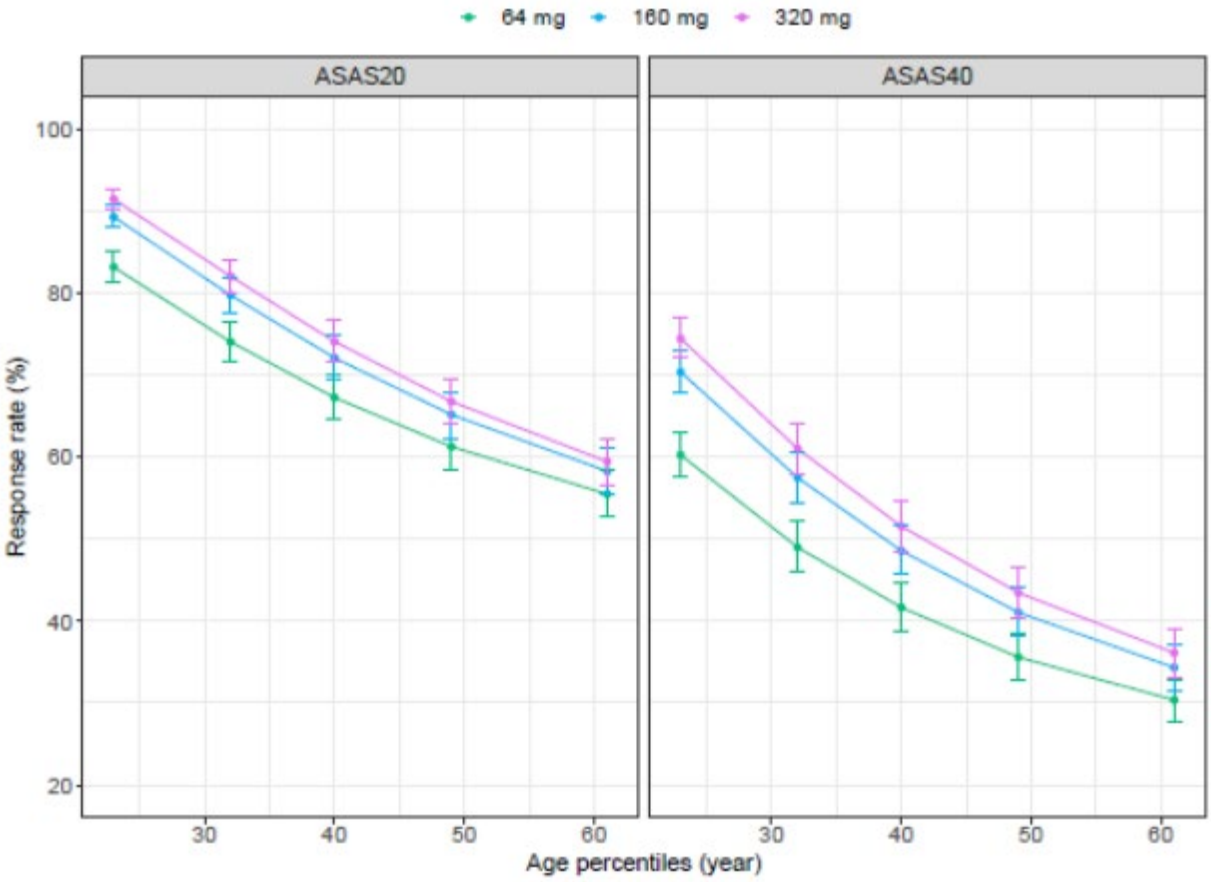


Figure 19: Predicted ASAS response rates at Week 16 versus age percentiles, colored by dose. The evaluated age values were the 5th, 25th, 50th, 75th and 95th percentiles, corresponding to 23, 32, 40, 49 and 61 years, respectively. The points and the vertical error bars represent the median and 95% PI of the mean response rates for each concentration. The plot is based on 591 bootstrap samples of 591 simulated study participants for each dose and age percentile

Gender

Based on the integrated popPK modelling, there was no evidence of a clinically relevant change in bimekizumab CL/F between males and females. Women were predicted to have 10% (95% CI 8%-12%) faster CL/F than men. Therefore, steady-state AUC and Ctrough exposures were predicted to be 9% and 13% lower, respectively, in women, compared to men. In the PK/PD analysis, sex was not identified as a covariate on ASAS response. As such, no dose adjustment for sex is required according to the MAH.

Race

The similarity in PK between Japanese and Caucasian healthy study participants was demonstrated in the clinical study UP0042, which was presented in original PSO application. These results were also confirmed in the previous popPK model in patients with moderate to severe PSO and further supported by consistent findings from the popPK modelling across indications.

In the integrated popPK model, Japanese patients were predicted to have 23% higher CL/F, and Chinese and other Asian patients were predicted to have 13% higher CL/F, compared to the reference Caucasian population. However, the effect of race on CL/F was less pronounced than the effect of WT. The median WTs in Japanese, Chinese and Caucasian patients were 69, 76 and 85 kg, respectively. Therefore, the smaller WTs in Japanese and Chinese patients offset the increase in CL/F and resulted in overall comparable PK exposure across the race subpopulations. The simulated AUCss, Cmax,ss and Ctrough,ss

for the 160 mg Q4W dose over 8 weeks are summarized for the reference race group (Caucasian, Black, American Indian or Alaska Native, Hawaiian or other Pacific islander, missing and others, referred to as Caucasian), Chinese and other Asian (referred to as Chinese), and Japanese participants in Table 27.

Table 27: Median and 2.5th-97.5th AUCSS, Cmax,SS and Ctrough,SS over 8 weeks, stratified by race, assuming a 160 mg Q4W dosing regimen

Race[a]	WT[b]	n[c]	AUC_{ss}[d,e] (µg · day/mL)	$C_{max,ss}$[d] (µg/mL)	$C_{trough,ss}$[d] (µg/mL)
Caucasian	85.0 [37.0 - 237]	3723	923 [424 - 2010]	22.0 [10.7 - 45.3]	10.8 [4.13 - 26.4]
Chinese	75.5 [42.0 - 131]	145	926 [434 - 1990]	22.6 [11.3 - 46.0]	10.4 [3.96 - 25.3]
Japanese	69.2 [40.6 - 127]	142	903 [417 - 1920]	22.5 [11.1 - 45.1]	9.72 [3.55 - 24.0]

[a]: Caucasian includes: Caucasian, Black, American Indian or Alska Native, Native Hawaiian or other Pacific Islander, Other and missing. Chinese includes; Chinese and other Asian.
[b]: Median [min-max] weight in category.
[c]: n corresponds to the number of study participants in the analysis data set.
[d]: Median [2.5^{th}-97.5^{th} percentiles]
[e]: The dosing regimen was Q4W, thus the AUC_{ss} was multiplied by 2 to obtain AUC_{ss} over 8 weeks.

Simulations based on the final popPK/PD model were performed to assess the impact of race on the ASAS response rates at Week 16. Figure 20 shows the predicted ASAS response rates at Week 16 versus WT percentiles in each race subgroup. There was no difference in response across races. Thus, based on the overall data, no dose adjustment for race or ethnicity is required, according to the MAH.

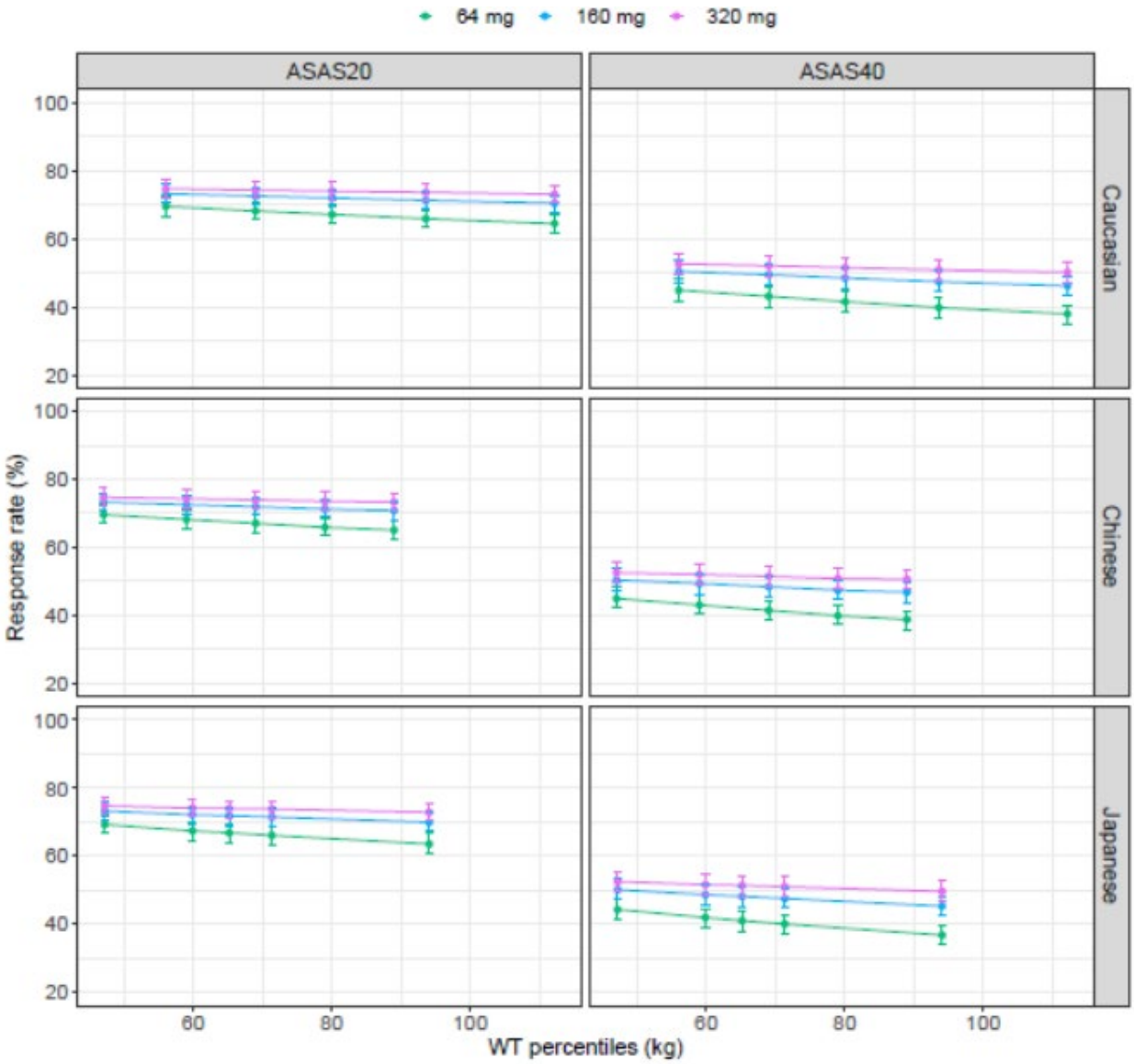


Figure 20: Predicted ASAS response rates at Week 16 versus WT percentiles, stratified by race and colored by dose. The points and the vertical error bars represent the median and 95% PI of the mean response rates for each WT. The plot is based on 591 bootstrap samples of 591 simulated study participants for each dose, race and weight percentile. The Caucasian race group includes Caucasian, Black, American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Other and missing. The Chinese race group includes Chinese and Other Asian

Bodyweight

In the integrated popPK model, WT had the largest impact on CL/F and impacted V/F to a lesser extent. Compared to the reference WT of 84 kg, the steady-state AUC was predicted to be approximately 30% lower for a subject weighing 122 kg and 50% higher for a subject weighing 57 kg. According to the MAH, the predicted magnitude of drop in exposure for a patient weighing 122 kg is less likely to be seen in patients with axSpA (or PsA) compared to patients with PSO, since more than 95% of patients with axSpA and PsA in Phase 2 and Phase 3 studies weighed less than 122 kg (the median WT for study participants with PSO, PsA and axSpA were 87.2, 84 and 79 kg, respectively). The simulated AUCss,

Cmax,ss, Ctrough,ss, Tmax, t1/2 and accumulation ratio (AR), stratified by weight categories of < 120 kg and ≥120 kg, are presented in Table 28.

Table 28: Median and 2.5th-97.5th AUCSS, Cmax,SS and Ctrough,SS over 8 weeks, stratified by dosing regimen and body weight category

Dosing regimen/WT	n[a]	AUC_{ss}[b,c] (µg · day/mL)	$C_{max,ss}$[b] (µg/mL)	$C_{trough,ss}$[b] (µg/mL)	T_{max}[b] (days)	$t_{1/2}$[b] (days)	AR[b]
160 mg Q4W							
<120 kg	3769	946 [454 - 2030]	22.5 [11.5 - 45.7]	11.1 [4.42 - 26.6]	3.87 [3.63 - 4.03]	22.6 [13.3 - 38.3]	1.74 [1.30 - 2.51]
>=120 kg	241	591 [300 - 1140]	14.5 [7.80 - 26.4]	6.54 [2.68 - 14.3]	3.83 [3.56 - 4.00]	20.1 [12.0 - 33.6]	1.62 [1.25 - 2.28]
320 mg Q8W							
<120 kg	3769	946 [454 - 2030]	31.3 [16.4 - 61.4]	6.55 [1.83 - 18.8]	4.41 [3.95 - 4.73]	22.6 [13.3 - 38.3]	1.22 [1.06 - 1.57]
>=120 kg	241	591 [300 - 1140]	20.7 [11.3 - 37.0]	3.59 [0.971 - 9.63]	4.32 [3.84 - 4.66]	20.1 [12.0 - 33.6]	1.17 [1.04 - 1.46]
320 mg Q4W							
<120 kg	3769	1890 [908 - 4060]	45.0 [23.0 - 91.4]	22.1 [8.83 - 53.1]	3.87 [3.63 - 4.03]	22.6 [13.3 - 38.3]	1.74 [1.30 - 2.51]
>=120 kg	241	1180 [599 - 2270]	29.0 [15.6 - 52.9]	13.1 [5.37 - 28.5]	3.83 [3.56 - 4.00]	20.1 [12.0 - 33.6]	1.62 [1.25 - 2.28]

[a]: n corresponds to the number of study participants in the analysis data set.
[b]: Median [2.5th-97.5th percentiles]
[c]: For Q4W dosing regimens, the AUC_{ss} was multiplied by 2 to obtain AUC_{ss} over 8 weeks.

Simulations based on the final popPK/PD model were performed to assess the impact of bodyweight on the ASAS response rates at Week 16. Figure 21 shows that the ASAS response rates at Week 16 slightly decreased with increasing WT, due to decreased exposure to bimekizumab, but the differences in the response rates were relatively small across the WT percentiles. The ASAS40 median response rate ranged from 46% at the 95th WT percentile (111 kg) to 50% at the 5th WT percentile (54 kg), for the 160 mg Q4W dose, and ranged from 50% at the 95th WT percentile to 53% at the 5th WT percentile, for the 320 mg Q4W dose. However, the 95% PIs for the 160 mg and 320 mg dose groups overlapped at each WT percentile. Additionally, bimekizumab exposure following 160mg Q4W at the higher end of the exposure range in study participants did not appear to be associated with increased incidences of overall TEAEs and infection TEAEs. Thus, no dose adjustment based on weight is warranted.

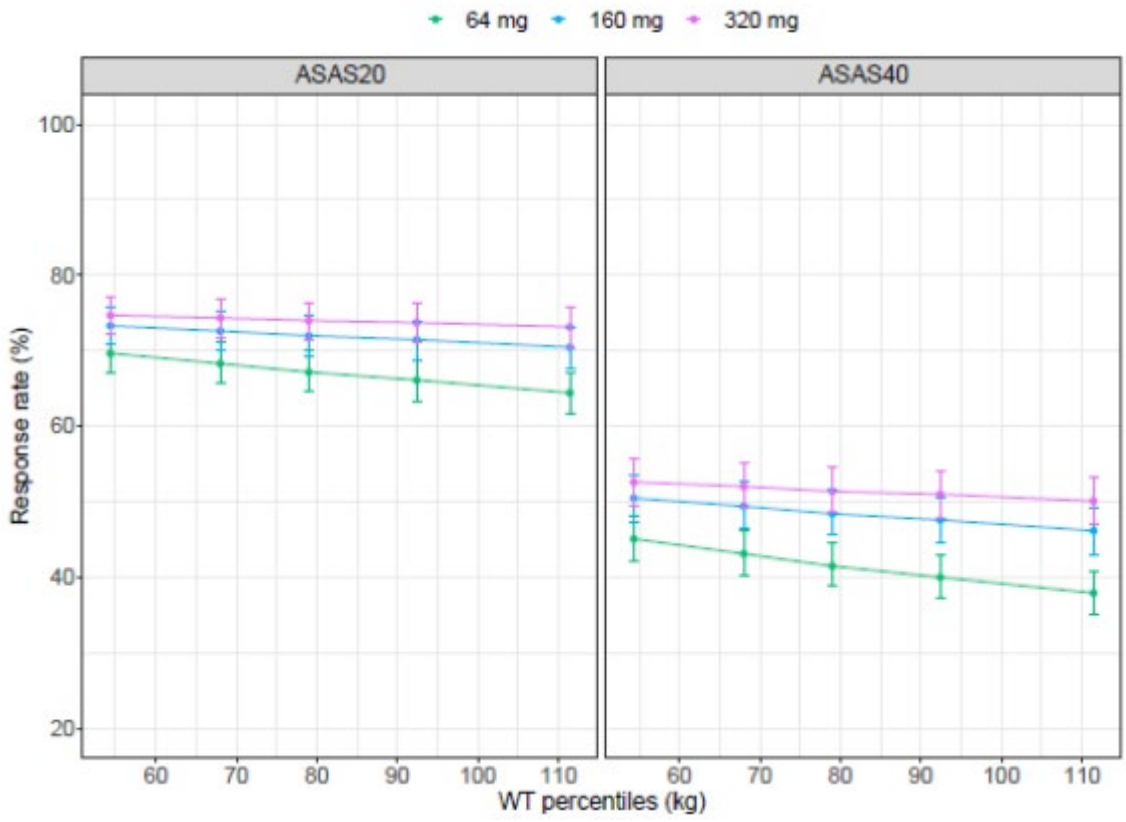


Figure 21: Predicted ASAS response rates at Week 16 versus WT percentiles, colored by dose. The evaluated WT values were the 5th, 25th, 75th and 95th percentiles, corresponding to 54, 68, 79, 92 and 111kg, respectively. The points and the vertical error bars represent the median and 95% PI of the mean response rates for each WT. The plot is based on 591 bootstrap samples of 591 simulated study participants for each dose and weight percentile

Drug interactions

No DDI studies have been conducted with bimekizumab.

PopPK modelling found no evidence of a statistically significant impact of use of medications concomitantly administered with bimekizumab in rheumatologic indications (MTX, corticosteroids, or cDMARDs) on bimekizumab CL/F. In addition, there was no evidence of a statistically significant impact for use of these concomitant medications on either probability of ASAS response or Emax in the popPK/PD analysis.

In the original PSO application, results of UP0034 showed that bimekizumab did not have an impact on the production of antibody titers to the influenza vaccine.

2.3.3. Pharmacodynamics

Mechanism of action

Bimekizumab is a humanised, full-length immunoglobulin G1 anti-IL-17 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.

Primary pharmacology

None of the cytokines or chemokines measured showed clinically relevant changes during the Double-blind period of study AS0008. At baseline, all but two participants had IL-17A concentrations below limit of quantification and so no formal statistical analysis was performed. Interleukin-17F was not measured in this study as per protocol, due to technical challenges in developing this assay. From the flow cytometry analysis for the Double-blind Period, there was an increase in CD4 T helper cells that was both dose- and time-dependent. None of the other immune cell subsets showed relevant changes either with dose or duration of treatment during the Double-blind Period.

Secondary pharmacology

Bimekizumab is a mAb and is not expected to interact with the hERG channel. A thorough QT/QTc clinical study has therefore not been conducted by the MAH. As described in the original PSO application, there were no cardiovascular findings that could be attributed to treatment with bimekizumab during nonclinical evaluation in the Cynomolgus monkey (8-week study NCD2260 and the 26-week study NCD2450). Additionally, no notable trends in abnormal ECG findings were observed in the axSpA clinical studies, and the incidence of major adverse cardiac events was low.

2.3.4. PK/PD modelling

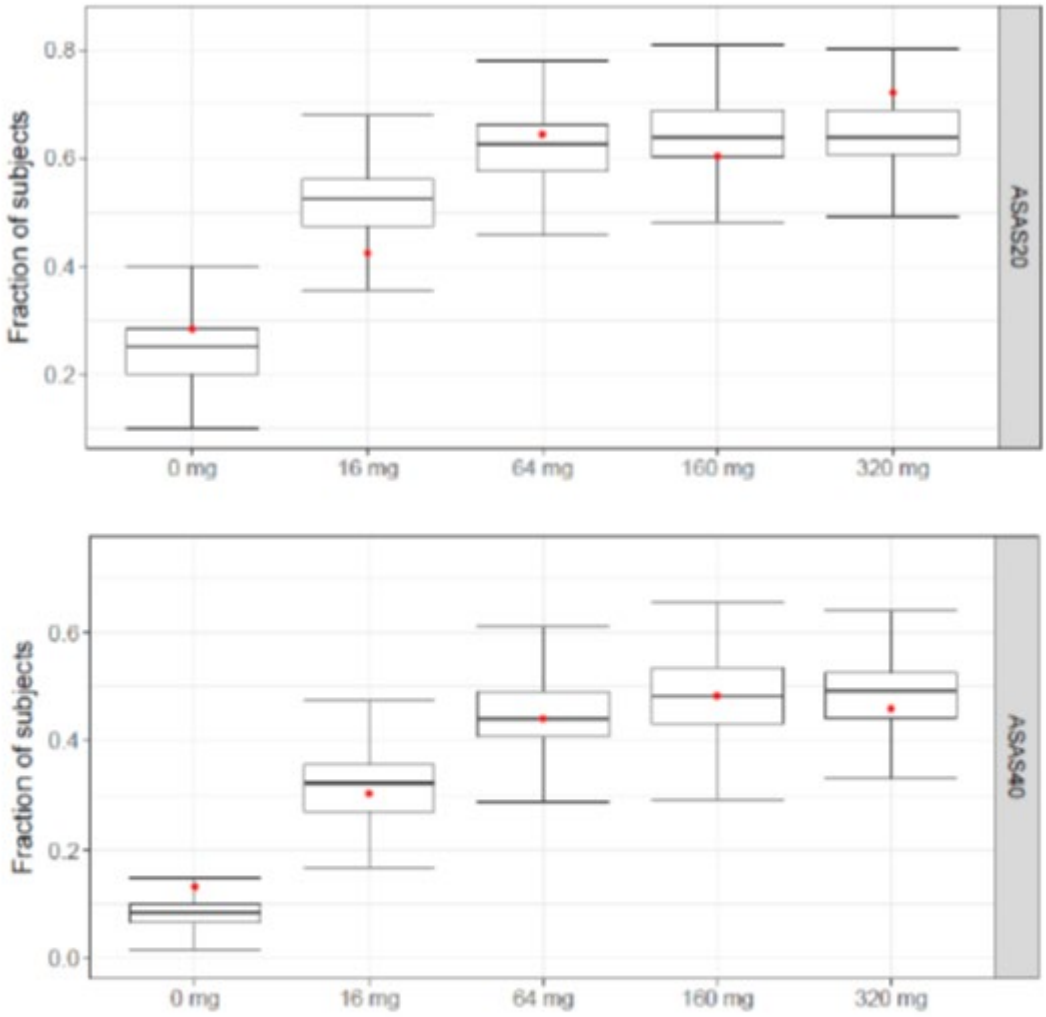
Population PK/PD modelling of ASAS response from Phase 2 study (AS0008)

A population PK model in study participants with active axSpA was developed using data from the Phase 2b study, AS0008. Data from the 12-week Double-blind Treatment Period and data up to the date of the data cut from the 36-week Dose-Blind Period were included in the analysis. The final popPK model was a one compartment model with linear absorption and elimination. Body weight on CL/F and V/F was the only statistically significant covariate included in the model.

Using data from the 12-week placebo-controlled period in AS0008, a population PK/PD model was then developed to establish the dose-exposure-response relationship between bimekizumab and ASAS response over time. This analysis supported dose regimen selection for the pivotal Phase 3 studies in the axSpA program.

The final popPK/PD model was based on 1,799 ASAS observations from 303 study participants. It was a proportional odds model fitted to the placebo dose group and the active treatment arms in the 12-week Double-Blind Treatment Period of study AS0008. The model provided a good description of the data it was developed on and could also predict the Dose-Blind Treatment Period of study AS0008 (which followed the initial 12 weeks) reasonably well. None of the tested covariates resulted in a significant improvement of the model fit; these included age, disease duration, high sensitivity C-reactive protein, weekly dose of methotrexate (MTX), body weight, Baseline ASDAS, ADAb, sex, csDMARD other than MTX as past medication, nonsteroidal anti-inflammatory drug at Baseline, previous anti-TNF use, prior biologic therapy).

The observed and model predicted fractions of ASAS20 and ASAS40 responder categories at Week 12 versus bimekizumab dose group for the final ASAS model are presented in Figure 22. These plots demonstrate that the final ASAS model provides a good description of the dose-response relationship at Week 12. Moreover, the fractions of ASAS responders increased when the dose was increased from 16 to 160mg, but increasing the dose to 320mg did not result in a clear improvement in the ASAS response.



ASAS20/40=Assessment of SpondyloArthritis International Society 20%/40% response criteria; IQR=inter-quartile range

Note: The simulations were based on the AS0008 study participant population, dosing regimens, and sample size.

Note: The middle horizontal lines within the boxes represent the median fraction of participants predicted by the model, the lower and upper horizontal lines of the boxes represent the 25th and 75th percentiles predicted by the model; the lower and upper whiskers represent the smallest/highest prediction greater/less than or equal to lower/upper hinge ±1.5 times the IQR.

Note: The red points represent the observed fraction of subjects in the analysis data set.

Figure 22: Simulated and observed fractions of ASAS20 and ASAS40 responders versus bimekizumab dose group at Week 12 (CL0536)

Population PK-PD modelling of ASAS response following bimekizumab subcutaneous administration in patients with axial spondyloarthritis

The aim of this analysis was to characterise the exposure-response relationship between bimekizumab plasma concentrations and the efficacy endpoint, assessment of SpondyloArthritis International Society (ASAS) response, in patients with axial spondyloarthritis (axSpA), using a population PK-PD modelling approach. The response was categorised as followed: non-response, 20% improvement in ASAS response (ASAS20), and 40% improvement in ASAS response (ASAS40).

The data originated from one Phase 2 study (AS0008) and two ongoing Phase 3 studies (AS0010, AS0011). The impact of the exploratory covariates was investigated using the SCM procedure with adaptive scope reduction. Covariates evaluated are presented in Table 29.

Table 29: Covariates tested in the PK-PD model

Model[a]	Type	Covariate[b]
ASAS response model parameters	Mechanistic	None
	Structural	None
	Exploratory	age, body weight, sex, race[c], region, disease indication[d], disease duration, ADAb and NAb status[e], prior use of biologics, prior anti-TNF therapy, MTX use at baseline, NSAIDs use at baseline, conventional synthetic DMARDs use at baseline, corticosteroids use at baseline, baseline hs-CRP, baseline MRI status, presence of extra-articular manifestations at baseline, baseline BASDAI, baseline PGADA, baseline BASFI, presence of HLA-B27 allele

[a] The structural and exploratory covariates were assessed on the probability of ASAS response and on EMAX.
[b] In this analysis, except for ADAb titer, no time-varying covariates were considered, the value at baseline was used, except for ADAb and NAb status which was defined on patient level.
[c] Specifically in this analysis, the race covariate had the following additional stratification for Asian study paticipants: Japanese (Asian study paticipants living in Japan), Chinese (Asian study paticipants living in China, Hong Kong or Taiwan) and others (other Asian study paticipants, excluding Japanese and Chinese). The latter was lumped with the race group defined as *others* at the modeling stage.
[d] r-axSpA versus nr-axSpA.
[e] Was tested as a unique combined covariate. The reference level was *ADAb negative*, and three parameters were estimated for the *ADAb positive* group: ADAb+ and NAb missing, ADAb+ and NAb negative and ADAb+ and NAb positive. Both ADAb and NAb status were derived on patient level, considering 12 (AS0008) or 16 (AS0010 and AS0011) week follow-up.

In total, 5816 ASAS response observations from 887 patients with axSpA were included in the analysis. The final ASAS model was a proportional odds model. The probability of being an ASAS20 or an ASAS40 responder was a function of the baseline probability, the treatment effect, 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, and consequently this parameter had no impact on the probability of response. The treatment effect included a placebo response model, and an active drug response model. The placebo response increased with increasing time (log-linear relationship). The active drug model was constituted of an Emax function of the individual predicted bimekizumab plasma concentration, and an exponential function of time. IIV terms were supported on the probability of response and on Emax. The final model included the effect of age and baseline hs-CRP on Emax. The ASAS response rates decreased with increasing age and increased with increasing baseline hs-CRP. The parameter estimates of the final model, compared to the base model, are presented in Table 30.

Table 30: Parameter estimates of the final ASAS response model, compared to the base model

	Final model	Base model
Run	41	32
OFV	6873.12	6928.70
Condition number	29.77	19.23

		Final model			Base model		
	Unit	Value	RSE (%)	SHR (%)	Value	RSE (%)	SHR (%)
BL_{20}: Baseline ASAS20 probability		-30.0	(FIX)		-30.0	(FIX)	
$DiffBL_{40}$: Baseline difference for ASAS40 probability		-2.22	3.56		-2.32	3.79	
Placebo slope	/day	710	(FIX)		710	(FIX)	
Placebo intercept		18.0	(FIX)		18.0	(FIX)	
E_{max}		3.21	13.3		3.17	15.3	
EC_{50}	µg/mL	2.67	45.7		2.43	53.7	
k_{tr}	/day	0.117	19.4		0.0729	24.7	
Age effect on E_{max}		-0.0342	18.8				
Baseline hs-CRP effect on E_{max}		0.222	23.0				
IIV on the probability of response		2.77	5.30	27.4	3.11	6.40	27.7
IIV on E_{max}		2.83	22.8	61.2	3.76	16.0	56.2

BL_{20} and $DiffBL_{40}$ probabilities are reported on the logit scale.
The RSE for IIV parameters are reported on the approximate SD scale.
The age effect is implemented as an exponential relationship, and the baseline hs-CRP effect is implemented as a power relationship.
The probabilities of response on the logit scale (LP) are calculated as followed:

$$LP_{20} = BL_{20} + \log(1 + Slope_{pbo} \cdot time) + Int_{pbo} + (1 - e^{-k_{tr} \cdot time}) \cdot \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + IIV_{response}$$

$$LP_{40} = BL_{20} + DiffBL_{40} + \log(1 + Slope_{pbo} \cdot time) + Int_{pbo} + (1 - e^{-k_{tr} \cdot time}) \cdot \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + IIV_{response}$$

OFV: objective function value; E_{max}: maximum effect; EC_{50}: concentration at half maximum effect; hs-CRP: high sensitivity C-reactive protein; IIV: interindividual variability; CV: coefficient of variation; RSE: relative standard error; SHR: shrinkage; SD: standard deviation

VPC plots for the final ASAS model are presented in Figure 23 and Figure 24.

In Figure 23, ASAS20-40 responders correspond to the study participants who were ASAS20 responders but not ASAS40 responders. These figures demonstrate that the final ASAS model provides a good description of the data. The proportion of non-responders in the 320 mg dose group appears to be slightly overestimated while the proportion of ASAS40 responders is slightly underestimated. However, the majority of the data were in the placebo and 160 mg Q4W group (approximately 300 and 400 study participants, respectively), while the 16, 64 and 320 mg Q4W groups only included approximately 60 study participants each.

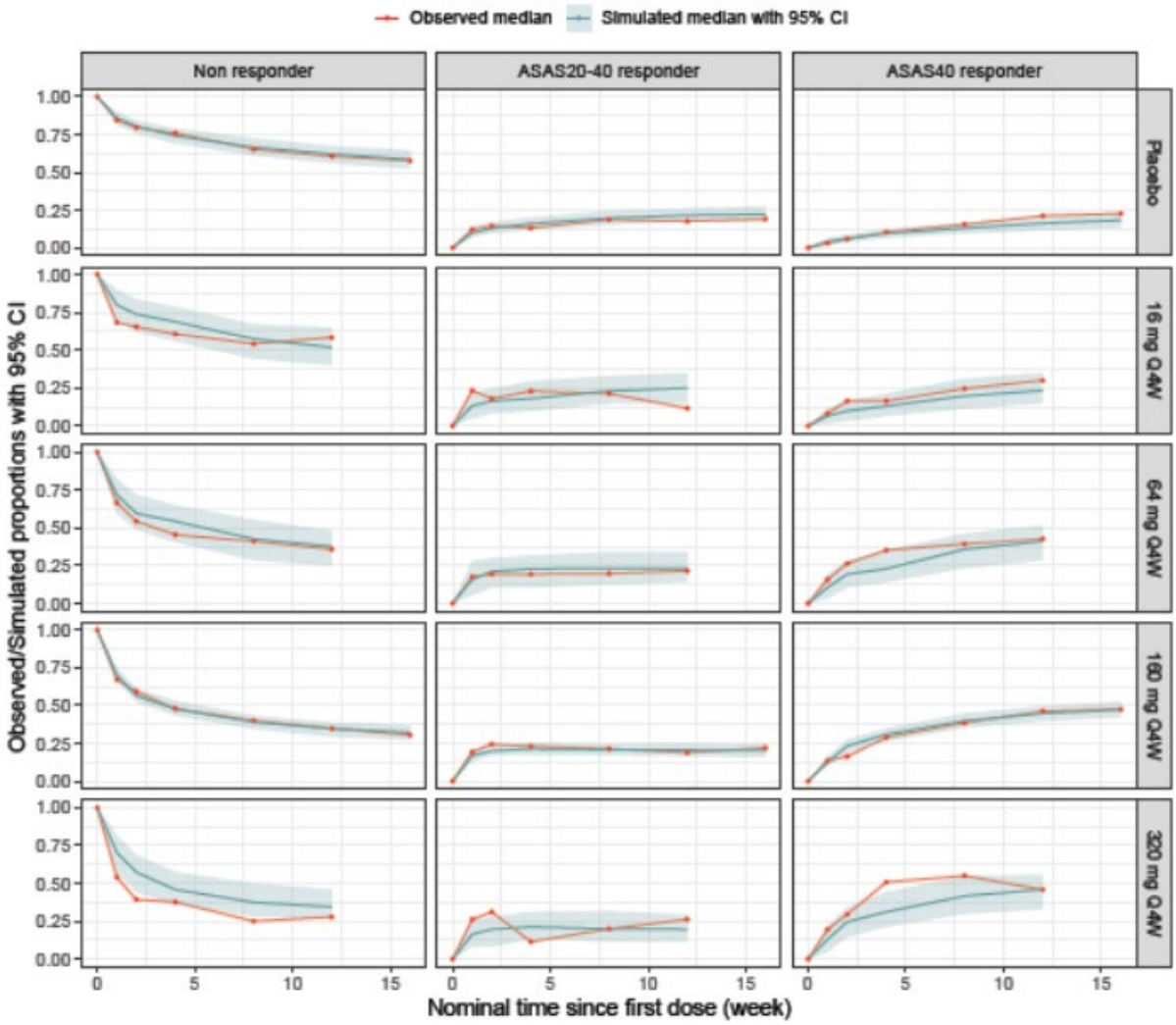


Figure 23: Visual predictive check of the proportion of ASAS non-responders, ASAS20-40 responders and ASAS40 responders versus nominal time since first dose, stratified by dose group, for the final ASAS response model (run 41). The blue line and the blue shaded areas represent the median and the 95% CI of the model predictions (based on 200 simulations); the red points represent the observed proportion of study participants in the analysis data set, and the red line is the observed median

Figure 24 shows the observed and model predicted transitions between the different ASAS responder categories (non-responder, ASAS20-40 responder and ASAS40 responder). For each patient in the analysis data set, each ASAS response observation was compared to the previous one. If the observation was the same as the previous one, it was classified as no transition; if the observation was in a higher response category compared to the previous one, it was classified as positive transition; if the observation was in a lower response category compared to the previous one, it was classified as negative transition. These figures show that the final ASAS response model describes the transitions between these categories reasonably well.

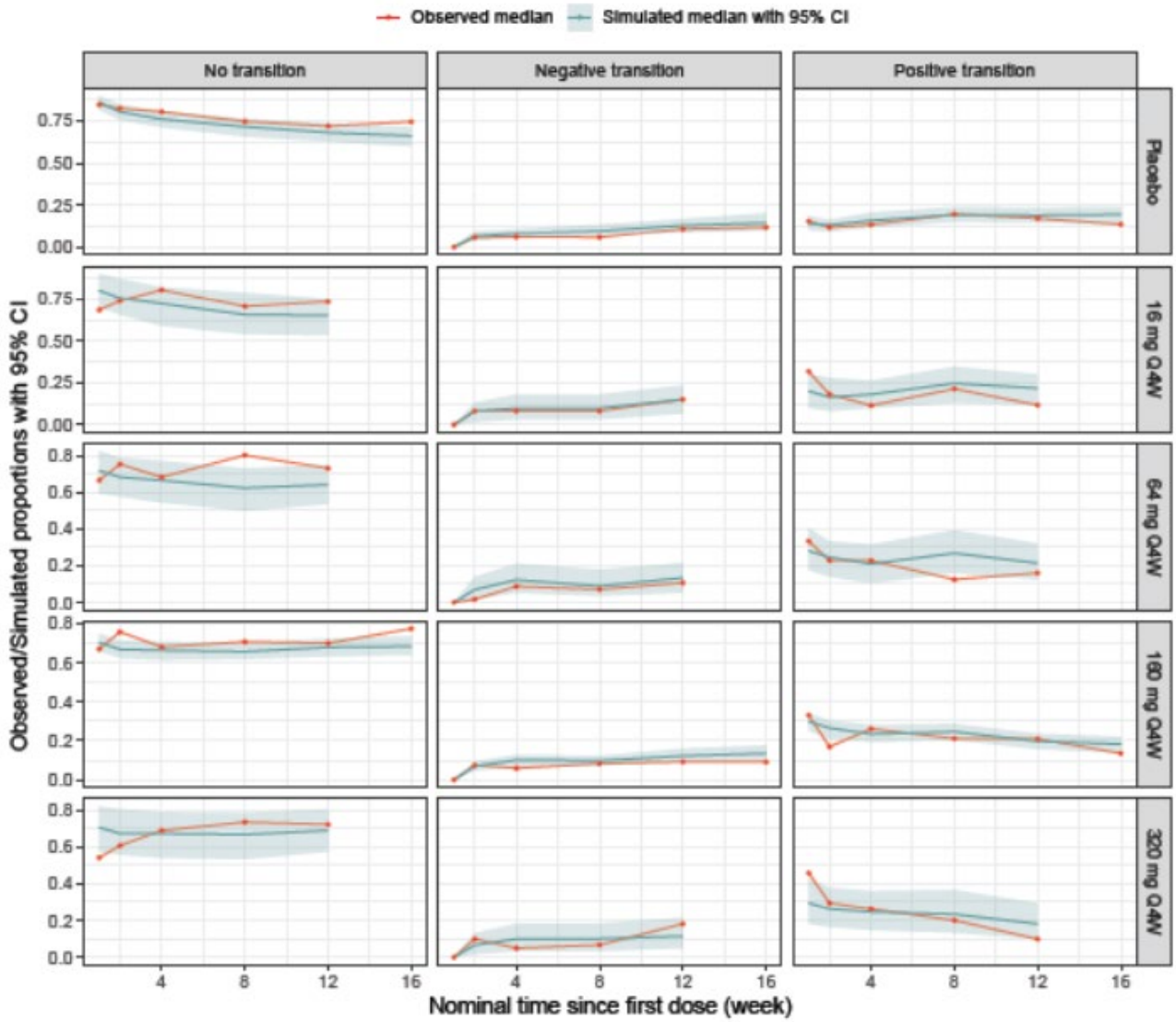


Figure 24: Visual predictive check of the proportion of study participants with no ASAS transition, negative ASAS transition, and positive ASAS transition from the previous visit, versus nominal time since first dose, stratified by dose group, for the final ASAS response model (run 41). The blue line and the blue shaded areas represent the median and the 95% CI of the model predictions (based on 200 simulations); the red points represent the observed proportion of study participants in the analysis data set, and the red line is the observed median

Simulations were performed to assess the impact of change in bimekizumab CL/F on the predicted ASAS response rates. The results are presented in Figure 25. The median ASAS response rates at Week 16 were slightly increased when exposure increased (lower CL/F), and slightly decreased when exposure decreased (higher CL/F). The ASAS20 response rate ranged from 69% to 74%, compared to 72% for a typical CL/F. The ASAS40 response rate ranged from 44% to 52%, compared to 49% for a typical CL/F.

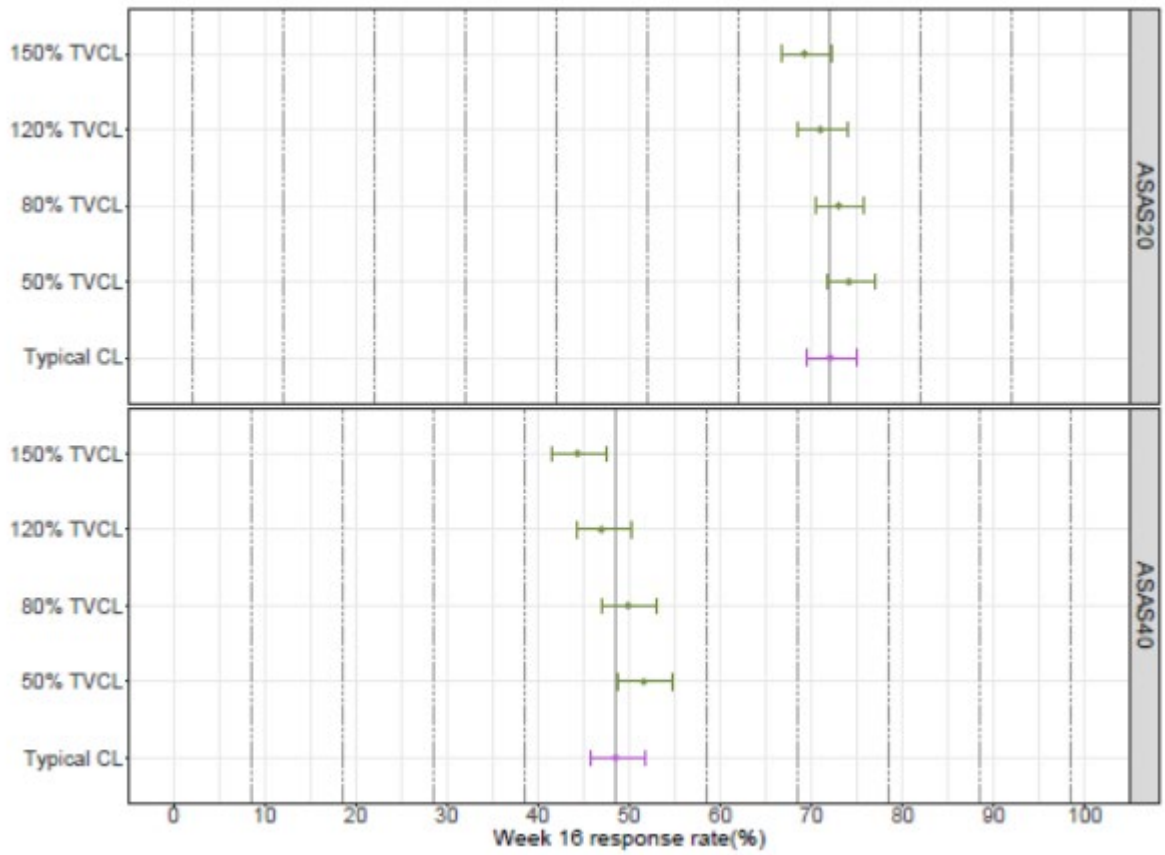


Figure 25: Impact of change in BKZ CL/F on Week 16 predicted ASAS response rates. The points and the horizontal error bars represent the median and 95% PI of the mean response rates for the different PK parameter values. The vertical grey line indicates the median response rate for typical PK parameters, and the vertical dashed lines represent 10% difference intervals, compared to the median response rate for typical PK parameters. The plot is based on 591 bootstrap samples of 591 simulated study participants for each CL/F value, with a dosing regimen of bimekizumab 160 mg Q4W

The simulated ASAS response rates for different dose levels at Week 16 and from baseline to Week 16 are presented in Figure 26 and Figure 27, respectively. The predicted median ASAS40 response rate at Week 16 increased with increasing dose, it was 16%, 27%, 41%, 48%, and 51% for placebo, 16 mg Q4W, 64 mg Q4W, 160 mg Q4W and 320 mg Q4W dosing regimens, respectively. Based on the 95% PI, the ASAS40 response rate at Week 16 for the 160 mg Q4W dose ranged from 45% to 51%, and was similar to the ASAS40 response rate for the 320 mg Q4W dose (ranged from 48% to 54%).

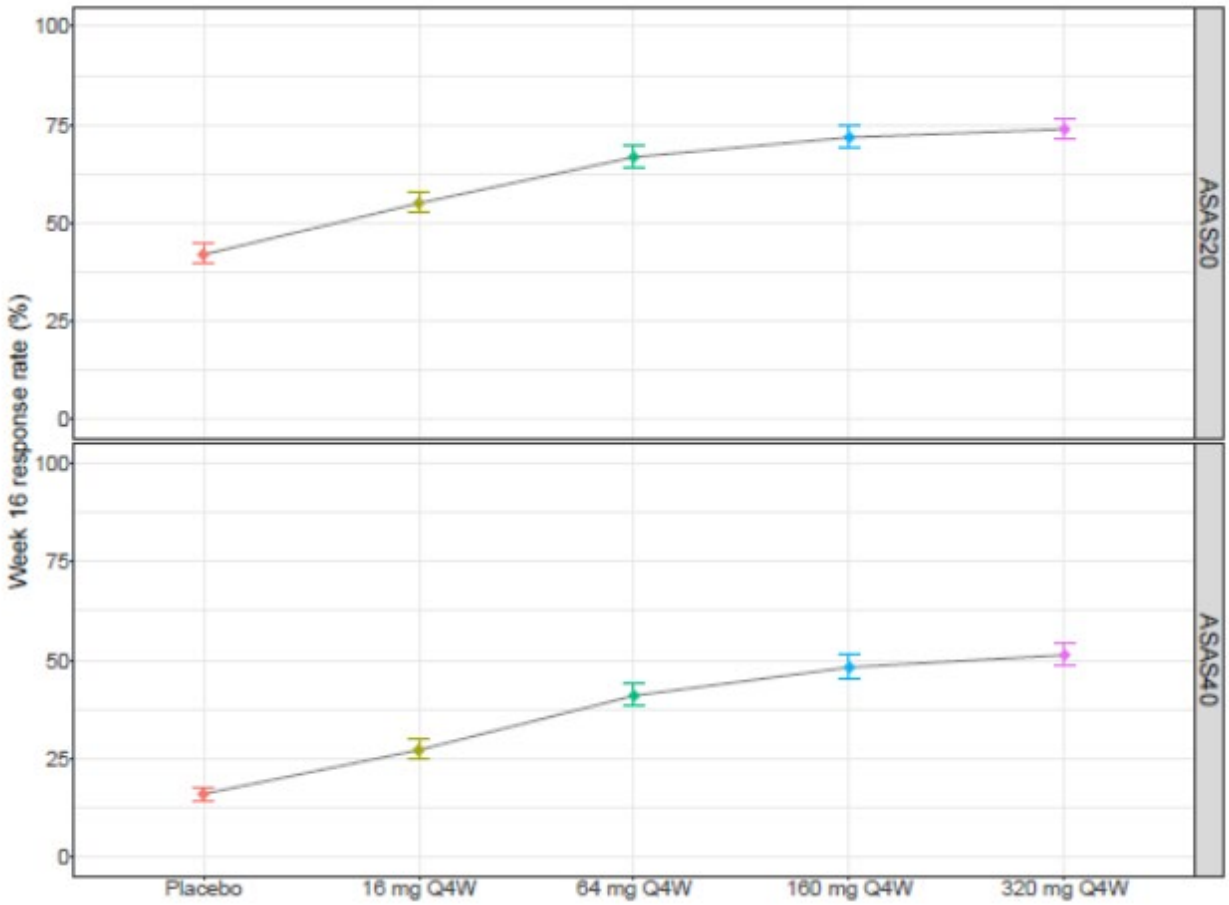


Figure 26: Predicted ASAS response rates at Week 16 versus dose. The points and the vertical error bars represent the median and 95% PI of the mean probabilities for each dose group. The plot is based on 591 bootstrap samples of 591 simulated study participants for each dose

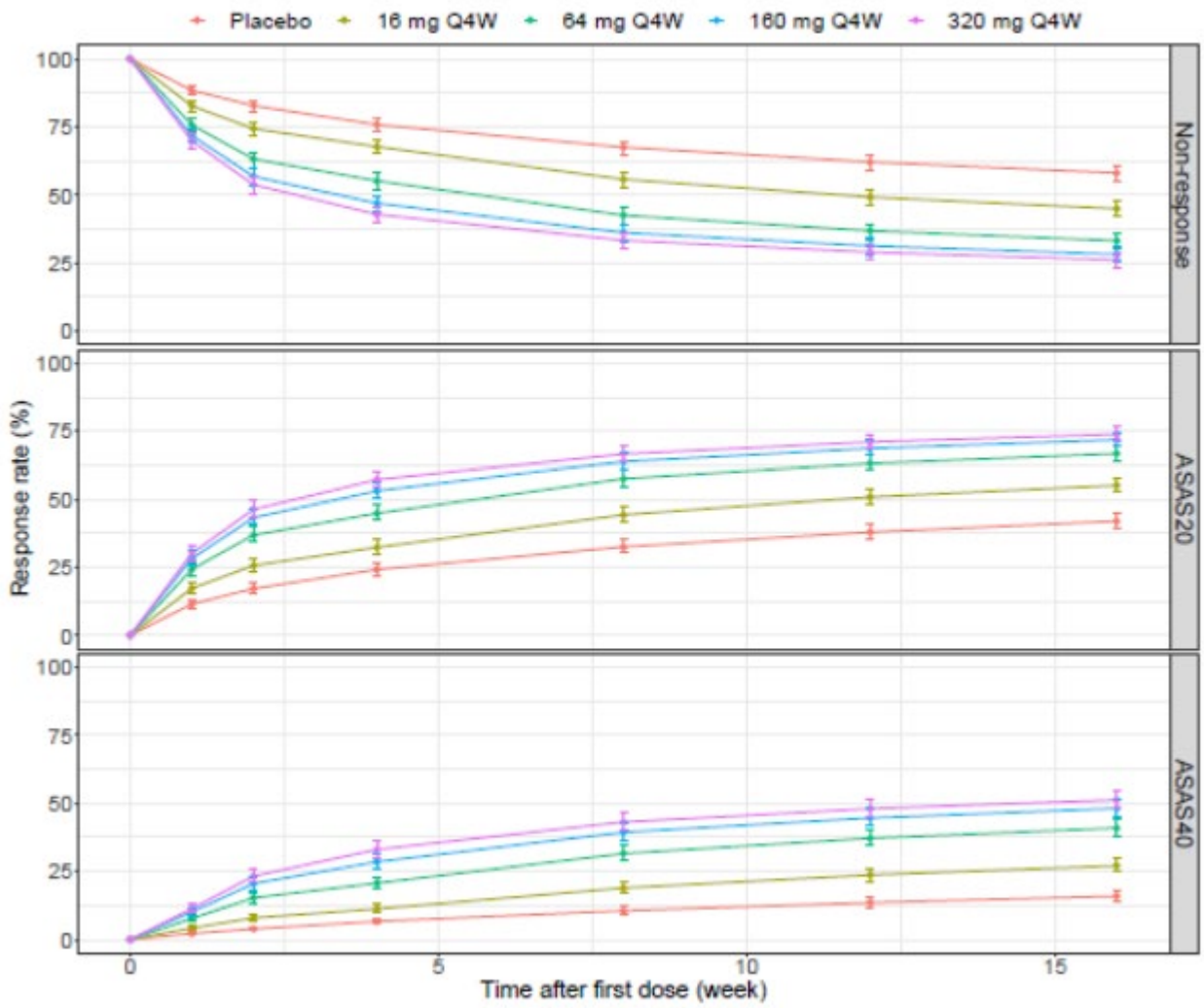


Figure 27: Predicted ASAS response rates versus time after first dose, stratified and colored by dose. The points and the vertical error bars represent the median and 95% PI of the mean response rates for each dose group. The plot is based on 591 bootstrap samples of 591 simulated study participants for each dose

Figure 28 shows the simulated ASAS response rates versus the observed bimekizumab concentration deciles at Week 16. The concentration-response curve is steep for low concentrations and then reaches a plateau. The median [5th to 95th percentile range] observed plasma concentrations in the 64 mg Q4W, 160 mg Q4W and 320 mg Q4W groups were 3.5 [1.3–7.8] µg/mL, 10.4 [4.1–20.4] µg/mL, and 20.7 [8.3–41.0] µg/mL, respectively. The median predicted ASAS40 response rate at the median [5th to 95th percentile range] observed plasma concentrations in the 64 mg Q4W, 160 mg Q4W and 320 mg Q4W groups was 39% [29%–46%], 48% [41%–51%], and 51% [46%–53%], respectively.

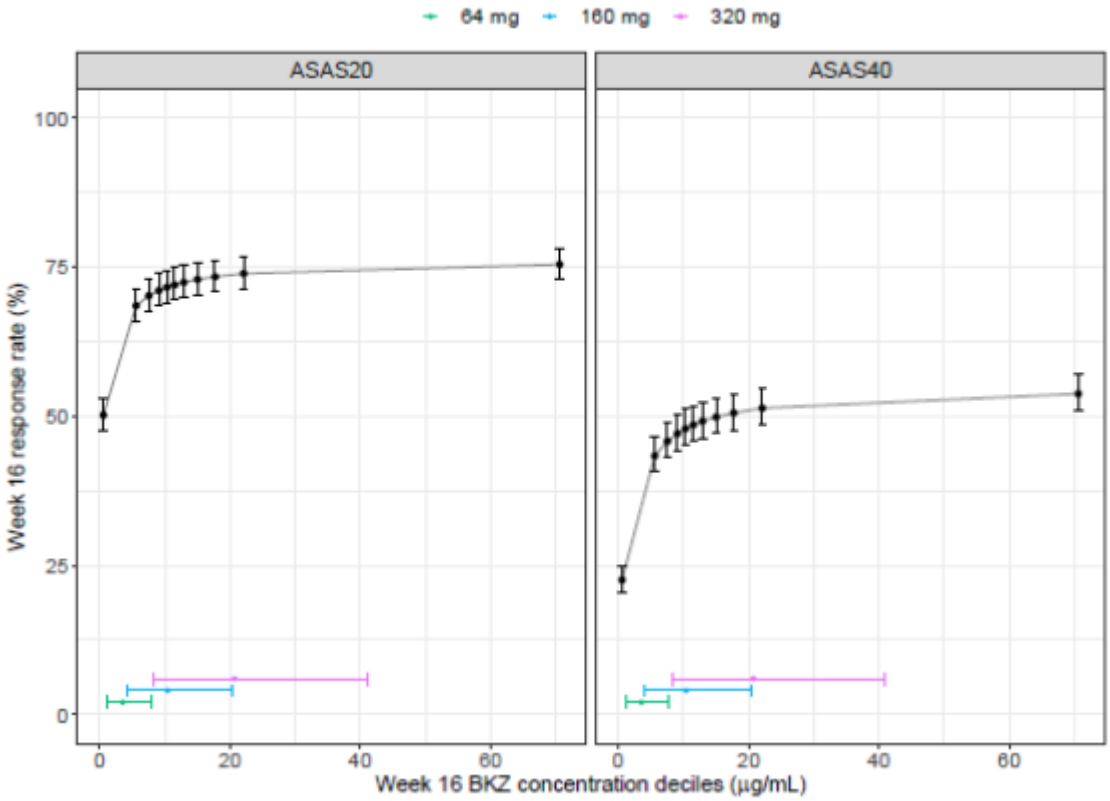


Figure 28: Predicted ASAS response rates at Week 16 versus bimekizumab concentration deciles. The points and the vertical error bars represent the median and 95% PI of the mean response rates for each concentration. The evaluated concentrations are the minimum, maximum and deciles of the observed Week 16 through concentrations in the 64, 160 and 320 mg dose groups in the axSpA population in the PK analysis data set (0.6 to 70.6 µg/mL). The colored horizontal error bars represent the range of concentrations at all time points (excluding SFU) in each dose group)5th to 95th percentile range, and the dot represents the median). The plot is based on 591 bootstrap samples of 591 simulated study participants for each concentration decile

In study participants with higher age or lower baseline hs-CRP levels, who were predicted to have lower ASAS response rates compared to a typical study participant, an increase in dose from 160 mg Q4W to 320 mg Q4W was expected to result in similar median ASAS response rate predictions, with overlapping prediction intervals:

- In study participants 61 years of age (95th percentile), the predicted median ASAS40 response was 34.3% (2.5th–97.5th percentile range, 31.5%–37.0%) for the 160 mg Q4W dose and 36.1% (2.5th–97.5th percentile range, 33.2%–38.9%) for the 320 mg Q4W dose, respectively.

- In study participants with baseline hs-CRP levels of 1 mg/L (5th percentile), the predicted median ASAS40 response was 37.8% (2.5th–97.5th percentile range, 35.1%–40.8%) for the 160 mg Q4W dose and 40.0% (2.5th–97.5th percentile range, 37.2%–43.0%) for the 320 mg Q4W dose, respectively.

Exposure-safety analysis of bimekizumab

The exposure-response relationships for safety include data from the Phase 3 studies, AS0010 and AS0011. These studies represent the majority of study participants who were treated with bimekizumab 160mg Q4W continuous dosing.

Infections were used in the exposure-response analysis since the incidence was high enough to result in a meaningful number of cases for comparison between the different plasma concentration quartiles. In addition, given the mechanism of action of bimekizumab, it is mechanistically considered possible to have an exposure-response relationship for infections.

Plasma bimekizumab trough concentrations were not associated with clinically-relevant increases in incidences of TEAEs or infection TEAEs. The incidences of TEAEs in the first, second, third, and fourth concentration quartiles for Pool SA2 were 81.0%, 83.8%, 73.8%, and 75.0%, respectively, and the incidences of infection TEAEs were 55.7%, 61.3%, 40.0%, and 48.7%, respectively (Table 31). Likewise, no clear pattern was observed for the incidences of TEAEs in the first, second, third, and fourth concentration quartiles for the high-level group term of fungal infectious disorders (12.7%, 22.5%, 12.5%, and 9.2%, respectively) or the high-level term of Candida infection (7.6%, 11.3%, 7.5%, and 5.3%, respectively). Thus, no clear trend was observed between bimekizumab exposure following 160mg Q4W in study participants with axSpA and the incidences of overall TEAEs, infection TEAEs, fungal infectious disorder TEAEs, or Candida infection TEAEs.

None of the most frequently reported TEAEs by PT (defined as ≥5% of study participants in any plasma concentration quartile) showed a meaningful increase in incidence with increasing bimekizumab trough plasma concentration quartile (Table 31).

Table 31: Incidence of TEAEs and Infection TEAEs per 100 participant-years reported by ≥5% of study participants at the PT level during the combined initial and Maintenance Treatment Period by Week 24 bimekizumab trough plasma concentration quartile (Study participants initially randomized to bimekizumab; Pool SA2)

	Phase 3 BKZ 160mg Q4W Trough Plasma Concentration Quartile			
MedDRA v19.0 PT	≤9.03µg/mL N=79 100 participant-yrs=0.74 n (%) [#] Incidence (95% CI)	>9.03 to ≤12.3µg/mL N=80 100 participant-yrs=0.73 n (%) [#] Incidence (95% CI)	>12.3 to ≤15.7µg/mL N=80 100 participant-yrs=0.75 n (%) [#] Incidence (95% CI)	>15.7ug/mL N=76 100 participant-yrs=0.70 n (%) [#] Incidence (95% CI)
Any TEAE	64 (81.0) [243] 211.5 (162.8, 270.0)	67 (83.8) [327] 275.0 (213.1, 349.3)	59 (73.8) [200] 166.9 (127.0, 215.2)	57 (75.0) [217] 170.8 (129.4, 221.3)
Any Infections TEAE [a]	44 (55.7) [80] 97.6 (70.9, 131.1)	49 (61.3) [113] 115.7 (85.6, 153.0)	32 (40.0) [66] 58.8 (40.2, 83.0)	37 (48.7) [65] 76.7 (54.0, 105.7)
Oral candidiasis	5 (6.3) [9] 7.2 (2.3, 16.7)	7 (8.8) [7] 10.3 (4.1, 21.1)	5 (6.3) [5] 6.9 (2.2, 16.1)	3 (3.9) [3] 4.4 (0.9, 12.8)
Gastroenteritis	4 (5.1) [6] 5.6 (1.5, 14.3)	3 (3.8) [3] 4.2 (0.9, 12.3)	1 (1.3) [1] 1.3 (0.0, 7.5)	1 (1.3) [1] 1.5 (0.0, 8.1)
Nasopharyngitis	10 (12.7) [12] 15.4 (7.4, 28.3)	12 (15.0) [15] 18.3 (9.5, 32.0)	9 (11.3) [10] 13.2 (6.1, 25.1)	6 (7.9) [7] 9.1 (3.3, 19.8)
Upper respiratory tract infection	9 (11.4) [10] 13.3 (6.1, 25.2)	4 (5.0) [4] 5.7 (1.6, 14.6)	5 (6.3) [5] 7.1 (2.3, 16.5)	5 (6.6) [6] 7.6 (2.5, 17.6)
Sinusitis	0	4 (5.0) [4] 5.6 (1.5, 14.3)	1 (1.3) [1] 1.4 (0.0, 7.5)	4 (5.3) [6] 6.0 (1.6, 15.3)
Corona virus infection	3 (3.8) [3] 4.1 (0.9, 12.0)	4 (5.0) [4] 5.5 (1.5, 14.1)	1 (1.3) [1] 1.4 (0.0, 7.6)	2 (2.6) [2] 2.9 (0.4, 10.5)
MedDRA v19.0 PT	≤9.03µg/mL N=79 100 participant-yrs=0.74 n (%) [#] Incidence (95% CI)	>9.03 to ≤12.3µg/mL N=80 100 participant-yrs=0.73 n (%) [#] Incidence (95% CI)	>12.3 to ≤15.7µg/mL N=80 100 participant-yrs=0.75 n (%) [#] Incidence (95% CI)	>15.7ug/mL N=76 100 participant-yrs=0.70 n (%) [#] Incidence (95% CI)

BKZ=bimekizumab; CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event; yrs=years

Note: n=number of study participants reporting at least 1 TEAE within the category being summarized. [#] is the number of individual occurrences of TEAEs within the category being summarized.

Note: Due to the relatively low number of study participants treated with the BKZ 160mg Q4W regimen in the Phase 2b studies, only data from the Phase 3 studies AS0010 and AS0011 included in Pool SA2 were pooled and are presented in this table.

Note: Bimekizumab trough plasma concentration quartiles were based on Week 24 PK samples. Study participants with Week 24 PK sample missing were not included in this table.

[a] Includes all TEAEs which coded to the System Organ Class of "Infections and infestations."

2.3.5. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

The PK method used a standard ligand binding approach based on the meso scale discovery (MSD) platform. Four PK assays were used, three of which were previously assessed in the initial MAA for psoriasis and therefore are considered to be appropriately validated. Method performance data from the clinical studies were provided by the MAH, and in general showed that the methods performed as expected.

The ADA method used a standard ligand binding MSD platform approach where samples and positive and negative controls were incubated with Biotin-UCB4940, Sulfo-Tag-UCB4940, anti-human IL-17A, and rabbit anti-human IL-17F. Any ADA present in the human plasma will form a bridge between the Biotin-UCB4940 and Sulfo-Tag-UCB4940 molecules, with the anti-human IL-17A and anti-human IL-17F. Five versions of the ADA assay were used throughout development, all of which were previously assessed in

the original MAA for the psoriasis indication. Bioanalytical reports from all relevant clinical studies have been provided and show that the assay passed routine control testing and performed as expected.

Competitive ligand binding assay methods were used to detect neutralising antibodies. The methods were assessed as part of the initial MAA submission for the PSO indication. Bioanalytical study reports were provided for each study and showed acceptable assay performance.

Additional validation data were submitted due to questionable performance of the NAb assays during sample analysis from plaque psoriasis patients and showed acceptable assay performance. Assay performance in patients with PsA and axSpA was appropriately described.

Bioavailability

Study UP0067

The study design and methodology of the Phase 1 study, UP0067, in healthy, Chinese subjects were appropriate. The rationale for and exclusion of participants from the PK analyses were acceptable. The results indicated dose-proportional PK of bimekizumab between the dose range studied (160mg to 320mg), which is consistent with other PK studies of bimekizumab in different populations. Apparent clearance (CL/F) was independent of dose. Similar half-life and apparent clearance (CL/F) to the other populations were observed.

Device use study (DV0004)

The design and methodology of the device use study (DV0004) are acceptable. Exclusion of participants from each study arm was adequately detailed and per protocol. Self-injection was investigated into the thigh or abdomen. The MAH has considered that self-administration into the upper arm is not convenient (especially for patients with limited hand dexterity) and was thus not evaluated in DV0004. This is acknowledged.

Overall, the results of the device presentation substudy demonstrated that there were no clinically meaningful differences observed in bimekizumab plasma trough concentrations between investigational device presentations (bimekizumab-SS-1mL and bimekizumab-AI-1mL), and injection by study personnel or self-injection.

Although the participant numbers were lower in study participants who chose to self-inject in the thigh compared with the abdomen, the bimekizumab trough concentrations were similar.

As expected, plasma trough concentrations were inversely related to BMI. This is in-line with the population PK analyses where body weight was a significant covariate on CL/F and V/F, explaining the decrease in plasma concentration with an increase in weight. See below Special Populations section for further discussion of the impact of body weight on bimekizumab exposure. Within each BMI tertile, plasma concentrations were generally similar irrespective of whether the previous dose had been administered by the study participant or study personnel.

It is agreed that symptoms associated with PsA, compared to axial spondyloarthritis (axSpA), are more likely to negatively impact dexterity and coordination of the patient’s hands and arms. Therefore, it is reasonable to expect that patients with axSpA will be able to self-inject safely and effectively if patients with PsA are able to do so. Therefore, by extrapolation, the results of DV0004 also support safe and effective self-administration using these device presentations in patients with axSpA.

Of note, in the pivotal Phase 3 studies (AS0010 and AS0011), dose administration in the lateral abdominal wall, upper arm and upper outer thigh by study staff was permitted. It was recommended to rotate between different injection sites during the study.

PK in the target population

Phase 2

The results of study AS0008 indicated dose-proportional PK of bimekizumab between the dose ranges studied (16mg, 64mg, 160mg and 320mg), which is consistent with other PK studies of bimekizumab in different populations. The results indicated steady state was reached between weeks 16-20, which is consistent with the bimekizumab half-life of 23 days.

Participants who remained on bimekizumab 160mg between studies AS0008 and AS0009 achieved and maintained steady state throughout the study. As expected, participants who moved from bimekizumab 320mg in study AS0008 to 160mg in study AS0009 had nearly 2-fold concentrations of bimekizumab at the entry visit and the concentration lowered and achieved steady state by Week 24. This is in line with other studies that showed bimekizumab concentrations normally reach steady state after approximately 16 weeks.

In study AS0013, the bimekizumab 160mg Q2W dosing regimen was selected as it was expected to provide similar overall exposure to bimekizumab 320mg Q4W due to bimekizumab PK being linear in this range. The Treatment Period (Week 0 to Week 12) was not considered sufficiently long to show steady state levels for bimekizumab 160mg Q2W. Nevertheless, given that this was an exploratory Phase IIa study to assess efficacy, the issue was not further pursued by CHMP.

Phase 3

The pharmacokinetic results from the Phase 3 studies were in line with other studies in this application, with steady state being reached at Week 16 in the bimekizumab 160mg groups. This has been adequately reflected in SmPC section 5.2.

Bimekizumab plasma concentrations observed in Japanese study participants were generally comparable with those observed in the overall study population following bimekizumab 160 mg Q4W in both studies. Due to the small number of Japanese study participants, conclusions are nevertheless limited.

Overall, final PK data from the phase 2 axSpA studies (AS0008 and AS0013) were provided and summarised with descriptive statistics. Summarised PK data up to Week 108 for the phase 2 study AS0009 and up to Week 24 for the phase 3 studies AS0010 and AS0011 were also provided by the MAH in this submission. The MAH committed to submit the final AS009 CSR in Q2 2023.

Population PK modelling

In the integrated popPK analysis, the methods used for model development and evaluation are considered acceptable. Data exclusions were well detailed and acceptable.

The starting model for this analysis was based on the previous popPK model for bimekizumab in patients with PSO. The key findings from this popPK analysis in patients with PSO, PsA, or axSpA were consistent with those made from the previous popPK analysis of PSO data only.

The final model, a one-compartment model with first-order absorption and elimination, adequately described the data. The choice of a one-compartment rather than a two-compartment structural model was adequately justified by the MAH. Among the tested covariates, only bodyweight on CL/F and V/F and race on CL/F were retained in the final model. Bodyweight had the largest impact on CL/F and impacted V/F to a lesser extent, with higher body weight being associated with reduced bimekizumab exposure. Japanese patients were predicted to have 23% higher CL/F, and Chinese and other Asian patients were predicted to have 13% higher CL/F, compared to the reference Caucasian population. See Special populations for further details.

All PK parameters (fixed and random effects) in the final model were estimated with good precision (RSE<22.5%). The IIV terms were associated with reasonable shrinkage values: 22%, 34% and 15% for CL/F, V/F and Frel, respectively. The GOF plots showed that the model described the observed data well. 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 PK/PD modelling analyses.

Immunogenicity

In the clinical phase 3 studies, treatment-emergent ADAb occurred as early as 4 weeks post first dose at the earliest sampling time point, and cumulative counts increased over time. The overall incidence of treatment-emergent ADAb was 31.3% following 16 weeks of treatment and 43.8% following 1 year of treatment with bimekizumab 160mg Q4W in the pooled Phase 3 axSpA studies based on the available data at the clinical data cut-off. The ADA positivity following 52 weeks of treatment was 57.1% (68/119) in nr-axSpA subjects and 44.3% (86/194) in AS subjects. The percentage of NAb-positive study participants in the bimekizumab following 52 weeks of treatment was 25.2% (30/119) in nr-axSpA subjects and 19.6% (38/194) in AS subjects. When pooled data are considered, 49.2% (154/313) of study participants had at least 1 ADAb-positive sample following 52 weeks of treatment.

The overall incidence of Nab-positive study participants in the bimekizumab 160mg Q4W group was 11.8% by Week 16 and 21.4% by Week 52 in all available study participants in the pooled Phase 3 axSpA studies.

Bimekizumab plasma concentrations were not impacted in the presence of ADAb or Nab at Week 16, but tended to be slightly lower in Nab-positive participants compared with ADAb-negative participants after Week 16.

The overall incidence of NAb-positive study participants in the bimekizumab following 52 weeks of treatment was 21.7% (68/313).

Key efficacy endpoints (ASAS40 and ASAS20) by ADAb and Nab status at Week 16 showed slightly lower response rates in ADAb-positive participants and lower response rates in Nab-positive participants or participants with high ADAb titers, compared with ADAb-negative participants. However, the number of Nab-positive study participants and study participants in each titer grouping was low, thus limiting interpretation.

ADAb status, ADAb titers, and Nab status were not identified as clinically relevant covariates in the population PK analysis. Further, ADAb and Nab status were not identified as statistically significant covariates in the popPK/PD (ASAS) analysis. In addition, ADAb or Nab positivity had no clinically meaningful impact on the safety profile of bimekizumab regarding serious immune-based adverse reactions and injection site reactions, an increase in hypersensitivity TEAEs with ADAb positivity was noted. See Clinical Safety section on ADAb.

Overall, based on all the available data, the presence of ADAb had no clinically meaningful impact on efficacy (as assessed by ASAS response at Week 16) in axSpA clinical studies. However, participants who were Nab-positive had a reduced response compared to those who were ADAb-negative. ADAb and Nab had no clinically meaningful impact on the safety profile of bimekizumab in axSpA regarding serious immune-based adverse reactions and injection site reactions, though, an increase in hypersensitivity TEAEs with ADAb positivity was noted.

As requested, the MAH did provide individual study and pooled data up to week 52 for further analysis of immunogenicity data. In the pooled analysis, bimekizumab plasma concentrations were similar in ADAb-positive and ADAb-negative participants while bimekizumab plasma concentrations tended to be slightly lower in NAb-positive compared with ADAb-negative participants based on overall NAb status at Week 52.

Data on ADA and Nab status up to week 52 from each individual studies AS0010 and AS0011 were adequately reflected in the SmPC section 4.8.

Special populations

A dose adjustment in terms of renal/hepatic impairment, age and sex is not considered warranted by the MAH. This is agreed.

Race

The impact of race on bimekizumab exposure was less pronounced than that of body weight. Simulations suggested that bimekizumab exposure following 160mg Q4W was comparable in Japanese, Chinese/other Asian, and Caucasian participants since the effect of faster clearance on exposure was offset by the smaller median body weight in Japanese and Chinese/other Asian participants compared with Caucasian participants. Therefore, a dose adjustment of bimekizumab in terms of race is not considered warranted by the MAH. This is agreed. SmPC section 5.2 has been updated to reflect that no clinically meaningful differences in bimekizumab exposure were observed in Chinese subjects compared to Caucasian subjects.

Body weight

In the popPK analysis, body weight had a significant impact on bimekizumab exposure following 160 mg Q4W. However, in the PK/PD model of ASAS response, the median ASAS response rates at Week 16 were only slightly increased when exposure increased (lower CL/F), and slightly decreased when exposure decreased (higher CL/F). The ASAS20 response rate ranged from 69% to 74%, compared to 72% for a typical CL/F. The ASAS40 response rate ranged from 44% to 52%, compared to 49% for a typical CL/F. Further, bimekizumab exposure following 160mg Q4W at the higher end of the exposure range in study participants with AxSpA did not appear to be associated with increased incidences of overall TEAEs and infection TEAEs. Therefore, a dose adjustment of bimekizumab in patients with axSpA is not considered warranted in terms of body weight, including overweight patients (≥120 kg).

Drug Interactions

The lack of DDI studies for this application is acceptable. Population PK data analyses indicated that the clearance of bimekizumab was not impacted by concomitant administration of conventional disease modifying antirheumatic drugs (cDMARDs) including methotrexate, or by prior exposure to biologics (See SmPC section 4.5).

Pharmacodynamics

Primary pharmacology

In study AS0008, the pharmacodynamic variables selected were appropriate. None of the immunological parameters selected showed significant dose or time dependent changes with bimekizumab treatment in adult participants with axSpA.

Secondary pharmacology

The omission of a thorough QT/QTC clinical study is acceptable.

PK/PD modelling

Phase 2

The Phase 2 population PK/PD analysis was conducted to select the dose regimen/s to be tested in the pivotal Phase 3 studies. Based on the results, the selected dose regimen of 160 mg Q4W for patients with axSpA in the Phase 3 studies is considered appropriate.

Phase 2 and Phase 3

The developed population PK-PD model provided a good description of the ER relationship between bimekizumab concentrations and the efficacy endpoint (ASAS). Covariates were identified and their impact on the ASAS response was evaluated. The results were used to inform the rationale for the proposed dose regimen in patients with axSpA.

The final ASAS response model was a proportional odds model, where the probability of being an ASAS20 or an ASAS40 responder was a function of the baseline probability, the treatment effect, and IIV. The probability of ASAS increased with increasing baseline hs-CRP, and with decreasing age. No further covariate effects were identified including disease indication (axSpa vs nr-axSpA), ADAb/Nab status, concomitant medications at Baseline (MTX, NSAIDs, csDMARDs, or corticosteroids) and WT. The VPCs indicated that the model was adequate for simulations.

The ER relationship of bimekizumab and ASAS response was shown to be steep but reached a plateau by 160 mg Q4W. The predicted median ASAS40 response rates at Week 16 were 16% for the placebo group and 27%, 41%, 48%, and 51% for 16 mg, 64 mg, 160 mg and 320 mg Q4W dosing regimens, respectively. This supports the proposed bimekizumab dose regimen of 160 mg Q4W for patients with axSpA.

Variation in bimekizumab PK, as a result of PK covariate relationships (weight and race), had a limited impact on the predicted probability of ASAS response, assuming a 160 mg Q4W dosing regimen. See special populations for further discussion.

The impact of baseline age and baseline hs-CRP on ASAS response rates was greater than the impact of PK covariate relationships. The ASAS response rates decreased with increasing age and increased with increasing baseline hs-CRP. However, in study participants with higher age or lower baseline hs-CRP levels, an increase in dose from 160 mg Q4W to 320 mg Q4W resulted in similar median ASAS response rate predictions, with overlapping prediction intervals.

Exposure-safety analysis

Bimekizumab plasma trough concentrations following 160 mg Q4W in Phase 3 studies were not associated with clinically relevant increases in incidences of TEAEs or infection. Bimekizumab doses up to 320mg Q4W were tested in the Phase 2b study AS0008 and all doses were well-tolerated and had no unexpected safety signals.

2.3.6. Conclusions on clinical pharmacology

The bimekizumab pharmacokinetics in adult patients with r-axSpA and nr-axSpA has been adequately characterised and the PK properties were similar in patients with plaque psoriasis and PsA. Section 5.2 of the SmPC was updated accordingly. The selected dose regimen of 160 mg Q4W for patients with axSpA in the Phase 3 studies is considered appropriate. Section 4.5 of the SmPC is updated to indicate that PK analyses have shown that drug clearance of bimekizumab was not impacted by concomitant administration of cDMARDs including methotrexate or by prior exposure to biologics.

2.4. Clinical efficacy

2.4.1. Dose response study

To support this extension of indication application, the MAH has submitted the results of a dose-finding study, AS0008.

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	AS0008/ NCT02963506/ Bulgaria, Canada, Czech Republic, Germany, Hungary, Poland, Russia, Spain, Ukraine, and US	AS0008 CSR and Addendum 1 PSO submission 5.3.5.1 Addendum 2 5.3.5.1	To evaluate the efficacy, PK, PD, and safety of BKZ	Phase 2b, randomized, DB, PBO-controlled, parallel-group, dose-ranging	Active AS	BKZ or PBO/ DB Period (12 weeks): BKZ 16mg, 64mg, 160mg, or 320mg Q4W, or PBO Q4W/ sc injection Dose-blind Period (36 weeks): If randomized to BKZ 160mg or 320mg Q4W in DB Period, then continued on the same treatment dose If received BKZ 16mg or 64mg Q4W or PBO Q4W during DB Period, rerandomized (1:1) to BKZ 160mg or 320mg Q4W/ sc injection	303 study participants randomized: DB Period: 61 BKZ 16mg 61 BKZ 64mg 60 BKZ 160mg 61 BKZ 320mg 60 PBO Dose-blind Period: 58 BKZ 160mg/160mg 61 BKZ 320mg/320mg 31 BKZ 16mg/160mg 27 BZK 16mg/320mg 34 BKZ 64mg/160mg 25 BKZ 64mg/320mg 24 PBO/BKZ 160mg 36 PBO/BKZ 320mg	48 weeks	Complete/ Final Two addenda to final report

This section will assess only the efficacy aspects of this clinical study. Other aspects are addressed in the relevant sections of this report.

Design

AS0008 was a Phase 2b, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study to investigate the efficacy, safety, PK, and PD of bimekizumab compared with placebo in adult study participants with active AS. Study participants were randomised 1:1:1:1:1 to 1 of 5 groups; placebo or bimekizumab 16mg, 64mg, 160mg, or 320mg sc Q4W.

A total of 303 study participants were randomised as follows: 60 study participants in the placebo group, 61 study participants in the bimekizumab 16mg group, 61 study participants in the bimekizumab 64mg group, 60 study participants in the bimekizumab 160mg group, and 61 study participants in the bimekizumab 320mg group. Overall, 297 study participants (98.0%) completed the Double-Blind Treatment Period, and the percentages of participants who completed the Double-Blind Treatment Period were high and similar across all groups.

Patient characteristics

Eligible subjects had to have active AS, determined by documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS (1984), including symptoms for ≥3 months and age of onset <45. Furthermore, subjects will have moderate to severe active disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4 and spinal pain ≥4 [BASDAI Question 2]). Subjects must have at least 1 of the following: 1) inadequate response to nonsteroidal anti-inflammatory drug (NSAID) therapy, 2) intolerance to administration of at least 1 NSAID, or 3) contraindication(s) to NSAID therapy.

The inclusion and exclusion criteria were similar to those applied in the pivotal phase 3 studies, AS0010 and AS0011.

Overall, treatment groups were well balanced, and demographics were similar across groups (age, gender, weight, race, ethnicity, and geographic region. The mean age of study participants was 42.16 years (range: 21.0 to 75.0 years)]. Most study participants were male (84.5%) and white (98.3%). The mean body weight and mean BMI were 80.32kg and 26.87kg/m2.

Treatment groups were well balanced with respect to AS-related and other baseline disease characteristics. Overall, the mean time since diagnosis of AS was 7.88 years (range: 0 to 37.3 years) with

a mean age at diagnosis of AS of 34.79 years. The mean time since the onset of the first AS symptoms was 14.57 years (range: 0.2 to 47.2 years). Most study participants (89.1%) were positive for HLA-B27, a genetic marker associated with AS.

Overall, these observed patient characteristics are similar to those observed in the later studies AS0010 and AS0011.

Efficacy results

The primary efficacy endpoint was the ASAS40 response at Week 12. The dose-response relationship between treatment and ASAS40 response at week 12 was assessed with an ordered categorical analysis using a non-parametric correlation statistic of Mantel and Haenszel (Mantel and Haenszel, 1959) and modified ridit scores (Bross, 1958) with the corresponding p-value. The analysis included geographic region and prior TNF inhibitor exposure (yes/no) as stratification factors. The correlation between dose and ASAS40 response was evaluated at a 2-sided significance level of α=0.05

- ASAS40 response at Week 12

Across the bimekizumab doses included in the Cochran-Mantel-Haenszel test, a statistically significant dose response was observed in ASAS40 responder rates at Week 12 (p<0.001). This dose response was linear at bimekizumab doses up to 160mg, with ASAS40 responder rates at Week 12 ranging from 29.5% (bimekizumab 16mg) to 46.7% (bimekizumab 160mg). The ASAS40 responder rate at Week 12 in the placebo group was 13.3%.

Based on the clinical data and the PK/PD analysis, a bimekizumab 160mg Q4W regimen was selected as the dose for both Initial Treatment Period (up to Week 16) and Maintenance Treatment Period (up to Week 52) in the 2 Phase 3 studies.

Table 32: Dose response of ASAS40 response at Week 12 with a Cochran-Mantel-Haenszel test (FAS [NRI]) (AS0008)

	Placebo N=60 n (%)	BKZ 16mg N=61 n (%)	BKZ 64mg N=61 n (%)	BKZ 160mg N=60 n (%)	BKZ 320mg N=61 n (%)	Correlation statistic [a]	p-value [a]
Responders	8 (13.3)	18 (29.5)	26 (42.6)	28 (46.7)	28 (45.9)	17.9	<0.001

ASAS40=Assessment of SpondyloArthritis International Society 40%; BKZ=bimekizumab; CSR=clinical study report; FAS=Full Analysis Set; IMP=investigational medicinal product; NRI=nonresponder imputation; TNF=tumor necrosis factor

Note: Percentages were based on the number of study participants in the FAS.

Note: Study participants with missing data at Week 12 or who discontinued IMP prior to Week 12 were counted as nonresponders.

[a] Statistic and p-value were calculated using a Cochran-Mantel-Haenszel test (correlation statistic) based on modified ridit scores and including geographic region and prior TNF inhibitor exposure as stratification factors.

2.4.2. Main studies

To support this extension of indication application, the MAH has submitted the results of 2 pivotal efficacy studies.

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment
Efficacy and safety	AS0010/ NCT03928704/ Belgium, Bulgaria, China, Czech Republic, France, Germany, Hungary, Japan, Netherlands, Poland, Spain, Turkey, UK, and US	5.3.5.1	To evaluate the efficacy and safety of BKZ in study participants with active nr-axSpA	Phase 3, randomized, DB, PBO-controlled	Active nr-axSpA	BKZ or PBO/ DB Period (16 weeks): BKZ 160mg Q4W or PBO Q4W/ sc injection Maintenance Period (36 weeks): BKZ 160mg Q4W/ sc injection	254 study participants randomized: DB Period: 128 BKZ 160mg 126 PBO Maintenance Period: 126 BKZ 160mg 116 PBO/BKZ 160mg	52 weeks
Efficacy and safety	AS0011/ NCT03928743/ Belgium, Bulgaria, China, Czech Republic, France, Germany, Hungary, Japan, Netherlands, Poland, Spain, Turkey, UK, and US	5.3.5.1	To evaluate the efficacy and safety of BKZ in study participants with active AS	Phase 3, randomized, DB, PBO-controlled	Active AS	BKZ or PBO/ DB Period (16 weeks): BKZ 160mg Q4W or PBO Q4W/ sc injection Maintenance Period (36 weeks): BKZ 160mg Q4W/ sc injection	332 study participants randomized: DB Period: 221 BKZ 160mg 111 PBO Maintenance Period: 210 BKZ 160mg 109 PBO/BKZ 160mg	52 weeks

These two efficacy studies, AS0010 and AS0011, were reported to be currently ongoing at the time of initial submission, and so the only complete dataset was related to that for patients who have completed the primary efficacy endpoint assessment at 16 weeks. However, data up to Week 24 was presented by the MAH. Upon CHMP's request, the MAH submitted the final dataset comprising of the full 52-week Maintenance phase.

The design and currently available efficacy results for these two studies are summarised in the following sections.

2.4.2.1. AS0010 (BE MOBILE 1)

Title of Study

A phase 3, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in subjects active nonradiographic axial spondyloarthritis (nr-axSpA).

Methods

AS0010 is a multicentre, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with nr-axSpA.

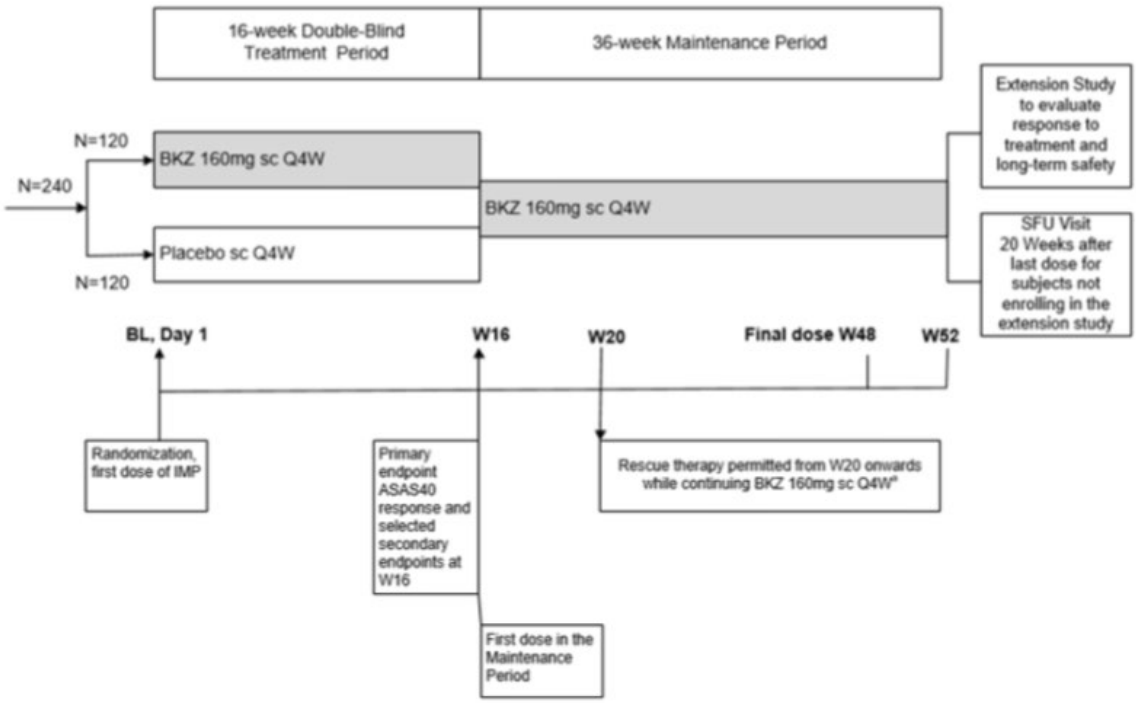
Study participants who completed Week 52 may be eligible for enrolment in an OLE study (AS0014) with bimekizumab. Study participants who are ineligible for, or elect not to participate in, the extension study at Week 52 undergo a Safety Follow-Up (SFU) Visit at the end of the SFU Period.

Interim analyses of all available data were conducted after the planned number of randomised study participants completed 24 weeks and were to be conducted after the completion of 52 weeks of treatment or withdrawal from IMP or the study. The final analysis of all available data was performed after all

randomised study participants have completed the SFU Visit or have withdrawn from the IMP and/or study, or enrolled in the OLE study.

An independent DMC and adjudication committees periodically review and monitor safety data from this study.

Figure 29: Schematic diagram: study overview



ASAS40=Assessment of SpondyloArthritis International Society 40% response criteria; BKZ=bimekizumab; BL=Baseline; IMP=investigational medicinal product; Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-up; W=week
Note: The planned enrollment was approximately 240 participants. For actual enrollment, see Table 7–1.
[a] Study participants were eligible for nonbiologic rescue therapy starting at Week 20, with treatment at the discretion of the Investigator, while continuing to receive BKZ. Treatment with non-BKZ biologics or prohibited treatment led to BKZ discontinuation.

Study participants

To qualify for enrolment into this study, study participants had to fulfil the following inclusion criteria;

- Study participant was male or female at least 18 years of age.
- Study participant had nr-axSpA with all the following criteria:
  - Adult-onset axSpA meeting ASAS classification criteria
  - Inflammatory back pain for at least 3 months prior to the Screening Visit
  - Age at symptom onset <45 years
- Study participants must NOT have had sacroiliitis as defined by mNY criteria, based on central reading of AP pelvis or sacroiliac x-rays taken at Screening or within the last 6 months prior to Screening.
- Study participants must have had active disease as defined by having both BASDAI ≥4 AND spinal pain ≥4 on a 0 to 10 NRS.

- Study participants must have had objective inflammation as defined by sacroiliitis on the Screening MRI AND/OR elevated CRP and no alternate diagnosis to explain these findings. Study participants who were MRI negative must have had elevated CRP and been HLA-B27 positive.
- Study participants had to have either failed to respond to 2 different NSAIDs given at the maximum tolerated dose for a total of 4 weeks or had a history of intolerance to, or a contraindication to, NSAID therapy.
- Study participants who were regularly taking NSAIDs/cyclooxygenase 2 inhibitor (COX-2) inhibitors or analgesics (including mild potency opioids) were required to be on a stable dose for at least 14 days before Baseline.
- Other background medicines were also allowed if patients were on stable dose regimens.
- Study participants who had taken a TNFα inhibitor must have experienced an inadequate response to previous treatment given at an approved dose for at least 12 weeks or have been intolerant to treatment.
- Female study participants must have been postmenopausal, permanently sterilised. Or must have been willing to use a highly effective method of contraception throughout the duration of the study.

The exclusion criteria related to patient safety, concomitant medications, or known safety concerns with the IMP, and were appropriate.

Those subjects who did not meet the radiographic inclusion criteria for AS0010 may have been eligible for inclusion to the related study AS0011.

Treatments

Eligible study participants were randomised 1:1 to receive either bimekizumab 160mg sc Q4W or placebo sc Q4W, and remain on allowable background medication, until Week 16. Thereafter, study participants randomised to bimekizumab remained on their randomised while those who received placebo were reallocated to receive bimekizumab 160mg Q4W.

Objectives

The primary objective was to demonstrate the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) compared to placebo in the treatment of study participants with active nr-axSpA.

The secondary objectives of the study were:

- To assess the efficacy of bimekizumab compared to placebo
- To assess the safety and tolerability of bimekizumab
- To assess the impact of bimekizumab on patient-reported quality of life
- To assess the impact of bimekizumab on spinal mobility
- To assess the impact of bimekizumab on enthesitis and on peripheral arthritis.

Outcomes/endpoints

The primary efficacy endpoint for this study was the ASAS40 response at Week 16.

The secondary efficacy endpoints for this study were as follows:

• ASAS40 response at Week 16 in TNFα inhibitor-naïve study participants

• Change from Baseline in BASDAI total score at Week 16

• ASAS 20% (ASAS20) response at Week 16

• ASAS partial remission (ASAS-PR) at Week 16

• Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) at Week 16

• ASAS 5 out of 6 criteria (ASAS5/6) response at Week 16

• Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16

• Change from Baseline in Nocturnal Spinal Pain score (based on NRS) at Week 16

• Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) total score at Week 16

• Change from Baseline in the Short Form 36-Item Health Survey (SF-36) physical component summary (PCS) score at Week 16

• Change from Baseline in Bath Ankylosing Spondylitis Disease Metrology Index (BASMI) at Week 16

• Change from Baseline in the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index in the subgroup of study participants with enthesitis at Baseline at Week 16

• Enthesitis-free state based on the MASES Index in the subgroup of study participants with enthesitis at Baseline at Week 16

Sample size

Approximately 240 study participants were planned to be randomly assigned in a 1:1 ratio to bimekizumab 160mg sc or placebo sc Q4W. All sample size and power calculations were done at a significance level of 0.05 in a 2-sided test.

The sample size assumptions for bimekizumab versus placebo were based on the ASAS40 response data from the Phase 2b bimekizumab study in study participants with active AS (AS0008) and assumed an ASAS40 response at Week 16 of 40% for the bimekizumab treatment group and 20% for the placebo group.

With 120 study participants in the bimekizumab treatment group and 120 study participants in the placebo group, the 2-sided 2-sample continuity-corrected chi square test for detecting statistical superiority of bimekizumab versus placebo based on ASAS40 response at Week 16 was powered with 90%.

Randomisation

Patients were appropriately randomised into treatment groups. An IXRS was used for assigning eligible study participants to a treatment regimen based on a predetermined randomisation schedule produced by the IXRS vendor. Study participants' treatment assignment was stratified by region and by presence of sacroiliitis on MRI and elevated CRP to ensure balanced treatment allocation across 3 levels: MRI positive/CRP positive, MRI positive/CRP negative, and MRI negative/CRP positive. Enrollment of TNFα inhibitor-experienced study participants was limited to 30% of the total study population.

Blinding (masking)

Due to differences in presentation between bimekizumab and placebo treatments, special precautions were taken to ensure study blinding, and 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. The unblinded personnel were not involved in the study in any way other than assuring the medication was taken from the correct kit and prepared according to the pharmacy manual instructions and administering the drug to the study participants.

Statistical methods

Statistical Analysis Plan

The original SAP, dated 05 June 2019, was amended twice.

- Amendment 1 of the SAP, dated 05 August 2021, was implemented in response to protocol amendment 4 (16 February 2021) and discussions and feedback provided at meetings between the sponsor and CRO technical teams or for clarifications, as well as to incorporate feedback from FDA on missing data methods. The main changes were rules for handling missing data and guidelines on the implementation of MI and latest guidelines from the bimekizumab AE of special monitoring convention document.
- Amendment 2 of the SAP, dated 12 Nov 2021, was implemented to fix formatting issues in the SAP document and to add clarifications on how to analyse specific data.

All amendments to the original SAP were comprehensively described in SAP Amendment 2.

Changes to the planned analyses

Changes to protocol-defined analyses

The following changes relative to the protocol-defined analyses were included in the SAP:

- The protocol mentioned that subgroup analyses using descriptive statistics were to be performed on the primary efficacy endpoint. In addition, Ors for the comparison of bimekizumab versus placebo and associated 95% CI were calculated.
- Race was analysed as additional subgroup endpoint.
- The MS was added as additional analysis set.
- The primary/main analysis of continuous secondary efficacy endpoints which were part of the sequential testing procedure, as well as the components of the primary ASAS40 endpoint, used a reference-based imputation method.

In addition, the impact of the COVID-19 pandemic on study procedures/conduct and on the primary efficacy endpoint and safety analyses (TEAEs, serious TEAEs, and IMP withdrawal due to TEAEs) were investigated and additional analysis outputs are provided as appropriate. These additional analyses were not planned as part of the protocol, as the pandemic was not ongoing at the time of protocol finalisation.

These additional analyses include analyses by period of the COVID-19 pandemic (prior/during/post), for study participant disposition, details of impacted visits and effects on collection and reporting of efficacy data, protocol deviations, exposure, and Aes.

In addition, the primary analysis for the primary efficacy endpoint was repeated by timing of the Week 16 Visit relative to the start and end of the COVID-19 pandemic.

For study participants participating in the MRI substudy, the protocol-defined time window for performing the MRIs of the spine and sacroiliac joints for MRI-positive and MRI-negative study participants at Week 16 and Week 52 was ±5 days. However, the MRIs performed within ±3 weeks were accepted for Week 16 and Week 52 after consultation with imaging experts.

Additional changes to the planned analyses

Exportation of samples from China was not possible at the time of Week 24 CSR preparation and thus the Immunogenicity SS was used for ADAb and Nab analyses in the interim Week 24 report.

Analysis Populations

The primary efficacy endpoint was analysed for all study participants in the Randomised Set (RS), and supportive analyses of the primary efficacy endpoint were performed on the Full Analysis Set (FAS) and the Per-Protocol Set (PPS). All other efficacy endpoints were based on the RS.

Demographics tables were produced using the RS as well as the Safety Set (SS), if the SS was different from the RS. Safety endpoints were summarized on the SS. Pharmacokinetic endpoints were analysed for all study participants in the SS and/or Pharmacokinetic Per-Protocol Set (PK-PPS).

The **Enrolled Set (ES)** was to consist of all study participants who had given informed consent.

The **Randomized Set (RS)** was to consist of all enrolled study participants that had been randomized.

The **Safety Set (SS)** was to consist of all subjects who received at least 1 dose of the IMP. Subjects in the SS were to be analysed according to the treatment they actually received.

The **Maintenance Set (MS)** was to consist of all study participants who received at least 1 dose of bimekizumab treatment in the Maintenance Period.

The **Full Analysis Set (FAS)** was to consist of all randomized subjects who received at least 1 dose of the IMP and had valid measurements of all components of the primary efficacy variable at Baseline.

The **Per-Protocol Set (PPS)** was to consist of all subjects in the RS who had no important protocol deviation (IPD) affecting the primary efficacy variable. Important protocol deviations were to be predefined and study participants with important protocol deviations evaluated during ongoing data cleaning and data evaluation meetings prior to unblinding of the data. Exclusions from the FAS were considered as an IPD that also resulted in exclusion from the PPS. Additional exclusions from the PPS due to a protocol-permitted decrease in dosing or dosing frequency of axSpA background medication due to intolerance/AE/side effects may have also been possible in case a potential impact on the primary endpoint cannot be excluded.

In addition, if after unblinding it was determined that there were study participants who were dosed with bimekizumab in place of placebo, then these study participants were removed from the PPS. Study participants who received a single dose with placebo in place of bimekizumab remained in the PPS, but participants who received more than a single dose with placebo (or received 1 dose with placebo and also missed 1 or more additional doses, therefore fulfilling the IPD criterion of more than 1 missed dose up to Week 12 during the Double-Blind Treatment Period) when randomised to bimekizumab were excluded from the PPS.

The **Pharmacokinetics Per-Protocol Set (PK-PPS)** was to consist of all randomised subjects who received at least 1 dose of bimekizumab and provided at least 1 quantifiable plasma concentration post-dose (after first IMP administration) without important protocol deviations that would affect the concentration.

A separate **Immunogenicity Safety Set** was defined in SAP Amendment 2 to include all randomised study participants, excluding China participants, who received at least 1 dose of IMP in the event that sample exportation from China was not approved. Exportation of all samples from China was not possible at the time of Week 24 CSR preparation and thus the Immunogenicity SS was used for ADAb and Nab analyses in this Week 24 report and only includes available samples from non-Chinese study participants.

The **COVID-19-free Set** consisted of all study participants in the RS who had no COVID-19 impact up to the primary efficacy endpoint.

Efficacy analyses were to be performed according to randomisation and not actual treatment received.

Analysis of primary endpoint – ASAS40 response at week 16

Derivation of the ASAS40 response

The ASAS40 response is defined as:

- An improvement of at least 40%, and an absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 following domains:
  - PGADA
  - Pain assessment (Total Spinal Pain, Question 1 from total and Nocturnal Spinal Pain)
  - Physical function (measured by the BASFI)
  - Inflammation (represented by the mean of the BASDAI Questions 5 and 6) concerning morning stiffness intensity and duration)
- And no worsening at all in the remaining domain.

The primary efficacy analysis evaluated the composite estimand (NRI) that combined the clinically meaningful improvement from Baseline in ASAS40 response at Week 16 and the IE of not discontinuing early from study treatment for any reason prior to Week 16. Note that only permanent discontinuations were considered as Ies. This definition was applicable to all analyses.

The following 4 attributes described the composite estimand that was used to define the treatment effect of interest for the primary efficacy analysis:

• **Population** = Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.

• **Study participant-level outcome** = ASAS40 at Week 16.

• **Intercurrent Event (IE) handling** = An IE was defined as discontinuation of study treatment prior to Week 16. A composite strategy was implemented in which a positive clinical outcome was defined as achieving ASAS40 at Week 16 and not discontinuing study treatment through Week 16.

• **Population-level summary measure** = Conditional OR comparing bimekizumab to placebo.

Intercurrent events were acknowledged as an unfavorable outcome for the composite estimand in considering study participants with Ies as nonresponders to the study treatment. Consequently, if the date of an IE (as defined in the SAP) occurred prior to or at Week 16, study participants were considered as nonresponders at Week 16. Additionally, missing data at Week 16 that were not preceded by an IE were imputed as nonresponders.

A logistic regression model was used to assess the treatment effect on ASAS40 response at Week 16. The model included fixed effects for treatment and stratification endpoints of MRI/CRP classification and region. The suitability of including these endpoints in the model was assessed using the Hosmer-

Lemeshow goodness-of-fit test. If the logistic regression model was unable to converge the stratification factors could be dropped to facilitate the model convergence.

The summary table results presented the number of responders, adjusted responder rates, and associated 95% confidence interval (CI) for bimekizumab and placebo, the adjusted OR and 95% CI for the comparison of bimekizumab versus placebo, and the p-value testing the null hypothesis that the OR=1. The treatment comparison was made using the 2-sided Wald test at a significance level of α=0.05.

The following supportive analyses for the primary efficacy variable were conducted:

- Analysis on the PPS
- Analysis on the FAS (to be performed if the number of study participants in RS and FAS differ)
- Analysis using a modified composite estimand where the single identified intercurrent event is defined as discontinuation due to AE or lack of efficacy
- Analysis of individual components of the ASAS40 (using hypothetical estimand where the single intercurrent event is discontinuation of study treatment prior to week 16 and

  missing data and nonmissing data after the IE (reset as missing) were imputed using reference-based MI)
- Analyses using treatment policy strategy for the single identified intercurrent event of discontinuation of study treatment prior to week 16
- Analysis of observed cases
- Tipping point analysis, including a worst-case scenario where study participants who had missing ACR50 response were set as nonresponders if they were randomized to bimekizumab and as responders if they were randomized to placebo
- Analysis including COVID-19 impact

Analysis of ranked secondary endpoints

Eleven key secondary endpoints were included in the testing hierarchy.

The following analyses were conducted for the secondary efficacy endpoints:

- For the secondary binary endpoints:
  - Composite Estimand – NRI: The same composite estimand structure as the one defined in for the primary efficacy analysis was used. The same analysis model was considered, and the analysis results were presented similarly as for the primary efficacy analysis. The imputation strategy for handling missing data was the same as for the primary endpoint; i.e. the NRI approach.
  - Modified Composite – MI: A similar modified composite estimand structure as the one defined for the primary efficacy analysis was used. The same analysis model was considered, and the analysis results were presented similarly as for the primary efficacy analysis.
  - Observed Case analysis

For the secondary continuous endpoints:

- Reference-Based Estimand – MI: The same hypothetical estimand structure as the one defined in for the analysis on component endpoints for the primary efficacy endpoint was used. The same analysis model and imputation strategy for handling missing data was also considered. The analysis results were presented similarly as for this analysis on the individual ASAS40 components.
- Hypothetical Estimand – MI where the single intercurrent event is discontinuation of study treatment prior to week 16 and missing data and nonmissing data after the IE (reset as missing) were imputed under a MAR assumption
- Observed Case Analysis
- to assess the impact of the COVID-19 pandemic, the primary analysis of all secondary efficacy endpoints included in the testing hierarchy were analysed on the CFS, using the reference-based estimand.

Subgroup analyses

Subgroups analyses were performed for the primary endpoint ASAS40, and ASDAS-MI as shown in the Table 33 below. In addition, ASAS40 was analysed based on the timing of participant enrolment and timing of the Week 16 Visit relative to the COVID-19 pandemic periods.

Subgroup	Categories
Age (years)	<45, ≥45
Gender	Male, Female
Race 1	Black, White, Other
Race 2	White, Asian, Other
Region 1 [a]	Asia, Eastern Europe, North America and Western Europe
Disease duration (years)	<2, ≥2
Body mass index (kg/m^2)	<18.5, ≥18.5 to <25, ≥25 to <30, ≥30
hs-CRP level	≤ULN [b], >ULN
MRI/CRP classification [c]	MRI positive/CRP positive, MRI positive/CRP negative, MRI negative/CRP positive
Prior TNFα inhibitor exposure	Yes, No
csDMARDs	Yes, No
ASDAS status	<1.3 [inactive disease], 1.3 to ≤2.1 [low disease activity], >2.1 to ≤3.5 [high disease activity], >3.5 [very high disease activity]
HLA-B27 positivity	Yes, No
Timing of study participant enrollment relative to COVID-19 pandemic periods as defined in Section 6.1.2.2.1	Enrolled prior to the COVID-19 pandemic, Enrolled during the COVID-19 pandemic, Enrolled after the COVID-19 pandemic
Timing of Week 16 Visit relative to the COVID-19 pandemic periods as defined in Section 6.1.2.2.1	Study participants who had the Week 16 Visit prior the COVID-19 pandemic, Study participants who had the Week 16 Visit during the COVID-19 pandemic, Study participants who had the Week 16 Visit after the COVID-19 pandemic

ASDAS=Ankylosing Spondylitis Disease Activity Score; COVID-19=coronavirus disease 2019; csDMARD=conventional synthetic disease-modifying antirheumatic drug; (hs-)CRP=(high sensitivity) C-reactive protein; HLA=human leukocyte antigen; MRI=magnetic resonance imaging; TNFα=tumor necrosis factor α; ULN=upper limit of normal

[a] The categories may be pooled as defined in Section 6.1.7.

[b] ULN refers to the central laboratory ULN definition (ie, 5mg/L).

[c] The actual MRI/CRP classification stratum the study participant belongs to was used for the subgroup analysis.

Multicentre study

The data from all centers were pooled for the purposes of the analysis. Centers were grouped in the geographic regions of North America/Western Europe, Eastern Europe, and Asia.

The percentage of randomised study participants was less than 10% in North America. To avoid modeling convergence issues across efficacy endpoints, North America was combined with Western Europe to create a new geographic region stratum for efficacy modeling. This new pooled geographic region stratum was then used for any modeling (including MI, logistic regression, and mixed model), including subgroup analyses.

No exploration of treatment by center interaction was investigated.

Type I error control

A fixed sequence testing procedure was applied for the primary endpoint and the key secondary endpoints. The testing procedure accounted for multiplicity and controlled the family-wise type I error rate at alpha=0.05 (2-sided).

For each test, on each binary efficacy endpoint, the null hypothesis was that the conditional odds ratio (OR) was equal to 1 (H_0: $OR_{T1T2} = 1$). The alternative hypothesis was that the conditional OR was not equal to 1 (H_A: $OR_{T1T2} \neq 1$).

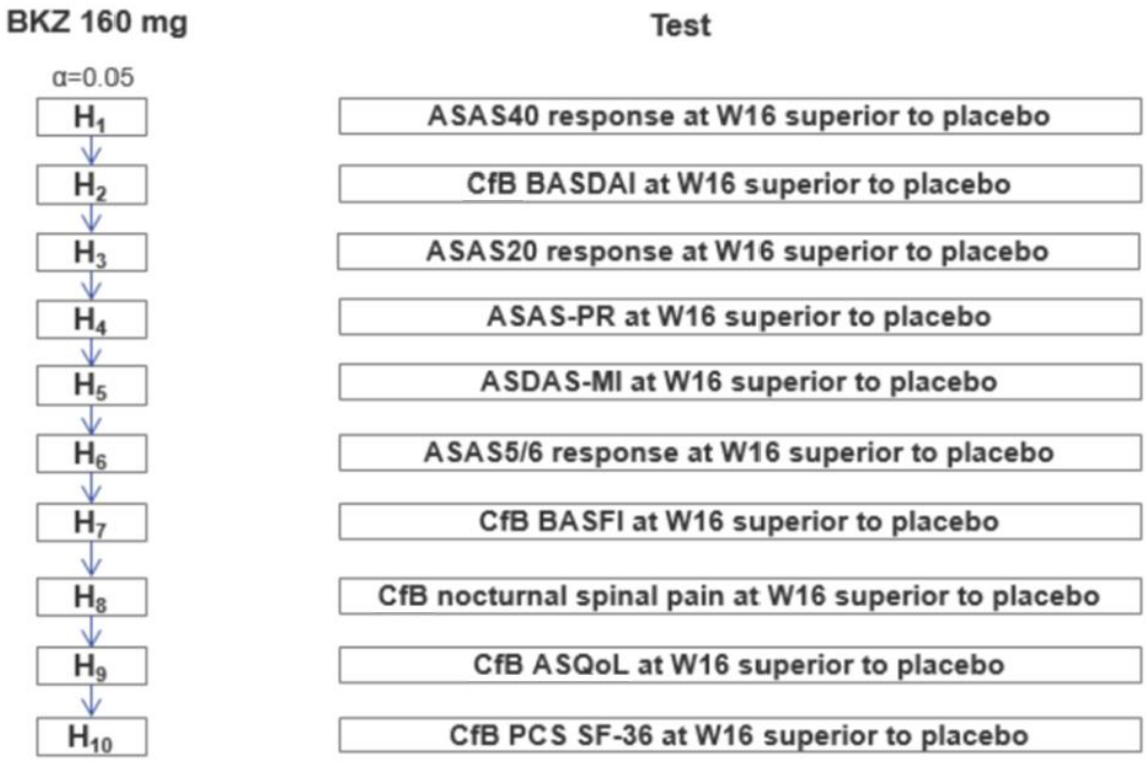
For each test, on each continuous efficacy endpoint, the null hypothesis was that there was no

difference between treatment groups (H_0: $T_1 - T_2 = 0$). The alternative hypothesis was that there was a difference between treatment groups (H_A: $T_1 - T_2 \neq 0$).

In these hypotheses, T_1 referred to bimekizumab and T_2 to placebo.

According to this strategy, the statistical testing of an endpoint could be investigated only if the null hypothesis for the previous endpoint had been rejected (ie, if $p<0.05$).

The testing order for these endpoints is shown in the figure below:



ASAS20, 40, 5/6=Assessment of SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria; ASAS-PR=Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; PCS=physical component summary; SF-36=Short Form 36-Item Health Survey; W=week

Interim analyses

In AS0010, two analyses were to be performed prior to the final analysis:

- Analysis 1: Week 24 analysis.
- Analysis 2: Week 52 analysis.

No formal alterations to the further study conduct (e.g., stopping rules, sample size re-estimation, or changes to eligibility criteria) were planned for the 2 interim analyses (Week 24 and Week 52). No separate SAP for the Week 24 analyses was to be provided. The TFL shells for the Week 24 and the Week 52 analyses were provided in the same document and appropriately identified. The type of efficacy and safety analyses to be provided for the 2 interim analyses was detailed in the SAP.

The final analysis for AS0010 consisted of a rerun of all analyses provided during the preceding interim analysis. This includes new SFU data that were not available for the Week 52 analysis. If there was no SFU data ongoing, the final analysis would be identical to the Week 52 analysis.

Results

Screening for AS0010 started on 25 April 2019 and completed on 11 June 2021.

A total of 781 study participants signed the ICF and were screened for the study, 527 of whom were screen failures (67.5%). The most common reason for screen failure was ineligibility due to not meeting one or more inclusion criteria.

A total of 254 study participants were randomised in the global population and started treatment in AS0010. Study participants were randomised 1:1 to either bimekizumab 160mg sc Q4W or placebo sc Q4W.

Most study participants completed the Double-Blind Treatment Period and were similar for both bimekizumab and placebo (98.4% and 93.7% respectively). The most common primary reasons for discontinuation during the Double-Blind Treatment Period were due to withdrawal by study participant (4 study participants [1.6%]) and an AE (4 study participants [1.6%]).

Recruitment

Recruitment was appropriately conducted in accordance with the protocol. Screening for AS0010 started on 25 Apr 2019 and completed on 11 Jun 2021. A total of 781 study participants signed the ICF and were screened for the study, 527 of whom were screen failures (67.5%). The most common reason for screen failure was ineligibility (499 study participants [63.9%]).

Conduct of the study

Overall, the study was conducted appropriately. There have been 4 protocol amendments to date; however, none of these are felt to have diminished the integrity of the trial.

The Covid-19 pandemic does not seem to have had any material impact on the conduct of the trial.

While 3.5% of patients did experience one or more protocol deviations, for the most part these were minor – bimekizumab 160mg Q4W (3.9%) and placebo (3.2%) groups. Overall, the most common protocol deviation was prohibited concomitant medication use, with an incidence of 1.6% in the bimekizumab group and 2.4% in the placebo group.

Baseline data

Overall, baseline characteristics were well balanced between treatment groups. There were some slight differences between the groups with respect to BMI and gender between the two groups (<25kg/m2: 43.8%; and males: 57.0% and females: 43.0% and <25kg/m2: 36.5%; and males: 51.6% and females: 48.4% between the treatment and placebo groups respectively).

The majority of study participants were White (86.2%). The mean body weight and mean BMI overall were 80.91kg and 27.42kg/m2, respectively. For each treatment group, the number of study participants in the MRI+/CRP- stratification level was slightly higher (41.7%) compared with MRI+/CRP+ (31.9%) and MRI-/CRP+ (26.4%) stratification levels.

Study participants were most commonly enrolled in the following countries: Poland (28.0%), the Czech Republic (20.9%), Spain (10.2%), Germany (9.4%), and the United States (7.1%).

The Baseline disease characteristics were reflective of a study population with active nr-axSpA and high burden of disease despite standard of care treatment. Overall, the mean times since first diagnosis and first symptoms of axSpA were 3.60 years (range: 0.1 to 31.3 years) and 9.02 years (range: 0.4 to 45.1 years), respectively. Most of the study participants (77.6%) were positive for HLA-B27, a genetic marker associated with axSpA. Treatment groups were generally well balanced with respect to nr-axSpA-related and other Baseline disease characteristics.

Prior anti-TNF therapy was used by 10.6% of all study participants. At Baseline, the majority of all study participants were using NSAID therapies (74.8%), 24.4% were on conventional synthetic DMARDs, 8.3% were taking oral corticosteroids, and 16.5% were on analgesic/opioid therapies.

Table 33: Study participant demographics (SS)

Variable	PBO N=126	BKZ 160mg Q4W N=128	All Study Participants N=254
Age (years)			
Mean (SD)	39.4 (11.8)	39.5 (11.1)	39.4 (11.5)
Median (min, max)	38.5 (18, 76)	39.0 (19, 67)	39.0 (18, 76)
Age, n (%) [a]			
18 to <65 years	123 (97.6)	125 (97.7)	248 (97.6)
65 to <85 years	3 (2.4)	3 (2.3)	6 (2.4)
≥85 years	0	0	0
Age, n (%) [b]			
≤18 years	2 (1.6)	0	2 (0.8)
19 to <65 years	121 (96.0)	125 (97.7)	246 (96.9)
≥65 years	3 (2.4)	3 (2.3)	6 (2.4)
Age, n (%)			
<45 years	87 (69.0)	86 (67.2)	173 (68.1)
≥45 years	39 (31.0)	42 (32.8)	81 (31.9)
Gender, n (%)			
Male	65 (51.6)	73 (57.0)	138 (54.3)
Female	61 (48.4)	55 (43.0)	116 (45.7)

Variable	PBO N=126	BKZ 160mg Q4W N=128	All Study Participants N=254
Racial group, n (%)			
American Indian/Alaskan native	0	0	0
Asian	13 (10.3)	15 (11.7)	28 (11.0)
Black	1 (0.8)	2 (1.6)	3 (1.2)
Native Hawaiian or other Pacific Islander	0	0	0
White	110 (87.3)	109 (85.2)	219 (86.2)
Other/mixed	1 (0.8)	1 (0.8)	2 (0.8)
Missing	1 (0.8)	1 (0.8)	2 (0.8)
Ethnicity, n (%)			
Hispanic or Latino	3 (2.4)	2 (1.6)	5 (2.0)
Not Hispanic or Latino	122 (96.8)	125 (97.7)	247 (97.2)
Missing	1 (0.8)	1 (0.8)	2 (0.8)
Weight (kg)			
Mean (SD)	81.64 (17.36)	80.19 (18.20)	80.91 (17.77)
Median (min, max)	81.30 (41.2, 127.1)	79.15 (43.0, 122.6)	80.20 (41.2, 127.1)
Weight, n (%)			
<70kg	33 (26.2)	37 (28.9)	70 (27.6)
≥70 to <95kg	64 (50.8)	62 (48.4)	126 (49.6)
≥95 to <115kg	23 (18.3)	24 (18.8)	47 (18.5)
≥115kg	6 (4.8)	5 (3.9)	11 (4.3)
Weight, n (%)			
≤100kg	109 (86.5)	108 (84.4)	217 (85.4)
>100kg	17 (13.5)	20 (15.6)	37 (14.6)
Height (cm)			
Mean (SD)	171.83 (11.03)	171.69 (9.52)	171.76 (10.28)
Median (min, max)	172.00 (135.0, 196.0)	170.25 (152.0, 195.0)	172.00 (135.0, 196.0)

Variable	PBO N=126	BKZ 160mg Q4W N=128	All Study Participants N=254
BMI (kg/m^2) [c]			
Mean (SD)	27.65 (5.54)	27.20 (6.04)	27.42 (5.79)
Median (min, max)	26.99 (17.3, 41.2)	26.38 (17.5, 46.3)	26.62 (17.3, 46.3)
BMI, n (%) [c]			
<25kg/m^2	46 (36.5)	56 (43.8)	102 (40.2)
25 to <30kg/m^2	41 (32.5)	40 (31.3)	81 (31.9)
≥30kg/m^2	39 (31.0)	32 (25.0)	71 (28.0)
MRI/CRP randomization classification, n (%) [d]			
MRI+/CRP+	40 (31.7)	41 (32.0)	81 (31.9)
MRI+/CRP-	54 (42.9)	52 (40.6)	106 (41.7)
MRI-/CRP+	32 (25.4)	35 (27.3)	67 (26.4)
MRI/CRP actual classification [e]			
MRI+/CRP+	39 (31.0)	39 (30.5)	78 (30.7)
MRI+/CRP-	56 (44.4)	53 (41.4)	109 (42.9)
MRI-/CRP+	31 (24.6)	36 (28.1)	67 (26.4)
MRI status at Screening			
Positive	95 (75.4)	92 (71.9)	187 (73.6)
Negative	31 (24.6)	36 (28.1)	67 (26.4)
hs-CRP status at Screening			
Negative (<1.2 ULN)	56 (44.4)	53 (41.4)	109 (42.9)
Positive (≥1.2 ULN)	70 (55.6)	75 (58.6)	145 (57.1)
Region, n (%) [d,f]			
Asia	13 (10.3)	15 (11.7)	28 (11.0)
Eastern Europe	71 (56.3)	73 (57.0)	144 (56.7)
North America	9 (7.1)	9 (7.0)	18 (7.1)
Western Europe	33 (26.2)	31 (24.2)	64 (25.2)

Variable	PBO N=126	BKZ 160mg Q4W N=128	All Study Participants N=254
Country, n (%)			
Belgium	2 (1.6)	3 (2.3)	5 (2.0)
Bulgaria	4 (3.2)	5 (3.9)	9 (3.5)
China	7 (5.6)	9 (7.0)	16 (6.3)
Czech Republic	25 (19.8)	28 (21.9)	53 (20.9)
France	1 (0.8)	1 (0.8)	2 (0.8)
Germany	11 (8.7)	13 (10.2)	24 (9.4)
Hungary	6 (4.8)	5 (3.9)	11 (4.3)
Japan	6 (4.8)	6 (4.7)	12 (4.7)
Netherlands	0	0	0
Poland	36 (28.6)	35 (27.3)	71 (28.0)
Spain	16 (12.7)	10 (7.8)	26 (10.2)
Turkey	0	0	0
United Kingdom	3 (2.4)	4 (3.1)	7 (2.8)
United States	9 (7.1)	9 (7.0)	18 (7.1)

BKZ= bimekizumab; BMI=body mass index; CRP=C reactive protein; EudraCT=European Clinical Trials Database; hs-CRP= high sensitivity C-reactive protein; IXRS=interactive voice or web response system; max=maximum; min=minimum; MRI=magnetic resonance imaging; PBO=placebo; Q4W=every 4 weeks; SD=standard deviation; SS=Safety Set

[a] EudraCT age categories.
[b] clinicaltrials.gov age categories.
[c] BMI was derived based on the height and weight variables collected in the database.
[d] Study participants were categorized based on the stratum within which they were randomized via the IXRS.
[e] Study participants were categorized in the stratum they actually belong to. Study participants with no evaluable MRI sacroiliitis imaging result at screening or study participants classified in MRI-/CRP- were assigned under the missing MRI/CRP category.
[f] Turkey was included in the Asian region.

Numbers analysed

The RS and SS consisted of the same study participants, with 128 study participants in the bimekizumab group and 126 study participants in the placebo/bimekizumab group. The MS included the same study participants as the RS and SS, except for the 10 study participants who discontinued during the Double-Blind Treatment Period and the 2 study participants who completed the Double-Blind Treatment Period but did not enter the Maintenance Period. The FAS included the same study participants as the RS and SS. Most of the study participants were included in the PPS (96.9%) and in the PK-PPS (96.1%). The Immunogenicity SS included a lower number of study participants, 93.0% in the bimekizumab group and 94.4% in the placebo/bimekizumab group, as this analysis set excluded Chinese study participants. The CFS included a majority of the same study participants as the RS for the bimekizumab group (92.2%) and the placebo/bimekizumab group (92.1%).

Table 34: Disposition of Analysis Sets (RS)

Analysis set	PBO/BKZ 160mg Q4W N=126 n (%)	BKZ 160mg Q4W N=128 n (%)	All Study Participants N=254 n (%)
RS	126 (100)	128 (100)	254 (100)
SS	126 (100)	128 (100)	254 (100)
ISS	119 (94.4)	119 (93.0)	238 (93.7)
MS	116 (92.1)	126 (98.4)	242 (95.3)
FAS	126 (100)	128 (100)	254 (100)
PPS	121 (96.0)	125 (97.7)	246 (96.9)
PK-PPS	116 (92.1)	128 (100)	244 (96.1)
CFS	116 (92.1)	118 (92.2)	234 (92.1)

BKZ=bimekizumab, CFS=COVID-19-Free Set; FAS=Full Analysis Set; ISS=Immunogenicity Safety Set; MS=Maintenance Set; PBO=placebo; PK-PPS=Pharmacokinetics Per-Protocol Set; PPS=Per-Protocol Set; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set

Outcomes and estimation

The results of the primary and key secondary efficacy variables are provided below. Overall, bimekizumab treatment resulted in statistically significant and clinically meaningful differences over placebo for the primary and all key secondary endpoints included in the predefined sequential testing sequence ($p<0.001$).

A tabular summary of these results is presented below.

Table 35: Summary of primary and key secondary efficacy analysis results based on the predefined sequential testing sequence at Week 16 (RS)

Ordered sequential procedure	Endpoint	PBO n (%)	BKZ 160mg Q4W n (%)	Treatment comparison (95% CI)	Measure	p-value	Significant [a]
Primary							
#1: BKZ 160mg Q4W vs PBO	ASAS40 response, n (%)	27 (21.4)	61 (47.7)	(2.00, 6.16)	Odds ratio	<0.001	Yes
Secondary							
#2: BKZ 160mg Q4W vs PBO	CfB BASDAI, LS mean	-1.55	-3.07	(-2.04, -0.98)	LS mean difference	<0.001	Yes
#3: BKZ 160mg Q4W vs PBO	ASAS20 response, n (%)	48 (38.1)	88 (68.8)	(2.17, 6.26)	Odds ratio	<0.001	Yes
#4: BKZ 160mg Q4W vs PBO	ASAS-PR response, n (%)	9 (7.1)	33 (25.8)	(2.06, 9.93)	Odds ratio	<0.001	Yes
#5: BKZ 160mg Q4W vs PBO	ASDAS-MI response, n (%)	9 (7.1)	35 (27.3)	(2.41, 12.23)	Odds ratio	<0.001	Yes
#6: BKZ 160mg Q4W vs PBO	ASAS5/6 response, n (%)	26 (20.6)	58 (45.3)	(1.87, 5.84)	Odds ratio	<0.001	Yes
#7: BKZ 160mg Q4W vs PBO	CfB BASFI, LS mean	-0.91	-2.39	(-1.99, -0.97)	LS mean difference	<0.001	Yes
#8: BKZ160mg Q4W vs PBO	CfB nocturnal spinal pain, LS mean	-1.71	-3.51	(-2.42, -1.18)	LS mean difference	<0.001	Yes
#9: BKZ 160mg Q4W vs PBO	CfB ASQoL, LS mean	-2.30	-4.94	(-3.66, -1.61)	LS mean difference	<0.001	Yes
#10: BKZ 160mg Q4W vs PBO	CfB SF-36 PCS, LS mean	5.36	9.32	(2.08, 5.83)	LS mean difference	<0.001	Yes

ANCOVA=analysis of covariance; ASAS20, 40 ,5/6=Assessment of SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria; ASAS-PR=Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BKZ=bimekizumab; CI=confidence interval; CfB=change from Baseline; CRP=C-reactive protein; LS=least squares; MRI=magnetic resonance imaging; PBO=placebo; PCS=Physical Component Summary; Q4W=every 4 weeks; RS=Randomized Set; SAP=Statistical Analysis Plan; SF-36=Short-Form 36-item Health Survey

Note: For binary endpoint: p-value obtained from logistic regression with treatment, MRI/CRP classification and region as factor/CIs obtained from the difference of adjusted odds ratios.

Note: For continuous endpoint: p-value obtained from ANCOVA with treatment, MRI/CRP classification, region as fixed effect and the Baseline value as covariate/CI obtained from the difference in LS means from the ANCOVA.

Note: For binary variables, study participants with missing data at Week 16 were imputed based on nonresponder imputation approach.

Note: For continuous variables, study participants with missing data at Week 16 were imputed using multiple imputation with a reference-based approach.

[a] All tests were performed at a 2-sided alpha level of 0.05. See Section 4.5 of the SAP for further details on the testing methodology.

Primary efficacy endpoint – ASAS40 at Week 16

The bimekizumab 160mg Q4W group had a higher ASAS40 response rate compared with the placebo group at Week 16 that was statistically significant and clinically meaningful (47.7% vs 21.4%, respectively; p<0.001).

The ASAS40 response rate further increased from week 16 (47.7%) to week 52 (60.9%) for participants in the bimekizumab 160mg Q4W group.

Table 36: ASAS40 response rates at Week 16 (RS [NRI])

	PBO N=126	BKZ 160mg Q4W N=128
Number of responders, n (%)	27 (21.4)	61 (47.7)
Adjusted response rate [a]	20.4	47.4
95% CI	13.5, 29.7	37.3, 57.7
Odds ratio vs Placebo [a]	-	3.51
95% CI for odds ratio	-	2.00, 6.16
p-value	-	<0.001

ASAS40=Assessment in SpondyloArthritis International Society 40%; BKZ=bimekizumab; CI=confidence interval; CRP=C-reactive protein; MRI=magnetic resonance imaging; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The conditional odds ratio evaluated the composite estimand combining the clinically meaningful improvement from Baseline in ASAS40 response and not having an intercurrent event.

Note: Study participants with missing ASAS40 data at Week 16 preceded by an intercurrent event were counted as nonresponders, as well as study participants with missing ASAS40 data at Week 16 that were not preceded by an intercurrent event.

[a] Adjusted response rate, odds ratio, and p-values for the comparison of bimekizumab/placebo have been calculated using logistic regression with factors for treatment, MRI/CRP classification and region.

In addition, the bimekizumab group had improvement over placebo for each of the ASAS40 components (shown as difference of bimekizumab-placebo): PGADA (-1.75); Total Spinal Pain (-1.63); BASFI score (function) (-1.48); BASDAI Q5/Q6 mean score (inflammation) (-1.73); and all other sensitivity analyses.

Table 37: Change from Baseline in individual components of ASAS40 response at Week 16 (RS [reference-based MI])

	PBO N=126	BKZ 160mg Q4W N=128	BKZ 160mg Q4W-Placebo [a]
PGADA			
LS mean (SE) [b]	-1.46 (0.253)	-3.22 (0.241)	-1.75 (0.304)
Diff: 95% CI [b]	-	-	-2.35, -1.16
Total Spinal Pain assessment			
LS mean (SE) [b]	-1.80 (0.259)	-3.43 (0.245)	-1.63 (0.308)
Diff: 95% CI [b]	-	-	-2.23, -1.03
BASFI score (function) [c]			
LS mean (SE) [b]	-0.91 (0.219)	-2.39 (0.210)	-1.48 (0.262)
Diff: 95% CI [b]	-	-	-1.99, -0.97
BASDAI Q5/Q6 mean score (inflammation)			
LS mean (SE) [b]	-1.97 (0.254)	-3.70 (0.244)	-1.73 (0.306)
Diff: 95% CI [b]	-	-	-2.33, -1.14

ANCOVA=analysis of covariance; ASAS40=Assessment in Axial SpondyloArthritis International Society 40%; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BKZ=bimekizumab; CI=confidence interval; CRP=C-reactive protein; IE=intercurrent event; LS=least squares; MI=multiple imputation; MRI=magnetic resonance imaging; PBO=placebo; Q=question; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error

Note: Inflammation component is calculated as the mean of the 2 scores relating to morning stiffness measurements (ie, Question 5 and Question 6).

Note: An IE is defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: For each individual component endpoints of the ASAS40 endpoint, missing data at Week 16 and nonmissing data after IE (which are reset to missing) for LS mean are imputed using MI based on a reference-based approach, in which the MI model is based on data from the placebo group.

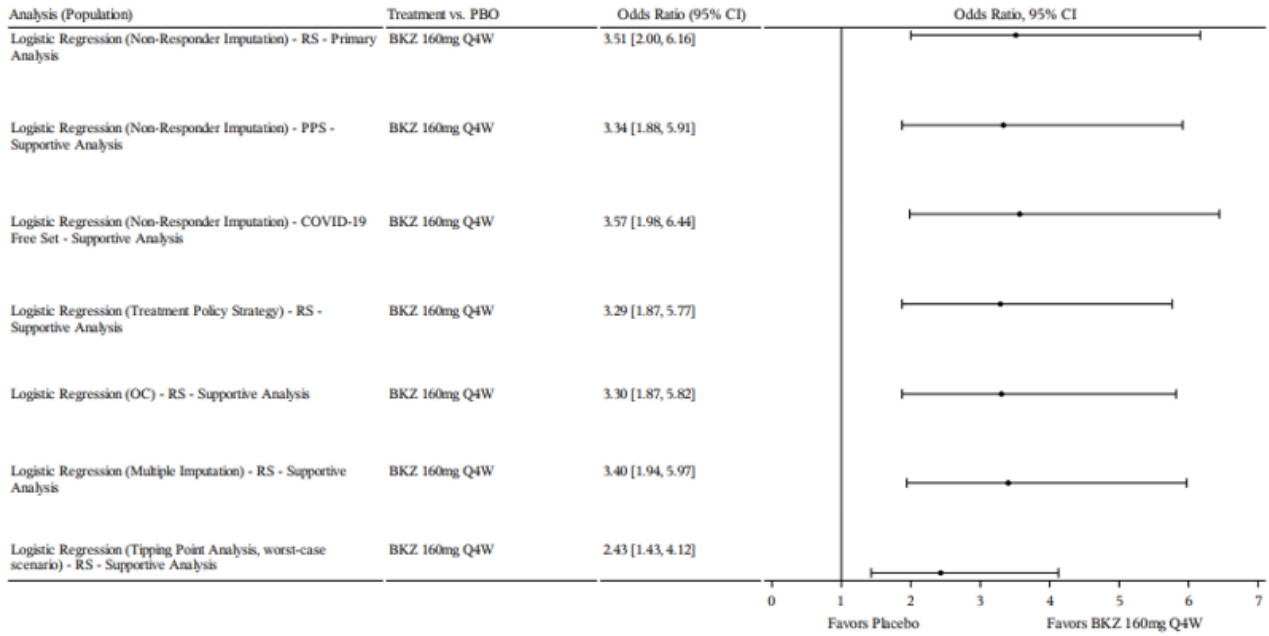
[a] LS mean difference between BKZ 160mg and placebo.

[b] ANCOVA with treatment, MRI/CRP classification and region as fixed effects, and Baseline value as covariate.

[c] This endpoint is included in the sequential testing hierarchy.

The supportive analyses of the primary endpoint were consistent with the results of the primary analysis. The results of the supportive analyses of the primary efficacy endpoints were in line with the primary efficacy results. When ASAS40 response rates were analysed with alternative missing data methods (MI, Treatment Policy Strategy, OC, or the Tipping Point Analysis) and with additional analysis sets (PPS and COVID-19 Free Set), the bimekizumab 160mg Q4W group had higher ASAS40 response rates compared with the placebo group (nominal $p \leq 0.001$ for all comparisons). Additionally, there was no evidence that the timing of the Week 16 Visit relative to the COVID-19 pandemic had an effect on ASAS40 response rates for bimekizumab and placebo.

Figure 30: Forest Plot Comparing Primary Analysis and Sensitivity Analyses of ASAS40 Responder Rate at Week 16
Analysis Set: Randomized Set



ASAS=assessment in axial spondyloarthritis international society, BKZ=bimekizumab, CI=confidence interval, COVID-19=coronavirus disease 2019, NRI=non-responder imputation, OC=observed case, PBO=Placebo, PPS=per-protocol set, RS=randomized set.

Subgroup analysis of primary efficacy endpoint

Overall, a consistent trend of increased ASAS40 response rates in the bimekizumab group compared with the placebo group was evident across all subgroups. The difference between response rates in the bimekizumab compared with placebo was less pronounced for female participants, participants ≥45 years of age, and participants in Western Europe and North America. Participants with a BMI of ≥30kg/m2 in the bimekizumab group had a response rate of 28.1% (OR 95% CI: 0.45 to 3.81) compared to 23.1% in the placebo group.

In participants <45 years of age, the ASAS40 response rate at Week 16 in the bimekizumab group (59.3%) was higher compared with the placebo group (26.4%). In participants ≥45 years of age, the ASAS40 response rate was lower than in participants <45 years of age. In this older age category, the ASAS40 response rate was higher in the bimekizumab group (23.8%) compared with the placebo group (10.3%).

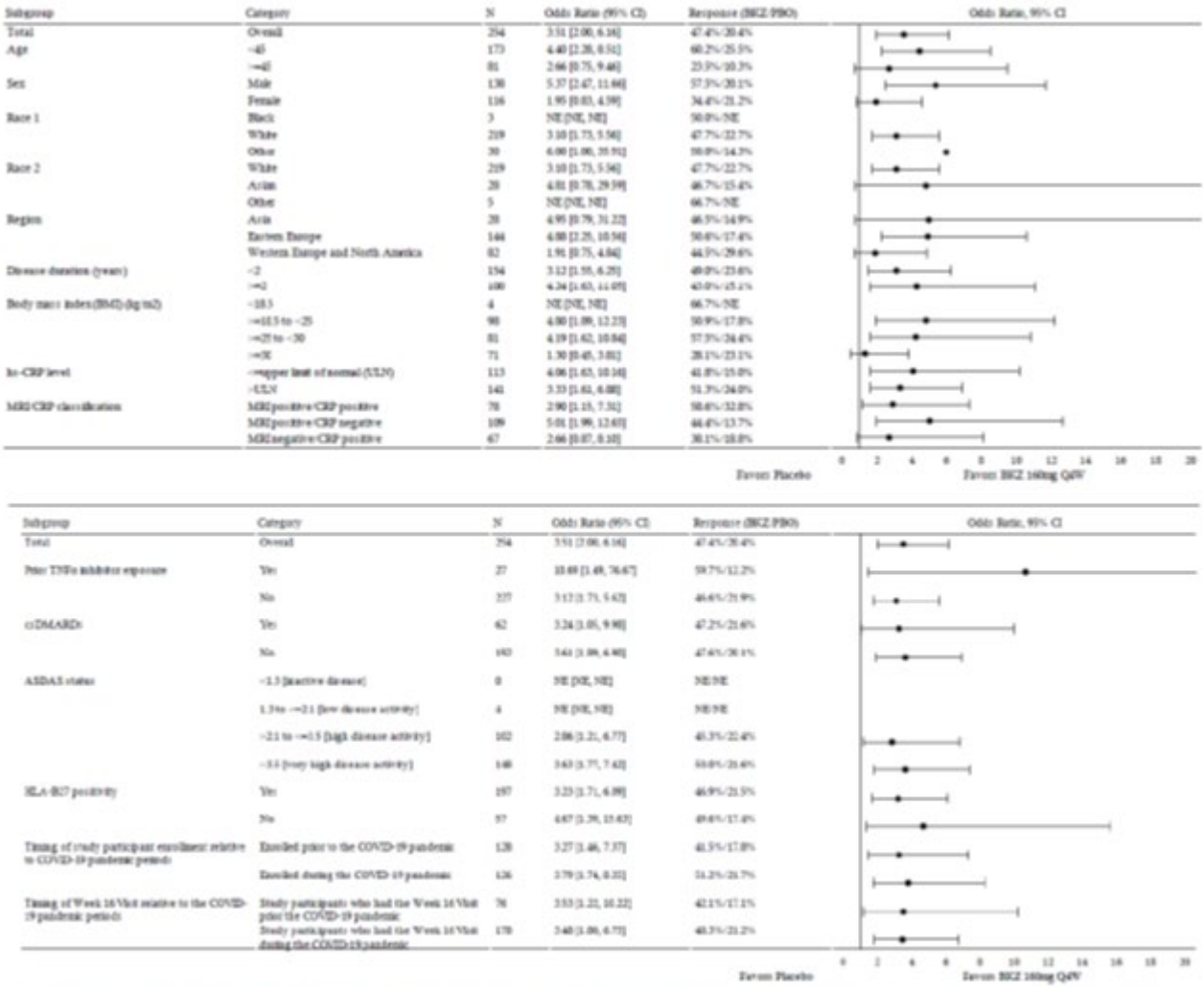
In participants with a BMI of ≥18.5 to <25kg/m2, the ASAS40 response rate in the bimekizumab group (50.9%) was higher compared with placebo (17.8%), which was similar in participants with a BMI of ≥25 to <30kg/m2 where the ASAS40 response rate was higher in the bimekizumab group (57.5%) compared with the placebo group (24.4%). In participants with a BMI of ≥30kg/m2, the ASAS40 response rate in the bimekizumab group (28.1%) was lower than in participants with a BMI of ≥18.5 to <25kg/m2 or ≥25 to <30kg/m2 and similar to the placebo group (23.1%).

In male participants, the ASAS40 response rate at Week 16 in the bimekizumab group (57.5%) was higher compared with the placebo group (21.5%). In female participants, the ASAS40 response rate was lower than male participants, but was higher in the bimekizumab group (34.5%) compared with the placebo group (21.3%).

In participants with prior TNFα inhibitor exposure, the ASAS40 response rate at Week 16 in the bimekizumab group (60.0%) was higher compared with placebo (11.8%). Results were similar in participants with no prior TNFα inhibitor exposure, where the ASAS40 response was higher in the bimekizumab group (46.6%) compared with the placebo group (22.9%). However, the sample size for study participants with prior TNFα inhibitor exposure was small, and conclusions should be drawn with caution.

For the region subgroups, the bimekizumab group had higher ASAS40 response rates compared with placebo in participants from Eastern Europe (50.7% vs 18.3%, respectively), Asia (46.7% vs 15.4%, respectively), and a slightly higher ASAS40 response rate in Western Europe and North America (42.5% vs 28.6%, respectively). In the bimekizumab group, the ASAS40 response rate was higher in Eastern Europe (50.7%) compared with Asia (46.7%), which was also higher compared with Western Europe and North America (42.5%).

Figure 31: Forest plot on ASAS40 odds ratio at Week by subgroups (RS [NRI])



ASAS=Assessment in SpondyloArthritis international society; ASDAS=ankylosing spondylitis disease activity score; BKZ=bimekizumab; BMI=body mass index; CI=confidence interval; COVID-19=coronavirus disease 2019; CRP=C-reactive protein; csDMARD=conventional synthetic disease-modifying antirheumatic drug; HLA-B27=human leukocyte antigen B27; hs-CRP=high sensitivity C-reactive protein; MRI=magnetic resonance imaging; NE=not evaluable; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor α; ULN=upper limit of normal value

Note: ULN value for hs-CRP=5mg/L

Note: Model-adjusted response rates are presented in this figure while nonadjusted rates are discussed below.

Secondary efficacy endpoints

Bimekizumab treatment resulted in statistically significant improvements over placebo for all key secondary endpoints included in the predefined sequential testing sequence, which resulted in meaningful improvement after bimekizumab treatment (as presented in Figure 31 above). In addition, improvements after bimekizumab treatment over placebo were observed for BASMI, MASES index, enthesitis-free state based on MASES, and ASAS40 response in TNFα inhibitor-naïve participants, as presented below.

The bimekizumab 160mg Q4W group had a LS mean decrease from Baseline in BASMI at week 16 (decreases reflect improvement) which was greater than the placebo group (-0.44 vs -0.11, respectively; nominal p=0.0005) (Table 38). A summary of change from Baseline in BASMI score at Week 16 is presented for the RS (MI) in Table 38.

Table 38: BASMI change from Baseline at Week 16 (RS [MI])

	PBO N=126	BKZ 160mg Q4W N=128
n	126	128
Mean (SE)	-0.0796 (0.0641)	-0.4077 (0.0735)
Median (min, max)	-0.0728 (-2.183, 2.068)	-0.3771 (-2.847, 2.358)
LS mean (SE) [a]	-0.11 (0.08)	-0.44 (0.08)
Difference vs placebo	–	-0.33
95% CI for difference	–	-0.52, -0.14
Nominal p-value	–	0.0005

ANCOVA=analysis of covariance; BASMI=Bath Ankylosing Spondylitis Disease Metrology Index; BKZ=bimekizumab; CI=confidence interval; CRP=C-reactive protein; LS=least squares; max=maximum; MI=multiple imputation; min=minimum; MRI=magnetic resonance imaging; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: Missing data at Week 16 and non-missing data after intercurrent event (which were reset to missing) were imputed using MI based on a reference-based approach, in which the MI model was based on data from the placebo group.

Note: Invalid measurements for BASMI components (according to Maksymowych et al 2006) were treated as missing. If 1 or 2 clinical measures for the BASMI were missing at 1 visit, the missing measure was imputed by carrying the last observation forward, and the BASMI was calculated accordingly. Where 2 attempted measurements for a clinical measure were available and 1 measurement was invalid and 1 measurement was valid, the valid measurement was used, and no imputation was performed.

[a] LS Means, SE, difference in LS Means, and CI and p-value for the comparison of bimekizumab to placebo have been calculated using ANCOVA with treatment, MRI/CRP classification and region as fixed effects, and Baseline BASMI value as covariate.

In the subgroup of study participants with enthesitis at Baseline (MASES index score >0), the bimekizumab 160mg Q4W group had a LS mean decrease from Baseline in the MASES index at Week 16 (decreases reflect improvement) which was greater than the placebo group (-2.16 vs -1.12, respectively; nominal p=0.014) (Table 39). A summary of change from Baseline in MASES index at Week 16 in the subgroup of study participants with enthesitis at Baseline is presented for the RS (MI) in Table 39.

Table 39: MASES index change from Baseline at Week 16 (RS [MI])

	PBO N=92	BKZ 160mg Q4W N=94
Baseline		
n	92	94
Mean (SE)	4.87 (0.37)	4.82 (0.32)
Median (min, max)	4.00 (1.0, 13.0)	4.00 (1.0, 13.0)
Week 16		
n	92	94
Mean (SE)	-1.3 (0.3)	-2.4 (0.3)
Median (min, max)	-1.0 (-9, 8)	-2.0 (-10, 5)
LS mean (SE) [a]	-1.11 (0.38)	-2.16 (0.37)
Difference vs PBO	–	-1.06
95% CI for difference	–	-1.88, -0.23
Nominal p-value	–	0.013

ANCOVA=analysis of covariance; BKZ=bimekizumab; CI=confidence interval; CRP=C-reactive protein; IE=intercurrent event; LS=least-square; MASES=Maastricht Ankylosing Spondylitis Enthesitis; max=maximum; MI=multiple imputation; min=minimum; MRI=magnetic resonance imaging; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The hypothetical estimand targeted the treatment difference in a hypothetical strategy where IE did not occur such that outcomes for study participants without an IE were as observed and outcomes for study participants with an intercurrent event were treated as though they had completed the randomized study treatment through Week 16.

Note: Study participants with missing data at Week 16 (including observed data after an intercurrent event that were set to missing) were imputed using MI based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).

Note: MASES was assessed in the subgroup of study participants with enthesitis at Baseline (MASES index score >0).

[a] LS means, SE, difference in LS means, and CI and p-value for the comparison of BKZ to PBO have been calculated using ANCOVA with treatment, MRI/CRP classification and region as fixed effects, and Baseline MASES value as covariate.

In the subgroup of study participants with enthesitis at Baseline (MASES index score >0), the bimekizumab 160mg Q4W group had a higher proportion of study participants reach an enthesitis-free state at Week 16 (based on the MASES index) compared with the placebo group (51.1% vs 23.9%, respectively; nominal p<0.001) (Table 40). A summary of enthesitis-free state based on the MASES index at Week 16 is presented for the RS (NRI) in Table 40.

Table 40: Enthesitis-free state based on the MASES index at Week 16 (RS [NRI])

	PBO N=92	BKZ 160mg Q4W N=94
Number of responders, n (%)	22 (23.9)	48 (51.1)
Adjusted response rate [a]	18.9	44.8
95% CI	10.9, 30.8	31.7, 58.7
Odds ratio vs Placebo [a]	–	3.49
95% CI for odds ratio	–	1.84, 6.62
Nominal p-value	–	<0.001

BKZ=bimekizumab; CI=confidence interval; CRP=C-reactive protein; MASES=Maastricht Ankylosing Spondylitis Enthesitis; MRI=magnetic resonance imaging; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The conditional odds ratio evaluated the composite estimand combining the clinically meaningful improvement from Baseline in enthesitis-free state based on the MASES index response and not having an intercurrent event.

Note: Study participants with missing enthesitis-free state based on MASES index data at Week 16 preceded by an intercurrent event were counted as nonresponders, as well as study participants with missing enthesitis-free state based on MASES index data at Week 16 that were not preceded by an intercurrent event.

Note: MASES was assessed in the subgroup of study participants with enthesitis at Baseline (MASES index score >0).

[a] Adjusted response rate, odds ratio, and p-values for the comparison of bimekizumab/placebo have been calculated using logistic regression with factors for treatment, MRI/CRP classification and region

The bimekizumab 160mg Q4W group had a higher ASAS40 response rate in TNFα inhibitor-naïve study participants compared with the placebo group at Week 16 (46.6% vs 22.9%, respectively; nominal p=0.0002) (Table 41). A summary of ASAS40 response at Week 16 in the TNFα inhibitor-naïve study participants is presented for the RS (NRI) in Table 41.

Table 41: ASAS40 response rates at Week 16 in TNF a inhibitor-naïve study participants (RS [NRI])

	PBO N=109	BKZ 160mg Q4W N=118
Number of responders, n (%)	25 (22.9)	55 (46.6)
Adjusted response rate [a]	22.7	47.4
95% CI	14.9, 33.0	37.1, 58.0
Odds ratio vs Placebo [a]	–	3.08
95% CI for odds ratio	–	1.71, 5.54
Nominal p-value	–	0.0002

ASAS40=Assessment of SpondyloArthritis International Society 40%; BKZ=bimekizumab; CI=confidence interval; CRP=C-reactive protein; MRI=magnetic resonance imaging; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The conditional odds ratio evaluated the composite estimand combining the clinically meaningful improvement from Baseline in ASAS40 response and not having an intercurrent event.

Note: Study participants with missing ASAS40 data at Week 16 preceded by an intercurrent event were counted as nonresponders, as well as study participants with missing ASAS40 data at Week 16 that were not preceded by an intercurrent event.

[a] Adjusted response rate, odds ratio, and p-values for the comparison of bimekizumab/placebo have been calculated using logistic regression with factors for treatment, MRI/CRP classification and region.

The results of the supportive analyses of the secondary efficacy endpoints were in line with the secondary efficacy results.

Upon CHMP's request, data at week 52 were presented by the MAH. The ASAS40 response rate in anti-TNF alpha naïve patients further increased from week 16 46.6% to week 52 61.9% for participants in the bimekizumab 160mg Q4W group. The ASAS20 response rate further increased slightly from Week 16 (68.8%) to Week 52 (73.4%) in the bimekizumab 160mg Q4W group. The ASAS-PR response rates further increased slightly from Week 16 (25.8%) to Week 52 (29.7%) for participants in the bimekizumab 160mg Q4W group. The ASDAS-MI response rates further increased from Week 16 (27.3%) to Week 52 (36.7%) for participants in the bimekizumab 160mg Q4W group.

The change from Baseline in MASES index score further decreased from Week 16 (-2.38) to Week 52 (-3.61) for participants in the bimekizumab 160mg Q4W group. The proportion of participants reaching an enthesitis-free state was similar at Week 16 (51.1%) and Week 52 (54.3%) for participants in the bimekizumab 160mg Q4W group.

The change from Baseline in mean NSP Score further decreased from Week 16 (-3.6) to Week 52 (-4.3) for participants in the bimekizumab 160mg Q4W group.

The change from Baseline in BASMI score further decreased from Week 16 (-0.4) to Week 52 (-0.6) for study participants in the bimekizumab 160mg Q4W group.

The mean change from Baseline in BASDAI total score further decreased from Week 16 (-3.1) to Week 52 (-3.9) for participants in the bimekizumab 160mg Q4W group.

Other secondary endpoints

The other secondary endpoints presented below were considered clinically relevant.

The proportion of patients in reaching ASDAS <2.1 (combining ASDAS-inactive disease (ID) and ASDAS-low disease (LD)) at Week 16 was 46.1% in the bimekizumab group versus 21.1% in the placebo group (multiple imputation). At Week 52, 61.6% of patients in the bimekizumab group achieved an ASDAS <2.1, including 25.2% in inactive disease state (ASDAS <1.3).

Table 42: ASDAS status (ID, LD, HD, and vHD) by visit (RS [MI])

	PBO/BKZ 160mg Q4W N=126 (%)				BKZ 160mg Q4W N=128 (%)			
Visit	ID	LD	HD	vHD	ID	LD	HD	vHD
Baseline	0	2.4	38.9	58.7	0	0.8	41.4	57.8
Week 2	0.8	6.6	49.2	43.4	2.4	17.2	58.6	21.9
Week 4	2.4	12.8	53.0	31.8	7.0	24.2	52.3	16.4
Week 8	2.4	16.8	44.6	36.3	12.5	21.9	50.3	15.4
Week 12	4.1	13.3	53.5	29.2	14.1	24.8	51.2	10.0
Week 16	6.4	14.7	42.9	35.9	18.8	27.3	41.0	12.9
Week 24	19.8	25.0	45.3	9.9	19.6	34.1	36.5	9.8
Week 36	23.4	30.0	39.1	7.5	27.3	34.7	30.2	7.9
Week 52	28.0	26.5	38.0	7.5	25.2	36.4	32.8	5.7

ASDAS=Ankylosing Spondylitis Disease Activity Score; BKZ=bimekizumab; CRP=C-reactive protein; HD=high disease; ID=inactive disease; IE=intercurrent event; LD=low disease; OC=observed case; PBO=placebo; Q4W=every 4 weeks; SS=Safety Set; vHD=very high disease
Note: An IE was defined as discontinuation of study treatment prior to Week 16 due to any reason.
Note: Missing data at the given week which were not preceded by an IE were imputed using MI on the ASDAS raw value before deriving the ASDAS status. Multiple imputation was based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).
Note: Percentages were based on the mean proportion in the multiply imputed database.
Note: ID=ASDAS-CRP <1.3, LD=ASDAS-CRP ≥1.3 to <2.1, HD ≥2.1 to ≤3.5, and vHD activity=ASDAS-CRP >3.5.

The BASDAI50 response rate for study participants in the bimekizumab 160mg Q4W group increased up to Week 16, and the BASDAI50 response rate was greater in the bimekizumab 160mg Q4W group (46.9%) compared with the placebo group (21.4%) at Week 16 (Table 43). The BASDAI50 response rates

further increased from Week 16 (46.9%) to Week 52 (53.9%) for participants in the bimekizumab 160mg Q4W group.

In participants who switched from placebo to bimekizumab 160mg Q4W, the BASDAI50 response rate markedly increased from Week 16 (21.4%) to Week 24 (46.0%) and was further increased slightly to Week 52 (49.2%) (Table 43).

Table 43: BASDAI50 response rate by visit (RS [NRI])

Visit	PBO/BKZ 160mg Q4W N=126 n (%)	BKZ 160mg Q4W N=128 n (%)
Week 1	10 (7.9)	14 (10.9)
Week 2	6 (4.8)	23 (18.0)
Week 4	22 (17.5)	34 (26.6)
Week 8	22 (17.5)	45 (35.2)
Week 12	25 (19.8)	52 (40.6)
Week 16	27 (21.4)	60 (46.9)
Week 24	58 (46.0)	64 (50.0)
Week 36	64 (50.8)	74 (57.8)
Week 52	62 (49.2)	69 (53.9)

BASDAI50=Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BKZ=bimekizumab; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: Study participants were summarized according to randomized treatment at Baseline in the Double-Blind Treatment Period. After the Double-Blind Treatment Period, study participants randomized to PBO switched to BKZ 160mg Q4W at Week 16.

Change from Baseline in hs-CRP

The geometric mean hs-CRP ratio to Baseline was lower in the bimekizumab 160mg Q4W group (0.445) compared with the placebo group (0.882) at week 2 (LS means difference 95% CI: -6.99 to -2.94; nominal p<0.001) (Table 44).

In the bimekizumab 160mg Q4W group, the geometric mean hs-CRP ratios to Baseline were similar from Week 2 (0.445) to Week 16 (0.438). In the placebo group, the geometric mean hs-CRP ratios to Baseline were similar from Week 2 (0.882) to Week 16 (0.721). At Week 16, hs-CRP ratios remained lower in the bimekizumab 160mg Q4W group (0.438) compared with the placebo group (0.721) (Table 44).

The geometric mean hs-CRP ratios to Baseline were similar at Week 16 (0.438) and Week 52 (0.361) for participants in the bimekizumab 160mg Q4W group.

In participants who switched from placebo to bimekizumab 160mg Q4W, geometric mean hs-CRP ratios to Baseline markedly decreased from Week 16 (0.721) to Week 24 (0.467) and further decreased slightly to Week 52 (0.402) (Table 44).

Table 44: hs-CRP (mg/L) ratio to Baseline by visit (RS [MI])

Visit	PBO/BKZ 160mg Q4W N=126	BKZ 160mg Q4W N=128
Baseline, GeoMean (GeoCV)	4.985 (230.5)	4.635 (297.7)
Week 2, GeoMean ratio (GeoCV) [a]	0.882 (104.3)	0.445 (205.1)
Week 4, GeoMean ratio (GeoCV) [a]	0.829 (119.6)	0.421 (200.7)
Week 8, GeoMean ratio (GeoCV) [a]	0.820 (135.3)	0.447 (210.2)
Week 12, GeoMean ratio (GeoCV) [a]	0.802 (138.3)	0.426 (220.3)
Week 16, GeoMean ratio (GeoCV) [a]	0.721 (204.8)	0.438 (238.0)
Week 24, GeoMean ratio (GeoCV) [a]	0.467 (275.9)	0.418 (345.7)
Week 36, GeoMean ratio (GeoCV) [a]	0.417 (369.7)	0.396 (238.8)
Week 52, GeoMean ratio (GeoCV) [a]	0.402 (291.3)	0.361 (433.7)

BKZ=bimekizumab; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; hs-CRP=high sensitivity C-reactive protein; LLOQ=lower limit of quantification; MI=multiple imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: Study participants were summarized according to randomized treatment at Baseline in the Double-Blind Treatment Period. After the Double-Blind Treatment Period, study participants randomized to PBO switched to BKZ 160mg Q4W at Week 16.

Note: Any hs-CRP values which were below the LLOQ were set to the midpoint between 0 and the LLOQ (LLOQ=0.05mg/L).

Note: Study participants with missing data at a given week were imputed using MI based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).

[a] Post-Baseline/Baseline Visit.

Change from Baseline in SPARCC MRI score (MRI substudy)

Table 45: SPARCC MRI score change from Baseline by visit (RS [OC])

Visit	PBO/BKZ 160mg Q4W N=70	BKZ 160mg Q4W N=82
Baseline, n	70	82
Mean (SD)	9.79 (12.62)	8.02 (9.94)
Median (min, max)	3.50 (0.0, 48.5)	3.50 (0.0, 32.0)
Week 16, n [a]	62	78
CfB Mean (SD)	-1.56 (8.23)	-6.15 (9.99)
Median (min, max)	0.00 (-33.5, 21.0)	-1.00 (-31.5, 16.0)
Week 52, n	56	67
CfB Mean (SD)	-6.38 (10.70)	-7.57 (10.47)
Median (min, max)	-1.00 (-34.5, 6.0)	-1.50 (-31.5, 5.0)

BKZ=bimekizumab; CfB=change from Baseline; CSR=Clinical Study Report; max=maximum; min=minimum; MRI=magnetic resonance imaging; OC=observed case; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; SPARCC=Spondyloarthritis Research Consortium of Canada

Note: Only study participants enrolled in the sacroiliac joints and spine MRI substudy were included in this analysis.

Note: Data from all eligible substudy participants with an MRI any time prior to the first IMP administration are presented in Table 8.4.28.1.

Note: At least 2 (up to 3) independent readers reviewed the assessments and provided a score result. If there were 2 readers, the average of the 2 scores was derived for the analysis. If there were 3 readers, the average of the 2 closest score values was used. In both cases, the derivation led to a noninteger SPARCC MRI score value.

[a] A small number of Week 16 MRIs that were not read by the Week 24 CSR cutoff date were read by the Week 52 CSR cutoff date; therefore, the number of study participants with an MRI reading at Week 16 in both treatment groups increased in the Week 52 CSR compared with the Week 24 CSR.

Table 46: ASspiMRI-a (Berlin modification) score change from Baseline by visit (RS [OC])

Visit	PBO/BKZ 160mg Q4W N=67	BKZ 160mg Q4W N=79
Baseline, n	67	79
Mean (SD)	1.58 (2.91)	1.58 (2.63)
Median (min, max)	0.50 (0.0, 14.0)	0.50 (0.0, 12.0)
Week 16, n [a]	60	74
CfB Mean (SD)	0.03 (1.39)	-0.36 (2.14)
Median (min, max)	0.00 (-6.5, 5.0)	0.00 (-8.0, 6.0)
Week 52, n	55	65
CfB Mean (SD)	-0.35 (2.01)	-0.70 (2.53)
Median (min, max)	0.00 (-7.0, 4.5)	0.00 (-9.5, 7.5)

ASspiMRI-a=Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity; BKZ=bimekizumab; CfB=change from Baseline; CSR=Clinical Study Report; max=maximum; min=minimum; MRI=magnetic resonance imaging; OC=observed case; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation

Note: Only study participants enrolled in the sacroiliac joints and spine MRI substudy were included in this analysis.

Note: Data from all eligible substudy participants with an MRI any time prior to the first IMP administration are presented in Table 8.4.27.1.

Note: At least 2 (up to 3) independent readers reviewed the assessments and provided a score result. If there were 2 readers, the average of the 2 scores was derived for the analysis. If there were 3 readers, the average of the 2 closest score values was used. In both cases, the derivation led to a noninteger ASspiMRI-a (Berlin modification) score value.

[a] A small number of Week 16 MRIs that were not read by the Week 24 CSR cutoff date were read by the Week 52 CSR cutoff date; therefore, the number of study participants with an MRI reading at Week 16 in both treatment groups increased in the Week 52 CSR compared with the Week 24 CSR.

Patients treated with bimekizumab reported meaningful reduction in fatigue as assessed by the FACIT-Fatigue score (Mean change from baseline at Week 16: 8.5 for bimekizumab versus 3.9 for placebo.

2.4.2.2. AS0011 (BE MOBILE 2)

Title of Study

A phase 3, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in subjects active axial spondyloarthritis.

Methods

AS0011 is a multicentre, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in study participants with active AS, a subtype of axSpA with radiographic sacroiliitis (r-axSpA). To be eligible to participate in this study, study participants must have been adults with a diagnosis of active AS (as defined), including at least 3 months of symptoms and age at symptom onset <45 years, and moderate to severe active disease at Baseline.

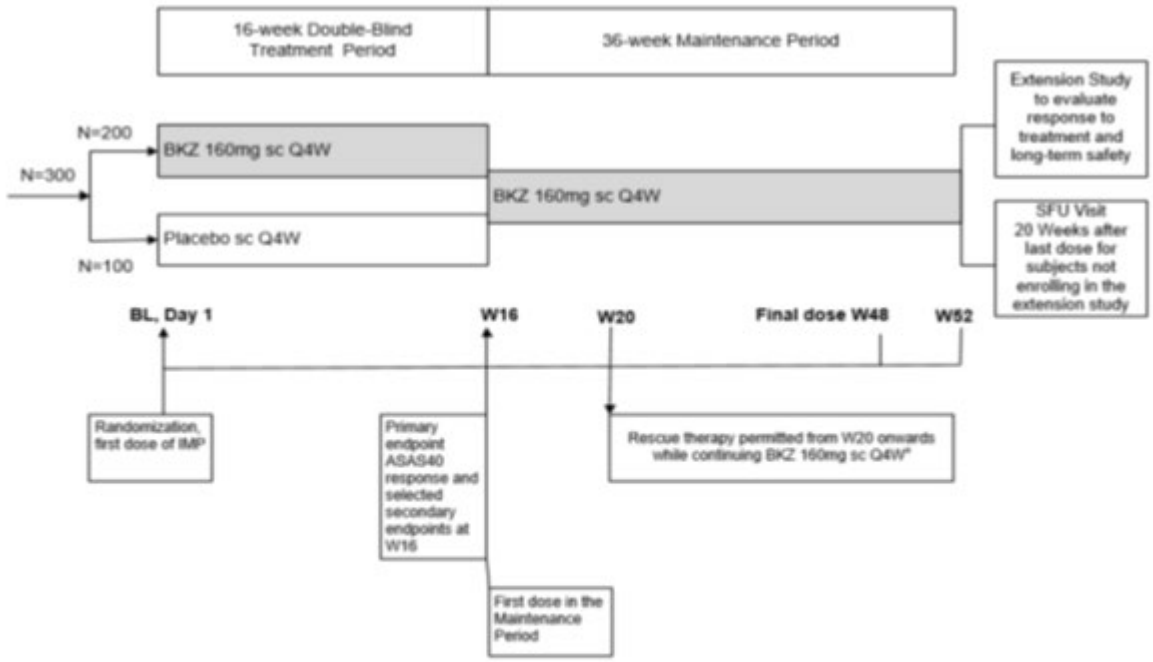
Eligible study participants were randomized 2:1 to receive 1 of 2 treatments (bimekizumab 160mg sc Q4W or placebo sc Q4W) and remained on their allowable background medication. At the end of the 16-week Double-Blind Treatment Period, study participants receiving placebo were re-allocated to bimekizumab 160mg Q4W treatment at Week 16 after all assessments had been completed.

Study participants who complete Week 52 may be eligible for enrolment in an OLE study with bimekizumab. Study participants who are ineligible for, or elect not to participate in, the extension study at Week 52 undergo a Safety Follow-Up (SFU) Visit at the end of the SFU Period.

Interim analyses of all available data were conducted after the planned number of randomised study participants completed 24 weeks and was conducted after the completion of 52 weeks of treatment or withdrawal from IMP or the study. The final analysis of all available data was performed after all randomised study participants have completed the SFU Visit or have withdrawn from the IMP and/or study, or enrolled in the OLE study.

An independent DMC and adjudication committees periodically review and monitor safety data from this study.

Figure 32: Schematic diagram: study overview



ASAS40=Assessment of SpondyloArthritis International Society 40% response criteria; BKZ=bimekizumab; BL=Baseline; IMP=investigational medicinal product; Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-Up; W=week
Note: The planned enrollment was approximately 300 participants. For actual enrollment, see Table 7–1.
* Study participants were eligible for nonbiologic rescue therapy starting at Week 20 with treatment at the discretion of the Investigator while continuing to receive BKZ. Treatment with nonBKZ biologics or prohibited treatment (see Section 3.6.5.2) led to BKZ discontinuation (Table 3–3).

Study participants

To qualify for enrolment into this study, study participants had to fulfil the following inclusion criteria;

- Study participant was male or female at least 18 years of age.
- Study participant had nr-axSpA with all of the following criteria:
  - Adult-onset AS meeting ASAS classification criteria
  - Inflammatory back pain for at least 3 months prior to the Screening Visit
  - Age at symptom onset <45 years

- Study participants must have had active disease as defined by having both BASDAI ≥4 AND spinal pain ≥4 on a 0 to 10 NRS.
- Study participants had to have either failed to respond to 2 different NSAIDs given at the maximum tolerated dose for a total of 4 weeks or had a history of intolerance to, or a contraindication to, NSAID therapy.
- Study participants who were regularly taking NSAIDs/cyclooxygenase 2 inhibitor (COX-2) inhibitors or analgesics (including mild potency opioids) were required to be on a stable dose for at least 14 days before Baseline.
- Other background medicines were also allowed if patients were on stable dose regimens.
- Study participants who had taken a TNFα inhibitor must have experienced an inadequate response to previous treatment given at an approved dose for at least 12 weeks or have been intolerant to treatment.
- Female study participants must have been postmenopausal, permanently sterilized. Or must have been willing to use a highly effective method of contraception throughout the duration of the study.

The exclusion criteria related to patient safety, concomitant medications, or known safety concerns with the IMP, and were appropriate.

Treatments

Eligible study participants were randomised 2:1 to receive either bimekizumab 160mg sc Q4W or placebo Q4w sc, and remain on allowable background medication, until Week 16. Thereafter, study participants randomised to bimekizumab remained on their randomised while those who received placebo were reallocated to receive bimekizumab 160mg Q4W.

Objectives

The primary objective was to demonstrate the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) compared to placebo in the treatment of study participants with active AS.

The secondary objectives of the study were:

- To assess the efficacy of bimekizumab compared to placebo
- To assess the safety and tolerability of bimekizumab
- To assess the impact of bimekizumab on patient-reported quality of life
- To assess the impact of bimekizumab on spinal mobility
- To assess the impact of bimekizumab on enthesitis and on peripheral arthritis.

Outcomes/endpoints

The primary efficacy endpoint for this study was the ASAS40 response at Week 16.

The secondary efficacy endpoints for this study were as follows:

• ASAS40 response at Week 16 in TNFα inhibitor-naïve study participants

• ASAS 20% (ASAS20) response at Week 16

• Change from Baseline in BASDAI total score at Week 16

• ASAS partial remission (ASAS-PR) at Week 16

• Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) at Week 16

• ASAS 5 out of 6 criteria (ASAS5/6) response at Week 16

• Change from Baseline in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16

• Change from Baseline in Nocturnal Spinal Pain score (based on NRS) at Week 16

• Change from Baseline in Ankylosing Spondylitis Quality of Life (ASQoL) total score at Week 16

• Change from Baseline in the Short Form 36-Item Health Survey (SF-36) physical component summary (PCS) score at Week 16

• Change from Baseline in Bath Ankylosing Spondylitis Disease Metrology Index (BASMI) at Week 16

• Change from Baseline in the Maastricht Ankylosing Spondylitis Enthesitis (MASES) Index in the subgroup of study participants with enthesitis at Baseline at Week 16

• Enthesitis-free state based on the MASES Index in the subgroup of study participants with enthesitis at Baseline at Week 16

Sample size

Approximately 300 study participants were planned to be randomly assigned in a 2:1 ratio to bimekizumab 160mg sc or placebo sc Q4W. All sample size and power calculations were done at a significance level of 0.05 in a 2-sided test.

The sample size assumptions for bimekizumab versus placebo were based on the ASAS40 response data from the Phase 2b bimekizumab study in study participants with active AS (AS0008) and assumed an ASAS40 response at Week 16 of 40% for the bimekizumab treatment group and 15% for the placebo group.

With 200 study participants in the bimekizumab treatment group and 100 study participants in the placebo group, the 2-sided, 2-sample, continuity-corrected chi-square test for detecting statistical superiority of bimekizumab versus placebo based on ASAS40 response at Week 16 was powered with >99%.

Blinding (masking)

Due to differences in presentation between bimekizumab and placebo treatments, special precautions were taken to ensure study blinding, and 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. The unblinded personnel were not involved in the study in any way other than assuring the medication was taken from the correct kit and prepared according to the pharmacy manual instructions and administering the drug to the study participants.

Randomisation

An IXRS was used for assigning eligible study participants to a treatment regimen based on a predetermined randomization schedule was produced by the IXRS vendor. Study participants' treatment assignment was stratified by region and prior TNFα inhibitor exposure (yes/no). Enrollment of TNFα inhibitor-experienced study participants was limited to 30% of the total study population.

Statistical methods

Statistical Analysis Plan

The original SAP, dated 05 June 2019, was amended twice.

- Amendment 1 of the SAP, dated 05 August 2021, was implemented in response to protocol amendment 4 (16 February 2021) and discussions and feedback provided at meetings between UCB and PAREXEL technical teams or for clarifications, as well as to incorporate feedback from FDA on missing data methods. The main changes are rules for handling missing data and guidelines on the implementation of MI and latest guidelines from the bimekizumab AE of special monitoring convention document.
- Amendment 2 of the SAP, dated 15 November 2021, was implemented to to fix formatting issues in the SAP document and to add clarifications on how to analyze specific data.

All amendments to the original SAP are comprehensively described in SAP Amendment 2.

Changes to the planned analyses

Changes to protocol-defined analyses

The following changes relative to the protocol-defined analyses were included in the SAP:

- The protocol mentioned that subgroup analyses using descriptive statistics were to be performed on the primary efficacy endpoint. In addition, Ors for the comparison of bimekizumab versus placebo and associated 95% CI were calculated.
- Race was analysed as additional subgroup endpoint.
- The MS was added as additional analysis set.
- The primary/main analysis of continuous secondary efficacy endpoints which were part of the sequential testing procedure, as well as the components of the primary ASAS40 endpoint, used a reference-based imputation method.

In addition, the impact of the COVID-19 pandemic on study procedures/conduct and on the primary efficacy endpoint and safety analyses (TEAEs, serious TEAEs, and IMP withdrawal due to TEAEs) were investigated and additional analysis outputs are provided as appropriate. These additional analyses were not planned as part of the protocol, as the pandemic was not ongoing at the time of protocol finalisation.

These additional analyses include analyses by period of the COVID-19 pandemic (prior/during/post), for study participant disposition, details of impacted visits and effects on collection and reporting of efficacy data, protocol deviations, exposure, and Aes.

In addition, the primary analysis for the primary efficacy endpoint was repeated by timing of the Week 16 Visit relative to the start and end of the COVID-19 pandemic.

For study participants participating in the MRI substudy, the protocol-defined time window for performing the MRIs of the spine and sacroiliac joints for MRI-positive and MRI-negative study participants at Week

16 and Week 52 was ±5 days. However, the MRIs performed within ±3 weeks were accepted for Week 16 and Week 52 after consultation with imaging experts.

Additional changes to the planned analyses

Exportation of samples from China was not possible at the time of Week 24 CSR preparation and thus the Immunogenicity SS was used for ADAb and Nab analyses in this Week 24 report.

Analysis Populations

The primary efficacy endpoint was analysed for all study participants in the Randomized Set (RS), and supportive analyses of the primary efficacy endpoint were performed on the Full Analysis Set (FAS) and the Per-Protocol Set (PPS). All other efficacy endpoints were based on the RS.

Demographics tables were produced using the RS as well as the Safety Set (SS), if the SS was different from the RS. Safety endpoints were summarized on the SS. Pharmacokinetic endpoints were analysed for all study participants in the SS and/or Pharmacokinetic Per-Protocol Set (PK-PPS).

The **Enrolled Set (ES)** was to consist of all study participants who had given informed consent.

The **Randomized Set (RS)** was to consist of all enrolled study participants that had been randomized.

The **Safety Set (SS)** was to consist of all subjects who received at least 1 dose of the IMP. Subjects in the SS were to be analysed according to the treatment they actually received.

The **Maintenance Set (MS)** was to consist of all study participants who received at least 1 dose of bimekizumab treatment in the Maintenance Period.

The **Full Analysis Set (FAS)** was to consist of all randomized subjects who received at least 1 dose of the IMP and had valid measurements of all components of the primary efficacy variable at Baseline.

The **Per-Protocol Set (PPS)** was to consist of all subjects in the RS who had no important protocol deviation (IPD) affecting the primary efficacy variable. Important protocol deviations were to be predefined and study participants with important protocol deviations evaluated during ongoing data cleaning and data evaluation meetings prior to unblinding of the data. Exclusions from the FAS were considered as an IPD that also resulted in exclusion from the PPS. Additional exclusions from the PPS due to a protocol-permitted decrease in dosing or dosing frequency of axSpA background medication due to intolerance/AE/side effects may have also been possible in case a potential impact on the primary endpoint cannot be excluded.

In addition, if after unblinding it was determined that there were study participants who were dosed with bimekizumab in place of placebo, then these study participants were removed from the PPS. Study participants who received a single dose with placebo in place of bimekizumab remained in the PPS, but participants who received more than a single dose with placebo (or received 1 dose with placebo and also missed 1 or more additional doses, therefore fulfilling the IPD criterion of more than 1 missed dose up to Week 12 during the Double-Blind Treatment Period) when randomized to bimekizumab were excluded from the PPS.

The **Pharmacokinetics Per-Protocol Set (PK-PPS)** was to consist of all randomized subjects who received at least 1 dose of bimekizumab and provided at least 1 quantifiable plasma concentration post-dose (after first IMP administration) without important protocol deviations that would affect the concentration.

A separate **Immunogenicity Safety Set** was defined in SAP Amendment 2 to include all randomised study participants, excluding China participants, who received at least 1 dose of IMP in the event that sample exportation from China was not approved. Exportation of all samples from China was not possible

at the time of Week 24 CSR preparation and thus the Immunogenicity SS was used for ADAb and Nab analyses in this Week 24 report and only includes available samples from non-Chinese study participants.

The **COVID-19-free Set** consisted of all study participants in the RS who had no COVID-19 impact up to the primary efficacy endpoint. This was defined as study participants (up to Week 16):

- not having a COVID-19 related IPD
- not having an impact based on the COVID-19 eCRF
- not having an AE related to COVID-19
- not discontinuing due to COVID-19

Efficacy analyses were to be performed according to randomisation and not actual treatment received.

Analysis of primary endpoint – ASAS40 response at week 16

Derivation of the ASAS40 response

The ASAS40 response is defined as:

- An improvement of at least 40%, and an absolute improvement of at least 2 units on a 0 to 10 NRS in at least 3 of the 4 following domains:
  - PGADA
  - Pain assessment (Total Spinal Pain, Question 1 from total and Nocturnal Spinal Pain)
  - Physical function (measured by the BASFI)
  - Inflammation (represented by the mean of the BASDAI Questions 5 and 6) concerning morning stiffness intensity and duration)
- And no worsening at all in the remaining domain.

The primary efficacy analysis evaluated the composite estimand (NRI) that combined the clinically meaningful improvement from Baseline in ASAS40 response at Week 16 and the IE of not discontinuing early from study treatment for any reason prior to Week 16. Note that only permanent discontinuations were considered as Ies. This definition was applicable to all analyses.

The following 4 attributes described the composite estimand that was used to define the treatment effect of interest for the primary efficacy analysis:

• **Population** = Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomized to IMP.

• **Study participant-level outcome** = ASAS40 at Week 16.

• **Intercurrent Event (IE) handling** = An IE was defined as discontinuation of study treatment prior to Week 16. A composite strategy was implemented in which a positive clinical outcome was defined as achieving ASAS40 at Week 16 and not discontinuing study treatment through Week 16.

• **Population-level summary measure** = Conditional OR comparing bimekizumab to placebo.

Intercurrent events were acknowledged as an unfavourable outcome for the composite estimand in considering study participants with Ies as nonresponders to the study treatment. Consequently, if the date of an IE (as defined in the SAP) occurred prior to or at Week 16, study participants were considered as nonresponders at Week 16. Additionally, missing data at Week 16 that were not preceded by an IE were imputed as nonresponders.

A logistic regression model was used to assess the treatment effect on ASAS40 response at Week 16. The model included fixed effects for treatment and stratification endpoints of MRI/CRP classification and region. The suitability of including these endpoints in the model was assessed using the Hosmer-Lemeshow goodness-of-fit test. If the logistic regression model was unable to converge the stratification factors could be dropped to facilitate the model convergence.

The summary table results presented the number of responders, adjusted responder rates, and associated 95% confidence interval (CI) for bimekizumab and placebo, the adjusted OR and 95% CI for the comparison of bimekizumab versus placebo, and the p-value testing the null hypothesis that the OR=1. The treatment comparison was made using the 2-sided Wald test at a significance level of α=0.05.

The following supportive analyses for the primary efficacy variable were conducted:

- Analysis on the PPS
- Analysis on the FAS (to be performed if the number of study participants in RS and FAS differ)
- Analysis using a modified composite estimand where the single identified intercurrent event is defined as discontinuation due to AE or lack of efficacy
- Analysis of individual components of the ASAS40 (using hypothetical estimand where the single intercurrent event is discontinuation of study treatment prior to week 16 and

  missing data and nonmissing data after the IE (reset as missing) were imputed using reference-based MI)
- Analyses using treatment policy strategy for the single identified intercurrent event of discontinuation of study treatment prior to week 16
- Analysis of observed cases
- Tipping point analysis, including a worst-case scenario where study participants who had missing ACR50 response were set as nonresponders if they were randomized to bimekizumab and as responders if they were randomized to placebo
- Analysis including COVID-19 impact

Analysis of ranked secondary endpoints

Eleven key secondary endpoints were included in the testing hierarchy (see further below).

The following analyses were conducted for the secondary efficacy endpoints:

- For the secondary binary endpoints:
  - Composite Estimand – NRI: The same composite estimand structure as the one defined in for the primary efficacy analysis was used. The same analysis model was considered, and the analysis results were presented similarly as for the primary efficacy analysis. The imputation strategy for handling missing data was the same as for the primary endpoint; i.e. the NRI approach.
  - Modified Composite – MI: A similar modified composite estimand structure as the one defined for the primary efficacy analysis was used. The same analysis model was considered, and the analysis results were presented similarly as for the primary efficacy analysis.
  - Observed Case analysis

For the secondary continuous endpoints:

- Reference-Based Estimand – MI: The same hypothetical estimand structure as the one defined in for the analysis on component endpoints for the primary efficacy endpoint was used. The same

analysis model and imputation strategy for handling missing data was also considered. The analysis results were presented similarly as for this analysis on the individual ASAS40 components.

- Hypothetical Estimand – MI where the single intercurrent event is discontinuation of study treatment prior to week 16 and missing data and non-missing data after the IE (reset as missing) were imputed under a MAR assumption
- Observed Case Analysis
- Analysis to assess the impact of the COVID-19 pandemic, the primary analysis of all secondary efficacy endpoints included in the testing hierarchy were analysed on the CFS, using the reference-based estimand.

Subgroup analyses

Subgroup analyses were performed for the primary endpoint ASAS40 and ASDAS-MI. In addition, ASAS40 was analysed based on the timing of participant enrolment and timing of the Week 16 visit relative to the COVID-19 pandemic periods. The complete list of subgroups is listed in the table below:

Subgroup	Categories
Age (years)	<45, ≥45
Gender	Male, Female
Race 1	Black, White, Other
Race 2	White, Asian, Other
Region 1 [a]	Asia, Eastern Europe, North America, Western Europe
Disease duration (years)	<2, ≥2
BMI (kg/m^2)	<18.5, ≥18.5 to <25, ≥25 to <30, ≥30
hs-CRP level	≤ULN [b], >ULN
Prior TNFα inhibitor exposure [c]	Yes, No
csDMARDs	Yes, No
ASDAS status	<1.3 [inactive disease], 1.3 to ≤2.1 [low disease activity], >2.1 to ≤3.5 [high disease activity], >3.5 [very high disease activity]
HLA-B27 positivity [d]	Yes, No
Timing of study participant enrollment relative to COVID-19 pandemic periods as defined in Section 6.1.2.2.1.	Enrolled prior to the COVID-19 pandemic, Enrolled during the COVID-19 pandemic, Enrolled after the COVID-19 pandemic
Timing of Week 16 Visit relative to the COVID-19 pandemic periods as defined in Section 6.1.2.2.1.	Study participants who had the Week 16 Visit: prior the COVID-19 pandemic, during the COVID-19 pandemic, after the COVID-19 pandemic

ASDAS= Ankylosing Spondylitis Disease Activity Score; BMI=body mass index; COVID-19=coronavirus disease 2019; HLA-B27=human leukocyte antigen B27; hs-CRP= high sensitivity C-reactive protein; csDMARD= conventional synthetic disease-modifying antirheumatic drug; TNFα= tumor necrosis factor alpha; ULN=upper limit of normal

[a] The categories may be pooled as defined in Section 6.1.7.

[b] ULN refers to the central laboratory ULN definition (ie, 5mg/L).

[c] The actual TNF alpha stratum the study participant belonged to was used for the subgroup analysis.

[d] HLA-B27 = human leukocyte antigen B27.

Multicentre studies

The data from all centres were pooled for the purposes of the analysis. Centres were grouped in the geographic regions of North America, Western Europe, Eastern Europe, and Asia.

No exploration of treatment by centre interaction was investigated.

Type I error control

A fixed sequence testing procedure was applied for the primary endpoint and the key secondary endpoints. The testing procedure accounted for multiplicity and controlled the family-wise type I error rate at alpha=0.05 (2-sided).

For each test, on each binary efficacy endpoint, the null hypothesis was that the conditional odds ratio (OR) was equal to 1 (H_0: $OR_{T1T2} = 1$). The alternative hypothesis was that the conditional OR was not equal to 1 (H_A: $OR_{T1T2} \neq 1$).

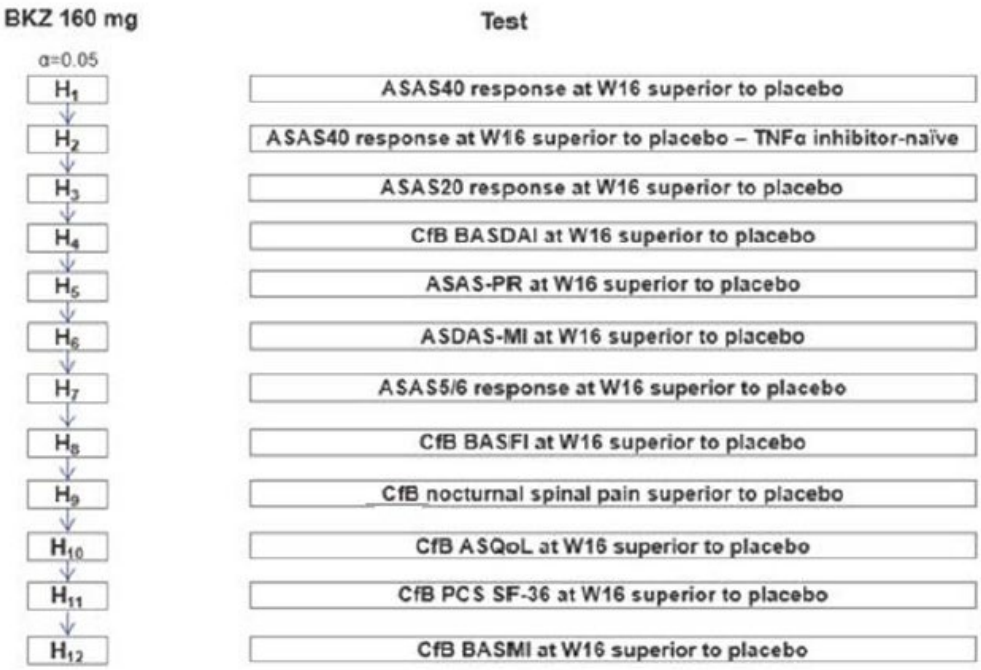
For each test, on each continuous efficacy endpoint, the null hypothesis was that there was no

difference between treatment groups (H_0: $T_1 - T_2 = 0$). The alternative hypothesis was that there was a difference between treatment groups (H_A: $T_1 - T_2 \neq 0$).

In these hypotheses, T_1 referred to bimekizumab and T_2 to placebo.

According to this strategy, the statistical testing of an endpoint could be investigated only if the null hypothesis for the previous endpoint had been rejected (ie, if $p<0.05$).

The testing order for these endpoints is shown in the figure below:



ASAS40 (20)=Assessment of SpondyloArthritis International Society 40% (20%) response criteria; ASAS5/6=Assessment of SpondyloArthritis International Society 5 out of 6 response criteria; ASAS-PR=Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Metrology Index; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; PCS=physical component summary; SF-36=Short Form 36-item Health Survey; TNFα=tumor necrosis factor alpha; W=Week

Interim analyses

In AS0011, two analyses are to be performed prior to the final analysis:

- Analysis 1: Week 24 analysis.

- Analysis 2: Week 52 analysis.

No formal alterations to the further study conduct (e.g., stopping rules, sample size re-estimation, or changes to eligibility criteria) were planned for the 2 interim analyses (Week 24 and Week 52). No separate SAP for the Week 24 analyses was to be provided. The TFL shells for the Week 24 and the Week 52 analyses were provided in the same document and appropriately identified. The type of efficacy and safety analyses to be provided for the 2 interim analyses was detailed in the SAP.

The final analysis for AS0011 will consist of a rerun of all analyses provided during the preceding interim analysis. This includes new SFU data that were not available for the Week 52 analysis. If there is no SFU data ongoing, the final analysis will be identical to the Week 52 analysis.

Results

Screening for AS0011 started on 25 April 2019 and completed on 21 April 2021.

A total of 612 study participants signed the ICF and were screened for the study, 280 of whom were screen failures. The most common reason for screen failure was ineligibility due to not meeting one or more inclusion criteria.

A total of 322 study participants were randomised in the global population and started treatment in AS0010. Study participants were randomised 2:1 to either bimekizumab 160mg sc Q4W (221 patients) or placebo sc Q4W ((111 patients).

Most study participants completed the Double-Blind Treatment Period and were similar for both bimekizumab and placebo (96.4% and 98.2% respectively). The most common primary reasons for discontinuation during the Double-Blind Treatment Period were due to withdrawal by study participant (4 study participants [1.2%]) and an AE (3 study participants [0.9%]).

A full breakdown of the patient flow figures can be found in Table 47 of the CSR (see Table 47 below).

Table 47: Disposition and study discontinuation reasons – Doubled-Blind Treatment Period (RS)

Disposition	PBO N=111 n (%)	BKZ 160mg Q4W N=221 n (%)	All Study Participants N=332 n (%)
Started Double-Blind Treatment Period	111 (100)	221 (100)	332 (100)
Completed Double-Blind Treatment Period	109 (98.2)	213 (96.4)	322 (97.0)
Completed Double-Blind Treatment Period not on randomized treatment	0	0	0
Discontinued during Double-Blind Treatment Period	2 (1.8)	8 (3.6)	10 (3.0)
Primary reason for study discontinuation			
AE	0	3 (1.4)	3 (0.9)
Lack of efficacy	0	1 (0.5)	1 (0.3)
Protocol violation	0	0	0
Lost to follow up	0	0	0
Withdrawal by study participant	1 (0.9)	3 (1.4)	4 (1.2)
Other	1 (0.9)	1 (0.5)	2 (0.6)

AE=adverse event; BKZ=bimekizumab; IMP=investigational medicinal product; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SFU=Safety Follow-up
Note: Started a period was based on treatment information.
Note: A study participant was considered as completing a study period if she/he had completed the last scheduled study visit for that period.
Note: Study participants who withdrew from the IMP but returned for all scheduled visits up to the last scheduled study visit for that period were considered as having completed the study period.
Note: Study participants were summarized according to randomized treatment at Baseline in the Double-Blind Treatment Period. After the Double-Blind Treatment Period, study participants randomized to placebo switched to BKZ 160mg Q4W at Week 16.

Conduct of the study

Overall, the study was conducted appropriately. There have been 4 protocol amendments to date; however, none of these are felt to have diminished the integrity of the trial.

The Covid-19 pandemic does not seem to have had any material impact on the conduct of the trial.

While 4.8% of patients did experience one or more protocol deviations, for the most part these were minor – bimekizumab 160mg Q4W (5.0%) and placebo (4.5%) groups. Overall, the most common protocol deviation was prohibited concomitant medication use, with an incidence of 1.4% in the bimekizumab group and 2.7% in the placebo group.

Baseline data

Overall, baseline characteristics were well balanced between treatment groups. There were some slight differences between the groups with respect to patients >45y ((37.1% and 30.6% in bimekizumab and placebo groups respectively).

The majority of study participants were White (80.4%). The mean body weight and mean BMI overall were 80.43kg and 26.86kg/m2, respectively. For each treatment group, the proportions of study participants enrolled in each region and study participants with or without prior TNFα exposure were similar.

Study participants were most commonly enrolled in the following countries: Poland (26.2%), the Czech Republic (16.9%), China (13.3%), and Spain (10.2%).

The Baseline disease characteristics were reflective of a study population with active AS and high burden of disease despite standard of care treatment. Overall, the mean times since first diagnosis and first symptoms of AS were 6.39 years (range: 0.1 to 41.0 years) and 13.46 years (range: 0.4 to 59.1 years), respectively. Most of the study participants (85.5%) were positive for HLA-B27. Treatment groups were generally well balanced with respect to AS-related and other Baseline disease characteristics.

Prior anti-TNF therapy was used by 16.3% of all study participants. At Baseline, the majority of all study participants were using NSAID therapies (79.8%), 29.9% were on conventional synthetic DMARDs, 6.9% were taking oral corticosteroids, and 13.6% were on analgesic/opioid therapies.

Table 48: Study participant demographics (SS)

Variable	PBO N=111	BKZ 160mg Q4W N=221	All Study Participants N=332
Age (years)			
Mean (SD)	39.2 (12.6)	41.0 (12.1)	40.4 (12.3)
Median (min, max)	38.0 (19, 75)	40.0 (19, 80)	39.0 (19, 80)
Age, n (%) [a]			
18 to <65 years	109 (98.2)	212 (95.9)	321 (96.7)
65 to <85 years	2 (1.8)	9 (4.1)	11 (3.3)
≥85 years	0	0	0
Age, n (%) [b]			
≤18 years	0	0	0
19 to <65 years	109 (98.2)	212 (95.9)	321 (96.7)
≥65 years	2 (1.8)	9 (4.1)	11 (3.3)
Age, n (%)			
<45 years	77 (69.4)	139 (62.9)	216 (65.1)
≥45 years	34 (30.6)	82 (37.1)	116 (34.9)
Gender, n (%)			
Male	80 (72.1)	160 (72.4)	240 (72.3)
Female	31 (27.9)	61 (27.6)	92 (27.7)

Variable	PBO N=111	BKZ 160mg Q4W N=221	All Study Participants N=332
Racial group, n (%)			
American Indian/Alaskan native	0	0	0
Asian	20 (18.0)	37 (16.7)	57 (17.2)
Black	1 (0.9)	0	1 (0.3)
Native Hawaiian or other Pacific Islander	0	0	0
White	90 (81.1)	177 (80.1)	267 (80.4)
Other/mixed	0	3 (1.4)	3 (0.9)
Missing	0	4 (1.8)	4 (1.2)
Ethnicity, n (%)			
Hispanic or Latino	1 (0.9)	2 (0.9)	3 (0.9)
Not Hispanic or Latino	110 (99.1)	218 (98.6)	328 (98.8)
Missing	0	1 (0.5)	1 (0.3)
Weight (kg)			
Mean (SD)	81.33 (18.52)	79.98 (19.11)	80.43 (18.90)
Median (min, max)	78.70 (42.6, 130.3)	77.50 (37.0, 159.0)	78.15 (37.0, 159.0)
Weight, n (%)			
<70kg	34 (30.6)	76 (34.4)	110 (33.1)
≥70 to <95kg	46 (41.4)	96 (43.4)	142 (42.8)
≥95 to <115kg	27 (24.3)	40 (18.1)	67 (20.2)
≥115kg	4 (3.6)	9 (4.1)	13 (3.9)
Weight, n (%)			
≤100kg	92 (82.9)	193 (87.3)	285 (85.8)
>100kg	19 (17.1)	28 (12.7)	47 (14.2)
Height (cm)			
Mean (SD)	173.17 (10.55)	172.59 (9.64)	172.78 (9.94)
Median (min, max)	175.00 (145.1, 204.0)	173.00 (140.1, 198.0)	173.60 (140.1, 204.0)

Variable	PBO N=111	BKZ 160mg Q4W N=221	All Study Participants N=332
BMI (kg/m^2) [c]			
Mean (SD)	27.08 (5.78)	26.75 (5.74)	26.86 (5.75)
Median (min, max)	26.12 (17.5, 45.7)	26.03 (15.2, 56.0)	26.10 (15.2, 56.0)
BMI, n (%) [c]			
<18.5kg/m^2	3 (2.7)	5 (2.3)	8 (2.4)
18.5 to <25kg/m^2	40 (36.0)	90 (40.7)	130 (39.2)
25 to <30kg/m^2	38 (34.2)	68 (30.8)	106 (31.9)
≥30kg/m^2	30 (27.0)	58 (26.2)	88 (26.5)
BMI, n (%) c			
<25kg/m^2	43 (38.7)	95 (43.0)	138 (41.6)
25 to <30kg/m^2	38 (34.2)	68 (30.8)	106 (31.9)
≥30kg/m^2	30 (27.0)	58 (26.2)	88 (26.5)
Actual randomization stratum: Prior TNFα exposure, n (%) [d]			
Yes	17 (15.3)	37 (16.7)	54 (16.3)
No	94 (84.7)	184 (83.3)	278 (83.7)
Region, n (%) [d, e]			
Asia	21 (18.9)	40 (18.1)	61 (18.4)
Eastern Europe	55 (49.5)	108 (48.9)	163 (49.1)
North America	3 (2.7)	6 (2.7)	9 (2.7)
Western Europe	32 (28.8)	67 (30.3)	99 (29.8)

Variable	PBO N=111	BKZ 160mg Q4W N=221	All Study Participants N=332
Country, n (%)			
Belgium	5 (4.5)	5 (2.3)	10 (3.0)
Bulgaria	8 (7.2)	7 (3.2)	15 (4.5)
China	17 (15.3)	27 (12.2)	44 (13.3)
Czech Republic	16 (14.4)	40 (18.1)	56 (16.9)
France	0	4 (1.8)	4 (1.2)
Germany	14 (12.6)	23 (10.4)	37 (11.1)
Hungary	2 (1.8)	3 (1.4)	5 (1.5)
Japan	3 (2.7)	9 (4.1)	12 (3.6)
Netherlands	2 (1.8)	0	2 (0.6)
Poland	29 (26.1)	58 (26.2)	87 (26.2)
Spain	10 (9.0)	24 (10.9)	34 (10.2)
Turkey	1 (0.9)	4 (1.8)	5 (1.5)
United Kingdom	1 (0.9)	11 (5.0)	12 (3.6)
United States	3 (2.7)	6 (2.7)	9 (2.7)

BKZ= bimekizumab; BMI=body mass index; EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; max=maximum; min=minimum; PBO=placebo; Q4W=every 4 weeks; SD=standard deviation; SS=Safety Set; TNFα=tumor necrosis factor alpha

Note: Four study participants had a missing race because they were randomized in France where law regulation forbids divulging race information. Similarly, 1 study participants had a missing ethnicity.

[a] EudraCT age categories.

[b] clinicaltrials.gov age categories.

[c] BMI was derived based on the height and weight variables collected in the database.

[d] Study participants were categorized in the stratum they actually belong to.

[e] Turkey was included in the Asian region.

Numbers analysed

The RS and SS consisted of the same study participants, with 221 study participants in the bimekizumab group and 111 study participants in the placebo/bimekizumab group. The MS included the same study participants as the RS and SS, except for the 10 study participants who discontinued during the Double-Blind Treatment Period and the 3 study participants who completed the Double-Blind Treatment Period but did not enter the Maintenance Period. The FAS included the same study participants as the RS and SS, except for 1 study participant in the bimekizumab group who was excluded from the FAS due to incomplete baseline PGADA assessment. Most of all study participants were included in the PPS (94.0%) and in the PK-PPS (99.4%).

Table 49: Disposition of Analysis Sets (RS)

Analysis set	PBO/BKZ 160mg Q4W N=111 n (%)	BKZ 160mg Q4W N=221 n (%)	All Study Participants N=332 n (%)
RS	111 (100)	221 (100)	332 (100)
SS	111 (100)	221 (100)	332 (100)
MS	109 (98.2)	210 (95.0)	319 (96.1)
FAS	111 (100)	220 (99.5)	331 (99.7)
PPS	106 (95.5)	206 (93.2)	312 (94.0)
PK-PPS	109 (98.2)	221 (100)	330 (99.4)
Immunogenicity SS	94 (84.7)	194 (87.8)	288 (86.7)
CFS	94 (84.7)	203 (91.9)	297 (89.5)

BKZ=bimekizumab, CFS=COVID-19 Free Set; COVID-19=coronavirus disease 2019; FAS=Full Analysis Set; MS=Maintenance Set; PBO=placebo; PK-PPS=Pharmacokinetic Per-Protocol Set; PPS=Per-Protocol Set; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set.

Outcomes and estimation

The results of the primary and key secondary efficacy variables are provided below. Overall, bimekizumab treatment resulted in statistically significant and clinically meaningful differences over placebo for the primary and all key secondary endpoints included in the predefined sequential testing sequence ($p<0.001$).

Table 50: Summary of primary and key secondary efficacy analysis results based on the predefined sequential testing sequence at Week 16 (RS)

Ordered sequential procedure	Variable	PBO	BKZ 160mg Q4W	Treatment comparison (95% CI)	Measure	p-value	Significant [a]
Primary							
#1: BKZ 160mg Q4W vs PBO	ASAS40 response, n (%)	25 (22.5)	99 (44.8)	2.88 [1.71, 4.87]	Odds ratio	<0.001	Yes
Secondary							
#2: BKZ 160mg Q4W vs PBO	ASAS40 response in TNFα inhibitor-naïve participants, n (%)	22 (23.4)	84 (45.7)	2.80 [1.59, 4.93]	Odds ratio	<0.001	Yes
#3: BKZ 160mg Q4W vs PBO	ASAS20 response, n (%)	48 (43.2)	146 (66.1)	2.66 [1.65, 4.28]	Odds ratio	<0.001	Yes
#4: BKZ 160mg Q4W vs PBO	CfB BASDAI, LS mean (SE)	-1.70 (0.21)	-2.74 (0.17)	-1.04 [-1.48, -0.59]	LS mean difference	<0.001	Yes
#5: BKZ 160mg Q4W vs PBO	ASAS-PR response, n (%)	8 (7.2)	53 (24.0)	4.26 [1.93, 9.39]	Odds ratio	<0.001	Yes
#6: BKZ 160mg Q4W vs PBO	ASDAS-MI response, n (%)	6 (5.4)	57 (25.8)	6.47 [2.67, 15.65]	Odds ratio	<0.001	Yes
#7: BKZ 160mg Q4W vs PBO	ASAS5/6 response, n (%)	21 (18.9)	109 (49.3)	4.36 [2.51, 7.57]	Odds ratio	<0.001	Yes
#8: BKZ 160mg Q4W vs PBO	CfB BASFI, LS mean (SE)	-0.95 (0.20)	-2.00 (0.16)	-1.05 [-1.48, -0.63]	LS mean difference	<0.001	Yes
#9: BKZ160mg Q4W vs PBO	CfB Nocturnal Spinal Pain, LS mean (SE)	-1.68 (0.25)	-3.16 (0.20)	-1.48 [-2.00, -0.96]	LS mean difference	<0.001	Yes
#10: BKZ 160mg Q4W vs PBO	CfB ASQoL, LS mean (SE)	-3.07 (0.41)	-4.59 (0.32)	-1.52 [-2.36, -0.68]	LS mean difference	<0.001	Yes
#11: BKZ 160mg Q4W vs PBO	CfB SF-36 PCS, LS mean (SE)	5.17 (0.82)	8.54 (0.67)	3.38 [1.67, 5.09]	LS mean difference	<0.001	Yes
#12: BKZ 160mg Q4W vs PBO	CfB BASMI, LS mean (SE)	-0.17 (0.09)	-0.45 (0.07)	-0.28 [-0.47, -0.08]	LS mean difference	0.006	Yes

ANCOVA=analysis of covariance; ASAS20,40,5/6=Assessment of SpondyloArthritis International Society 20%, 40%, 5 out of 6 response criteria; ASAS-PR=Assessment of SpondyloArthritis International Society partial remission; ASDAS-MI=Ankylosing Spondylitis Disease Activity Score major improvement; ASQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BASMI=Bath Ankylosing Spondylitis Disease Metrology Index; BKZ=bimekizumab; CI=confidence interval; CfB=change from Baseline; LS=least squares; MI=multiple imputation; PBO=placebo; PCS=physical component summary; Q4W=every 4 weeks; RS=Randomized Set; SAP=statistical analysis plan; SE=standard error; SF-36=Short-Form 36-item Health Survey; TNFα=tumor necrosis factor alpha

Note: For binary endpoints: p-value obtained from logistic regression with treatment, prior TNFα inhibitor exposure and region as factor/CIs obtained from the difference of adjusted odds ratios.

Note: For continuous endpoints: p-value obtained from ANCOVA with treatment, prior TNFα inhibitor exposure, region as fixed effect and the Baseline value as covariate/CI obtained from the difference in LS means from the ANCOVA.

Note: For binary endpoints, study participants with missing data at Week 16 were imputed based on nonresponder imputation approach.

Note: For continuous endpoints, study participants with missing data at Week 16 were imputed using MI with a reference-based approach.

[a] All tests are performed at a 2-sided alpha level of 0.05. See Section 4.5 of the SAP for further details on the testing methodology.

Primary efficacy endpoint – ASAS40 at Week 16

The bimekizumab 160mg Q4W group had a higher ASAS40 response rate compared with the placebo group at Week 16 that was statistically significant and clinically meaningful (44.8% vs 22.5%, respectively; p<0.001).

Table 51: ASAS40 response rates at Week 16 (RS [NRI])

	PBO N=111	BKZ 160mg Q4W N=221
Number of responders, n (%)	25 (22.5)	99 (44.8)
Adjusted response rate [a]	19.8	41.5
95% CI	[12.9, 29.2]	[33.3, 50.3]
Odds ratio vs Placebo [a]	-	2.88
95% CI for odds ratio	-	[1.71, 4.87]
p-value	-	<0.001

ASAS40=Assessment in Axial spondyloArthritis International Society 40%; BKZ=bimekizumab; CI=confidence interval; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The conditional odds ratio evaluated the composite estimand combining the clinically meaningful improvement from Baseline in ASAS40 response and not having an intercurrent event.

Note: Study participants with missing ASAS40 data at Week 16 preceded by an intercurrent event were counted as nonresponders, as well as study participants with missing ASAS40 data at Week 16 who were not preceded by an intercurrent event.

[a] Adjusted response rate, odds ratio, and p-values for the comparison of bimekizumab/placebo have been calculated using logistic regression with factors for treatment, prior TNFα inhibitor exposure and region.

The ASAS40 response rate for study participants in the bimekizumab 160mg Q4W group further increased from Week 16 (44.8%) to Week 52 (58.4%).

The bimekizumab 160mg Q4W group had an improvement over placebo for each of the ASAS40 components (shown as difference of bimekizumab-placebo): PGADA (-1.28); Total Spinal Pain (-1.43); BASFI score (function) (-1.05); and BASDAI Q5/Q6 mean score (inflammation) (-1.13). and all other sensitivity analyses.

Table 52: Change from Baseline in individual components of ASAS40 response at Week 16 (RS [reference-based MI])

	PBO N=111	BKZ 160mg Q4W N=221	BKZ 160mg Q4W-Placebo [a]
PGADA			
LS mean (SE) [b]	-1.39 (0.247)	-2.67 (0.196)	-1.28 (0.262)
Diff: 95% CI [b]	-	-	[-1.79, -0.76]
Total Spinal Pain assessment			
LS mean (SE) [b]	-1.71 (0.239)	-3.14 (0.189)	-1.43 (0.254)
Diff: 95% CI [b]	-	-	[-1.93, -0.93]
BASFI score (function) [c]			
LS mean (SE) [b]	-0.95 (0.204)	-2.00 (0.162)	-1.05 (0.216)
Diff: 95% CI [b]	-	-	[-1.48, -0.63]
BASDAI Q5& Q6 mean score (inflammation)			
LS mean (SE) [b]	-1.86 (0.231)	-2.99 (0.183)	-1.13 (0.246)
Diff: 95% CI [b]	-	-	[-1.61, -0.65]

ANCOVA=analysis of covariance; ASAS40=assessment in axial spondyloarthritis international society 40%; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BKZ=bimekizumab; CI=confidence interval; IE=intercurrent event; LS=least squares; MI=multiple imputation; PBO=placebo; PGADA=Patient's Global Assessment of Disease Activity; Q=question; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error; TNFα=tumor necrosis factor alpha

Note: Inflammation component is calculated as the mean of the 2 scores relating to morning stiffness measurements (ie, Question 5 and Question 6).

Note: An intercurrent event is defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: For each individual component endpoints of the ASAS40 endpoint, missing data at Week 16 and nonmissing data after IE (which are reset to missing) are imputed using MI based on a reference-based approach, in which the MI model is based on data from the placebo group.

[a] LS mean difference between BKZ 160mg and placebo.

[b] ANCOVA with treatment, prior TNFα inhibitor exposure and region as fixed effects, and Baseline value as covariate.

[c] This endpoint is included in the sequential testing hierarchy.

The supportive analyses of the primary endpoint were consistent with the results of the primary analysis. When ASAS40 response rates were analysed with alternative methods for handling missing data (MI, Treatment Policy Strategy, OC, or the Tipping Point Analysis), or with additional analysis sets (PPS, FAS, and COVID-19 Free Set), the bimekizumab 160mg Q4W group had higher ASAS40 response rates compared with the placebo group (nominal $p<0.001$ for all comparisons). Additionally, there was no evidence that the timing of the Week 16 Visit relative to the COVID-19 pandemic had an effect on ASAS40 response rates for bimekizumab and placebo.

Subgroup analysis

Overall, a consistent trend of increased ASAS40 response rates in the bimekizumab group compared with the placebo group was evident across all subgroups, except for the subgroup of participants with a BMI of ≥30kg/m2 (see Figure 33 below).

In participants <45 years of age, the ASAS40 response rate at Week 16 in the bimekizumab group (53.2%) was higher compared with placebo (22.1%), while in participants ≥45 years of age, the ASAS40 response rate was lower than in participants <45 years of age. In this older age category, the ASAS40 response rate was slightly higher in the bimekizumab group (30.5%) compared with the placebo groups (23.5%).

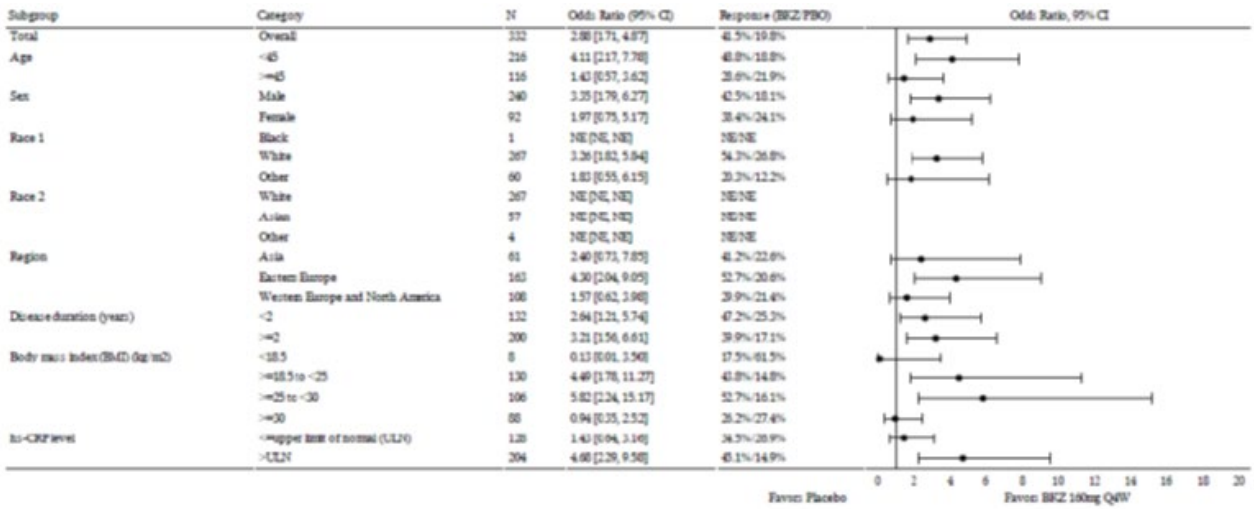
In participants with a BMI ≥18.5 to 25kg/m2, the ASAS40 response rate in the bimekizumab group (47.8%) was higher compared with placebo (17.5%), which was similar in in participants with a BMI of ≥25 to <30kg/m2 where the ASAS40 response rate was higher in the bimekizumab group (57.4%) compared with the placebo group (18.4%). In participants with a BMI of ≥30kg/m2, the ASAS40 response rate in the bimekizumab group (27.6%) was lower than in participants with a BMI ≥18.5 to 25kg/m2 or ≥25 to <30kg/m2 and similar to the placebo group (30.0%).

In male participants, the ASAS40 response rate at Week 16 in the bimekizumab group (46.3%) was higher compared with placebo (21.3%), while in female participants, the ASAS40 response rate was slightly lower than in male participants but was higher in the bimekizumab group (41.0%) compared with the placebo group (25.8%).

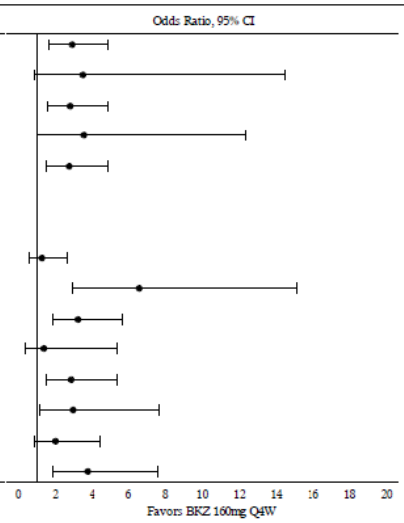
In participants with prior TNFα inhibitor exposure, the ASAS40 response rate at Week 16 in the bimekizumab group (40.5%) was higher compared with placebo (17.6%). Results were similar in participants with no prior TNFα inhibitor exposure, where the ASAS40 response was higher in the bimekizumab group (45.7%) compared with the placebo group (23.4%). However, the sample size for study participants with prior TNFα inhibitor exposure was small, and conclusions should be drawn with caution.

For the region subgroups, the bimekizumab group had higher ASAS40 response rates compared with placebo in participants from Eastern Europe (54.6% vs 21.8%, respectively), Asia (42.5% vs 23.8%, respectively), and a slightly higher ASAS40 response rate in Western Europe and North America (31.5% vs 22.9%, respectively). In the bimekizumab group, the ASAS40 response rate was higher in Eastern Europe (54.6%) compared with Asia (42.5%), which was also higher compared with Western Europe and North America (31.5%).

Figure 33: Forest plot of ASAS40 odds ratio at Week 16 by subgroups (RS [NRI])



Subgroup	Category	N	Odds Ratio (95% CI)	Response (BKZ/PBO)
Total	Overall	332	2.88 [1.71, 4.87]	41.5%/19.8%
Prior TNFα inhibitor exposure	Yes	54	3.48 [0.84, 14.40]	39.7%/15.9%
	No	278	2.79 [1.59, 4.91]	44.2%/22.1%
csDMARDs	Yes	66	3.51 [1.00, 12.30]	42.9%/17.6%
	No	266	2.76 [1.55, 4.91]	41.1%/20.2%
ASDAS status	<1.3 [inactive disease]	0	NE [NE, NE]	NE/NE
	1.3 to <=2.1 [low disease activity]	3	NE [NE, NE]	31.2%/NE
	>2.1 to <=3.5 [high disease activity]	131	1.24 [0.59, 2.63]	39.2%/34.2%
	>3.5 [very high disease activity]	197	6.59 [2.88, 15.04]	42.8%/10.2%
HLA-B27 positivity	Yes	284	3.22 [1.82, 5.70]	43.5%/19.3%
	No	48	1.37 [0.35, 5.42]	29.6%/23.5%
Timing of study participant enrollment relative to COVID-19 pandemic periods	Enrolled prior to the COVID-19 pandemic	213	2.86 [1.52, 5.39]	44.4%/21.8%
	Enrolled during the COVID-19 pandemic	119	2.97 [1.16, 7.61]	38.2%/17.3%
Timing of Week 16 Visit relative to the COVID-19 pandemic periods	Study participants who had the Week 16 Visit prior the COVID-19 pandemic	125	1.99 [0.89, 4.45]	36.2%/22.2%
	Study participants who had the Week 16 Visit during the COVID-19 pandemic	207	3.75 [1.86, 7.56]	44.2%/17.5%



ASAS=assessment in axial spondyloarthritis international society; ASDAS=ankylosing spondylitis disease activity score; BKZ=bimekizumab; CI=confidence interval; COVID-19=coronavirus disease 2019; csDMARD=conventional synthetic disease-modifying; HLA-B27=human leukocyte antigen B27; hs-CRP=high sensitivity C-reactive protein; NE=not evaluable; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; TNF=tumor necrosis factor; ULN=upper limit of normal value

Note: ULN value for hs-CRP was 5mg/L.

Note: Model-adjusted response rates are presented in this figure while nonadjusted rates are discussed below.

Secondary efficacy endpoints

Bimekizumab treatment resulted in statistically significant improvements over placebo for all key secondary endpoints included in the predefined sequential testing sequence (p-values were $p \leq 0.005$; ASAS40 in TNFα inhibitor naïve participants, ASAS20, BASDAI, ASAS-PR, ASDAS-MI, ASAS5/6, BASFI, Nocturnal Spinal Pain, ASQoL, SF-36 PCS score, and BASMI), which resulted in meaningful improvement after bimekizumab treatment (see Table 50). Additionally, improvements after bimekizumab treatment over placebo were observed for MASES and enthesitis-free state, see below.

Table 53: MASES index change from Baseline at Week 16 in study participants with entheistis at Baseline (RS [MI])

	PBO N=67	BKZ 160mg Q4W N=132
Baseline		
n	67	132
Mean (SE)	4.40 (0.33)	4.18 (0.25)
Median (min, max)	4.00 (1.0, 13.0)	3.00 (1.0, 12.0)
n	67	132
Mean (SE)	-1.5 (0.3)	-2.4 (0.2)
Median (min, max)	-1.0 (-7, 3)	-2.0 (-9, 5)
LS mean (SE) [a]	-1.04 (0.33)	-2.12 (0.26)
Difference vs placebo	-	-1.08
95% CI for difference	-	[-1.79, -0.37]
Nominal p-value	-	0.003

ANCOVA=analysis of covariance; BKZ=bimekizumab; CI=confidence interval; LS=least squares; max=maximum; MASES=Maastricht Ankylosing Spondylitis Enthesitis; MI=multiple imputation; min=minimum; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error; TNFα=tumor necrosis factor alpha

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The hypothetical estimand targets the treatment difference in a hypothetical strategy where intercurrent event did not occur such that outcomes for study participants without an intercurrent event were as observed and outcomes for study participants with an intercurrent event were treated as though they had completed the randomized study treatment through Week 16.

Note: Study participants with missing data at Week 16 (including observed data after an intercurrent event that are set to missing) were imputed using multiple imputation based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).

Note: MASES was assessed in the subgroup of study participants with enthesitis at Baseline (MASES index score >0).

[a] LS Means, SE, difference in LS Means, and CI and nominal p-value for the comparison of bimekizumab to placebo have been calculated using ANCOVA with treatment, prior TNFα inhibitor exposure at Baseline and region as fixed effects, and Baseline MASES value as covariate.

Table 54: Enthesitis-free state based on the MASES index at Week 16 (RS [NRI])

	PBO N=67	BKZ 160mg Q4W N=132
Number of responders, n (%)	22 (32.8)	68 (51.5)
Adjusted response rate [a]	23.9	43.8
95% CI	[14.5, 36.9]	[33.1, 55.0]
Odds ratio vs Placebo [a]		2.47
95% CI for odds ratio		[1.30, 4.68]
Nominal p-value		0.006

BKZ=bimekizumab; CI=confidence interval; MASES=Maastricht Ankylosing Spondylitis Enthesitis; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: The conditional odds ratio evaluated the composite estimand combining the clinically meaningful improvement from Baseline in enthesitis-free state based on the MASES index response and not having an intercurrent event.

Note: Study participants with missing enthesitis-free state based on MASES index data at Week 16 preceded by an intercurrent event were counted as nonresponders, as well as study participants with missing enthesitis-free state based on MASES index data at Week 16 that were not preceded by an intercurrent event.

[a] Adjusted response rate, odds ratio, and nominal p-values for the comparison of bimekizumab/placebo have been calculated using logistic regression with factors for treatment, prior TNFα inhibitor exposure and region.

The results of the supportive analyses of the secondary efficacy endpoints were in line with the results of the primary analyses of these endpoints.

Upon CHMP's request, data at week 52 were presented by the MAH. The ASAS40 response rate in anti-TNF alpha naïve patients further increased from week 16 (45.7%) to week 52 (58.7%) for participants in the bimekizumab 160mg Q4W group. The ASAS20 response rate further increased slightly from Week 16 (66.1%) to Week 52 (71.5%) in the bimekizumab 160mg Q4W group. The ASAS-PR response rates further increased slightly from Week 16 (24.0%) to Week 52 (29.9%) for participants in the bimekizumab 160mg Q4W group. The ASDAS-MI response rates further increased from Week 16 (25.8%) to Week 52 (32.1%) for participants in the bimekizumab 160mg Q4W group.

The change from Baseline in mean NSP Score further decreased from Week 16 (-3.3) to Week 52 (-4.1) for participants in the bimekizumab 160mg Q4W group.

The change from Baseline in BASMI score further decreased from Week 16 (-0.4774) to Week 52 (-0.7213) for study participants in the bimekizumab 160mg Q4W group.

The mean change from Baseline in BASDAI total score further decreased from Week 16 (-2.90) to Week 52 (-3.58) for participants in the bimekizumab 160mg Q4W group.

The change from Baseline in MASES index score for participants in the bimekizumab 160mg Q4W group further decreased from Week 16 (-2.37) to Week 24 (-2.84) and was sustained to Week 52 (-2.88). The proportion of participants who reached an enthesitis-free state was similar at Week 16 (51.5%) and Week 52 (50.8%) for study participants in the bimekizumab 160mg Q4W group.

The below other secondary endpoints were considered as clinically relevant.

- ASDAS < 2.1

Table 55: ASDAS status (ID, LD, HD, and vHD) by visit (RS [MI])

	PBO/BKZ 160mg Q4W N=111 %				BKZ 160mg Q4W N=221 %			
Visit	ID	LD	HD	vHD	ID	LD	HD	vHD
Baseline	0	0	42.3	57.7	0	1.4	38.0	60.6
Week 2	0.9	7.5	50.6	41.0	3.8	20.8	61.1	14.4
Week 4	2.7	12.6	42.4	42.3	7.8	26.2	53.6	12.4
Week 8	5.4	9.5	44.9	40.2	12.3	27.3	46.3	14.0
Week 12	3.6	16.5	50.1	29.8	14.5	33.5	41.2	10.8
Week 16	4.6	12.8	48.4	34.2	16.4	28.4	44.9	10.3
Week 24	25.6	31.1	36.8	6.5	21.1	32.9	39.1	6.9
Week 36	24.5	36.9	34.7	3.9	22.8	34.2	37.4	5.6
Week 52	37.1	29.3	30.3	3.4	23.4	33.7	38.1	4.7

ASDAS=Ankylosing Spondylitis Disease Activity Score; BKZ=bimekizumab; EDC=electronic data capture; HD=high disease; hs-CRP=high sensitivity C-reactive protein; ID=inactive disease; LD=low disease; MI=multiple imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; vHD=very high disease

Note: An intercurrent event was defined as discontinuation of study treatment prior to Week 16 due to any reason.

Note: Missing data at the given week which were not preceded by an intercurrent event were imputed using MI on the ASDAS raw value before deriving the ASDAS status. Multiple imputation was based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).

Note: Percentages are based on the mean proportion in the multiply imputed database.

Note: ID=ASDAS-CRP <1.3, LD=ASDAS-CRP ≥1.3 to <2.1, HD ≥2.1 to≤3.5 and vHD activity=ASDAS-CRP >3.5.

- ASspiMRI-a (Berlin modification) score (MRI substudy)

Table 56: ASspiMRI-a (Berlin modification) score change from Baseline by visit (RS [OC])

Visit	PBO/BKZ 160mg Q4W N=48	BKZ 160mg Q4W N=89
Baseline, n	48	89
Mean (SD)	3.15 (4.07)	3.25 (4.54)
Median (min, max)	1.00 (0.0, 15.0)	1.50 (0.0, 20.5)
Week 16, n [a]	46	81
CfB Mean (SD)	-0.34 (1.59)	-2.23 (3.62)
CfB Median (min, max)	0.00 (-7.5, 4.0)	-0.50 (-15.0, 1.0)
Week 52	42	77
CfB mean (SD)	-2.06 (3.41)	-2.38 (3.90)
Median (min, max)	-0.50 (-12.0, 1.0)	-0.50 (-19.5, 2.0)

ASspiMRI-a=Ankylosing Spondylitis spine Magnetic Resonance Imaging-activity; BKZ=bimekizumab; CfB=change from Baseline; IMP=investigational medicinal product; max=maximum; min=minimum; MRI=magnetic resonance imaging; OC=observed case; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation

Note: Only study participants enrolled in the sacroiliac joint and spine MRI substudy were included in this analysis.

Note: Data from all eligible substudy participants with an MRI any time prior to the first IMP administration are presented in Table 8.4.28.1.

Note: At least 2 (up to 3) independent readers reviewed the assessments and provided a score result. If there were 2 readers, the average of the 2 scores was derived for the analysis. If there were 3 readers, the average of the 2 closest score values were used. In both cases, the derivation led to a non-integer ASspiMRI-a score value.

[a] A small number of Week 16 MRI that were not read by the Week 24 CSR data cutoff date were read by the Week 52 CSR data cutoff date; therefore, the number of study participants with an MRI reading available at Week 16 in both treatment groups increased in the Week 52 CSR compared with the Week 24 CSR.

- Change from Baseline in SPARCC MRI score (MRI substudy)

Table 57: SPARCC MRI score change from Baseline by visit (RS [OC])

Visit	PBO/BKZ 160mg Q4W N=48	BKZ 160mg Q4W N=90
Baseline, n	48	90
Mean (SD)	3.79 (6.05)	5.39 (8.39)
Median (min, max)	1.00 (0.0, 29.0)	1.00 (0.0, 40.0)
Week 16, n	46	81
CfB Mean (SD)	0.59 (5.27)	-4.51 (7.77)
Median (min, max)	0.00 (-11.0, 20.0)	-0.50 (-38.0, 4.5)
Week 52	41	78
CfB Mean (SD)	-2.77 (6.12)	-4.67 (8.22)
Median (min, max)	0.00 (-29.0, 2.5)	0.00 (-40.0, 1.5)

BKZ=bimekizumab; CfB=change from Baseline; IMP=investigational medicinal product; OC=observed case; max=maximum; min=minimum; MRI=magnetic resonance imaging; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; SPARCC=Spondyloarthritis Research Consortium of Canada

Note: Only study participants enrolled in the sacroiliac joint and spine MRI substudy were included in this analysis.

Note: Data from all eligible substudy participants with an MRI any time prior to the first IMP administration are presented in Table 8.4.29.1.

Note: At least 2 (up to 3) independent readers reviewed the assessments and provided a score result. If there were 2 readers, the average of the 2 scores was derived for the analysis. If there were 3 readers, the average of the 2 closest score values were used. In both cases, the derivation led to a non-integer SPARCC MRI score value.

BASDAI50 response

The BASDAI50 response rate for study participants in the bimekizumab 160mg Q4W group increased up to Week 16, and the BASDAI50 response rate was greater in the bimekizumab 160mg Q4W group (46.6%) compared with the placebo group (26.1%) at Week 16 (Table 58). The BASDAI50 response rates further increased from Week 16 (46.6%) to Week 52 (53.8%) for study participants in the bimekizumab 160mg Q4W group.

In participants who switched from placebo to bimekizumab 160mg Q4W, the BASDAI50 response rate markedly increased from Week 16 (26.1%) to Week 52 (62.2%) (Table 58).

Table 58: BASDAI50 response rate by visit (RS [NRI])

Visit	PBO/BKZ 160mg Q4W N=111 n (%)	BKZ 160mg Q4W N=221 n (%)
Week 1	8 (7.2)	28 (12.7)
Week 2	8 (7.2)	39 (17.6)
Week 4	14 (12.6)	63 (28.5)
Week 8	17 (15.3)	79 (35.7)
Week 12	24 (21.6)	104 (47.1)
Week 16	29 (26.1)	103 (46.6)
Week 24	59 (53.2)	110 (49.8)
Week 36	56 (50.5)	117 (52.9)
Week 52	69 (62.2)	119 (53.8)

BASDAI50=Bath Ankylosing Spondylitis Disease Activity Index 50% improvement; BKZ=bimekizumab; NRI=nonresponder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: Study participants were summarized according to randomized treatment at Baseline in the Double-Blind Treatment Period. After the Double-blind Treatment Period, study participants randomized to placebo switched to BKZ 160mg Q4W at Week 16.

Change from Baseline in hs-CRP

The geometric mean hs-CRP ratio (decreases reflect improvement) was lower in the bimekizumab 160mg Q4W group (0.376) compared with the placebo group at week 2 (0.893) (LS means difference 95% CI: -9.29 to -4.91; nominal p<0.001) (Table 59).

In the bimekizumab 160mg Q4W group, the geometric mean hs-CRP ratios were similar from Week 2 (0.376) to Week 16 (0.365). In the placebo group, the geometric mean hs-CRP ratios were similar from Week 2 (0.893) to Week 16 (0.893). At Week 16, hs-CRP ratios remained lower in the bimekizumab 160mg Q4W group (0.365) compared with the placebo group (0.893) (Table 59).

The geometric mean hs-CRP ratios were similar at Week 16 (0.365) and Week 52 (0.333) for study participants in the bimekizumab 160mg Q4W group.

In participants who switched from placebo to bimekizumab 160mg Q4W, geometric mean hs-CRP ratios markedly decreased from Week 16 (0.893) to Week 24 (0.283) and were sustained to Week 52 (0.298) (Table 59).

Table 59: Hs-CRP (mg/L) ratio to Baseline by visit (RS [MI])

Visit	PBO/BKZ 160mg Q4W N=111	BKZ 160mg Q4W N=221
Baseline, geoMean (geoCV%)	6.721 (197.4)	6.539 (275.0)
Week 2, geoMean ratio (geoCV%)[a]	0.893 (79.1)	0.376 (206.0)
Week 4, geoMean ratio (geoCV%)[a]	0.868 (70.9)	0.334 (158.5)
Week 8, geoMean ratio (geoCV%)[a]	0.888 (95.3)	0.379 (204.7)
Week 12, geoMean ratio (geoCV%)[a]	0.936 (115.7)	0.378 (223.9)
Week 16, geoMean ratio (geoCV%)[a]	0.893 (94.9)	0.365 (235.4)
Week 24, geoMean ratio (geoCV%)[a]	0.283 (202.1)	0.331 (236.7)
Week 36, geoMean ratio (geoCV%)[a]	0.287 (230.6)	0.319 (293.4)
Week 52, geoMean ratio (geoCV%)[a]	0.298 (336.6)	0.333 (265.5)

BKZ=bimekizumab; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; hs-CRP=high sensitivity C-reactive protein; LLOQ=lower limit of quantification; MI=multiple imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error

Note: Study participants are summarized according to randomized treatment at Baseline in the Double-Blind Treatment Period. After the Double-Blind Treatment Period, study participants randomized to PBO switch to BKZ 160mg Q4W at Week 16.

Note: High sensitivity C-reactive protein values which are below the LLOQ are set to the midpoint between 0 and the LLOQ (LLOQ=0.05mg/L).

Note: Study participants with missing data at a given week were imputed using MI based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).

[a] PostBaseline/Baseline Visit.

Patients treated with bimekizumab reported meaningful reduction in fatigue as assessed by the FACIT-Fatigue score (Mean change from baseline at Week 16: 8.4for bimekizumab versus 5.0 for placebo.

In pooled data from BE MOBILE 1 (nr-axSpA) and BE MOBILE 2 (AS), at Week 16, the proportion of patients developing a uveitis event was lower with bimekizumab (0.6%) compared to placebo (4.6%). The incidence of uveitis remained low with long-term treatment with bimekizumab (1.2/100 patient-years in the pooled phase 2/3 studies).

Summary of main studies

The following Table 60 and Table 61 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 60: Summary of efficacy for AS0010

Title: A Phase 3, Multicenter, Randomised, Double-Blind, Placebo-controlled Study evaluating the Efficacy And Safety Of Bimekizumab In Study Participants With Active Nonradiographic Axial Spondyloarthritis	
Study identifier	AS0010 EudraCT Number: 2017-003064-13 NCT03928704

Design	AS0010 is a Phase 3, multicenter study consisting of a 16-week, randomized, double-blind, parallel-group Initial Treatment Period followed by a 36-week Maintenance Period to evaluate the efficacy and safety of bimekizumab (BKZ) in adult study participants with active nonradiographic axial spondyloarthritis (nr-axSpA). After the 36-week Maintenance Period, study participants were allowed to enroll in the open-label extension study, AS0014.		
	Duration of Double-Blind Period: Duration of Maintenance Period: Duration of Safety Follow-up (SFU) Period:		16 weeks 36 weeks SFU Visit was planned 20 weeks after the final dose of investigational medicinal product (IMP) (for study participants not enrolling in open-label study AS0014)
Hypothesis	Superiority to placebo (PBO)		
Treatments groups	Double-Blind Treatment Period (Weeks 0-16)	BKZ 160mg every 4 weeks (Q4W)	BKZ 160mg administered Q4W 128 randomized
		PBO Q4W	PBO administered Q4W 126 randomized
	Maintenance Treatment Period (Weeks 16-52)	BKZ 160mg Q4W	BKZ 160mg Q4W 126 continued
		PBO/BKZ 160mg Q4W	PBO Q4W 16 weeks and switched to BKZ 160mg Q4W in Maintenance Period 116 continued
Endpoints and definitions	Primary endpoint	Assessment of SpondyloArthritis International Society 40 (ASAS40) response at Week 16	Proportion of participants who achieved an ASAS40 response at Week 16 (BKZ vs PBO)
	Major secondary endpoints (in predefined testing hierarchy)	Change from Baseline (CfB) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 16	CfB in BASDAI total score at Week 16
		ASAS20 response at Week 16	Proportion of participants who achieved an ASAS20 response at Week 16
		Assessment of SpondyloArthritis International Society partial remission at (ASAS-PR) at Week 16	Proportion of participants who achieved ASAS-PR at Week 16
		Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) at Week 16	Proportion of participants with ASDAS-MI at Week 16

		Assessment of SpondyloArthritis International Society 5 out of 6 response criteria (ASAS5/6) at Week 16	Proportion of participants who achieved an ASAS5/6 at Week 16
		CfB in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16	CfB in BASFI total score at Week 16
		CfB in nocturnal spinal pain at Week 16	CfB in nocturnal spinal pain score at Week 16
		CfB in the Ankylosing Spondylitis Quality of Life (ASQoL) at Week 16	CfB in ASQoL total score at Week 16
		CfB in the Short-Form 36-item Health Survey physical component summary (SF-36 PCS) at Week 16	CfB in SF-36 PCS score at Week 16

Results and Analysis			
Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Randomized Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	PBO Q4W	BKZ 160mg Q4W
	Number of study participants	126	128
	ASAS40 Week 16, n (%)	27 (21.4%)	61 (47.7%)
Effect estimate per comparison	Primary endpoint	Comparison groups	BKZ versus PBO
		Odds ratio (OR) vs placebo	3.51
		95% confidence interval (CI) for OR	(2.00, 6.16)
		P-value (logistic regression with factors for treatment, magnetic resonance imaging/C-reactive protein (MRI/CRP) classification and region	<0.001
Notes	The primary endpoint at Week 16 was highly statistically significant demonstrating superiority over placebo with p<0.001.		
Analysis description	**Secondary analysis of endpoints**		

Analysis population and time point description	Intent to treat (Randomized Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	PBO Q4W	BKZ 160mg Q4W
	Number of study participants	126	128
	BASDAI Week 16 Least square (LS) Mean Standard error (SE)	-1.55 (0.22)	-3.07 (0.21)
	ASAS20 response Week 16 n (%)	48 (38.1)	88 (68.8)
	ASAS-PR Week 16 n (%)	9 (7.1)	33 (25.8)
	ASDAS-MI Week 16 n (%)	9 (7.1)	35 (27.3)
	ASAS5/6 Week 16 n (%)	26 (20.6)	58 (45.3)
	BASFI at Week 16 LS Mean (SE)	-0.91 (0.22)	-2.39 (0.21)
	Nocturnal spinal pain Week 16 LS Mean (SE)	-1.71 (0.27)	-3.51 (0.25)
	ASQoL at Week 16 LS Mean (SE)	-2.30 (0.43)	-4.94 (0.42)
	SF-36 PCS Week 16 LS Mean (SE)	5.36 (0.79)	9.32 (0.76)
Effect estimate per comparison	Secondary endpoints in predefined testing hierarchy	Comparison groups	BKZ versus PBO
		p-value	p<0.001
Notes	All secondary endpoints in pre-defined testing hierarchy were highly statistically significant in favor of bimekizumab treatment with p<0.001.		

Table 61: Summary of efficacy for AS0011

Title: A Phase 3, Multicenter, Randomised, Double-Blind, Placebo-controlled Study evaluating the Efficacy And Safety Of Bimekizumab In Study Participants With Active Ankylosing Spondylitis			
Study identifier	AS0011 EudraCT Number: 2017-003065-95 NCT03928743		
Design	AS0011 is a Phase 3, multicenter study consisting of a 16-week, randomised, double-blind, parallel-group Initial Treatment Period followed by a 36-week Maintenance Period to evaluate the efficacy and safety of bimekizumab (BKZ) in adult study participants with active ankylosing spondylitis (r-axSpA). After the 36-week Maintenance Period, study participants were allowed to enroll in the open-label extension study, AS0014.		
	Duration of Double-Blind Period: Duration of Maintenance Period: Duration of Safety Follow-up (SFU) Period:		16 weeks 36 weeks SFU Visit was planned 20 weeks after the final dose of investigational medicinal product (IMP) (for study participants not enrolling in open-label study AS0014)
Hypothesis	Superiority to placebo (PBO)		
Treatments groups	Double-Blind Treatment Period (Weeks 0-16)	BKZ 160mg every 4 weeks (Q4W)	BKZ 160mg administered Q4W 221 randomised
		PBO Q4W	PBO administered Q4W 111 randomised
	Maintenance Treatment Period (Weeks 16-52)	BKZ 160mg Q4W	BKZ 160mg Q4W 210 continued
		PBO/BKZ 160mg Q4W	PBO Q4W 16 weeks and switched to BKZ 160mg Q4W in Maintenance Period 109 continued
Endpoints and definitions	Primary endpoint	Assessment of SpondyloArthritis International Society 40 (ASAS40) response at Week 16	Proportion of participants who achieved an ASAS40 response at Week 16 (bimekizumab vs PBO)

	Major secondary endpoints (in predefined testing hierarchy)	ASAS40 response in tumour necrosis factor alpha (TNFα) naïve at Week 16	Proportion of TNFα inhibitor-naïve participants who achieved a ASAS40 response at Week 16
		ASAS20 response at Week 16	Proportion of participants who achieved an ASAS20 response at Week 16
		Change from Baseline (CfB) in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) at Week 16	CfB in BASDAI total score at Week 16
		Assessment of SpondyloArthritis International Society partial remission at (ASAS-PR) at Week 16	Proportion of participants who achieved ASAS-PR at Week 16
		Ankylosing Spondylitis Disease Activity Score major improvement (ASDAS-MI) at Week 16	Proportion of participants with ASDAS-MI at Week 16
		Assessment of SpondyloArthritis International Society 5 out of 6 response criteria (ASAS5/6) at Week 16	Proportion of participants who achieved an ASAS5/6 at Week 16
		CfB in Bath Ankylosing Spondylitis Functional Index (BASFI) at Week 16	CfB in BASFI total score at Week 16
		CfB in nocturnal spinal pain at Week 16	CfB in nocturnal spinal pain score at Week 16
		CfB in the Ankylosing Spondylitis Quality of Life (ASQoL) at Week 16	CfB in ASQoL total score at Week 16
		CfB in the Short-Form 36-item Health Survey physical component summary (SF-36 PCS) at Week 16	CfB in SF-36 PCS score at Week 16
		CfB in the Bath Ankylosing Spondylitis Metrology Index (BASMI) Change from Baseline at Week 16	CfB in BASMI total score at Week 16
Database lock	Interim analysis clinical cut-off once all study participants completed Week 24: 16 Nov 2021		
Results and Analysis			

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Randomized Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	PBO Q4W	BKZ 160mg Q4W
	Number of study participants	111	221
	ASAS40 Week 16, n (%)	25 (22.5)	99 (44.8)
Effect estimate per comparison	Primary endpoint	Comparison groups	BKZ versus PBO
		Odds ratio (OR) vs placebo	2.88
		95% confidence interval (CI) for OR	(1.71, 4.87)
		P-value (logistic regression with factors for treatment, prior TNFα exposure, and region	<0.001
Notes	The primary endpoint at Week 16 was highly statistically significant demonstrating superiority over placebo with p<0.001.		
Analysis description	**Secondary analysis of endpoints**		
Analysis population and time point description	Intent to treat (Randomized Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	PBO Q4W	BKZ 160mg Q4W
	Number of study participants	111	221
	Secondary endpoints in predefined testing hierarchy		
	ASAS40 response in TNFα naïve Week 16, n (%)	22 (23.4)	84 (45.7)
	ASAS20 response Week 16 n (%)	48 (43.2)	146 (66.1)
	BASDAI Week 16 LS Mean (SE)	-1.70 (0.21)	-2.74 (0.17)
	ASAS-PR Week 16 n (%)	8 (7.2)	53 (24.0)
	ASDAS-MI Week 16 n (%)	6 (5.4)	57 (25.8)
	ASAS5/6 Week 16 n (%)	21 (18.9)	109 (49.3)
	BASFI at Week 16 LS Mean (SE)	-0.95 (0.20)	-2.00 (0.16)

	Nocturnal spinal pain Week 16 LS Mean (SE)	-1.68 (0.25)	-3.16 (0.20)
	ASQoL at Week 16 LS Mean (SE)	-3.07 (0.41)	-4.59 (0.32)
	SF-36 PCS Week 16 LS Mean (SE)	5.17 (0.82)	8.54 (0.67)
	BASMI Week 16 LS Mean (SE)	-0.17 (0.09)	-0.45 (0.07)
Effect estimate per comparison	Secondary endpoints in predefined testing hierarchy	Comparison groups	BKZ versus PBO
		p-value	p<0.006
Notes	Secondary endpoints in pre-defined testing hierarchy were highly statistically significant in favor of bimekizumab treatment with p<0.001 with the exception of BASMI; p value for BASMI was p<0.006.		

Supportive studies

AS0014

AS0014 is an ongoing Phase 3 open-label extension study including patients from AS0010 and AS0011, designed to assesses the long-term safety, tolerability, and efficacy of bimekizumab in both AS and nr-axSpA. A summary of the study is presented below.

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	AS0014/ NCT04436640/ Belgium, Bulgaria, China, Czech Republic, France, Germany, Hungary, Japan, Netherlands, Poland, Spain, Turkey, UK, and US	5.3.5.2	To assess the long-term safety, tolerability, and efficacy of BKZ administered to study participants who complete AS0010 or AS0011	Phase 3, OL extension	Study participants with active nr-axSpA or active AS who complete AS0010 or AS0011	BKZ/ BKZ 160mg Q4W/ sc injection	351 study participants	Up to 112 weeks	Ongoing/ clinical data cut on 20 Dec 2021 (safety data included in Pool SA2)

AS=ankylosing spondylitis; BKZ=bimekizumab; BL=Baseline; CSR=clinical study report; CZP=certolizumab pegol; DB=double-blind; LD=loading dose; NA=not applicable; NCT number=ClinicalTrials.gov identifier; nr-axSpA=nonradiographic axial spondyloarthritis; OL=open-label; PBO=placebo; PD=pharmacodynamics; PK=pharmacokinetics; PSO=psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks; sc=subcutaneous; W=Week

The results from the open-label extension trial, AS0014 did not have an impact on the assessment of the clinical efficacy data.

2.4.3. Discussion on clinical efficacy

Bimekizumab is currently approved for plaque psoriasis (PSO). This application aims to extend the indication to treatment of active axial spondyloarthritis (axSpA), including both radiographic (raxSpA) and non-radiographic disease (nr-axSpA). According to the proposed SmPC, the recommended posology is 160 mg (given as 1 subcutaneous injection) every 4 weeks.

Design and conduct of clinical studies

Bimekizumab was investigated in the dose finding study AS0008 and the associated OLE study AS0009. Main efficacy studies were the 1-year phase III studies AS0010 and AS0011.

AS0008 was a phase 2b, multicenter, randomised, double-blind, placebo-controlled, parallel-group, 48 week dose-ranging study to investigate the efficacy, safety, pharmacokinetics (PK), and pharmacodynamics (PD) of bimekizumab compared with placebo in adult subjects with active ankylosing spondylitis (AS) in order to guide the selection of doses and clinical indices in the Phase 3 development program.

Eligible subjects had to have active AS, determined by documented radiologic evidence (X-ray) fulfilling the Modified New York criteria for AS (1984), including symptoms for ≥3 months and age of onset <45. Furthermore, subjects will have moderate to severe active disease (Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] ≥4 and spinal pain ≥4 [BASDAI Question 2]). Subjects must have at least 1 of the following: 1) inadequate response to nonsteroidal anti-inflammatory drug (NSAID) therapy, 2) intolerance to administration of at least 1 NSAID, or 3) contraindication(s) to NSAID therapy.

The primary objective was to assess the dose-response based on the efficacy of bimekizumab administered subcutaneously (sc) Q4W for 12 weeks in the treatment of subjects with active AS. The primary efficacy variable was the Assessment in Axial SpondyloArthritis International Society 40% response criteria (ASAS40) response at Week 12. Subjects were randomised in a 1:1:1:1:1 ratio for the following treatment regimens in the double blind treatment period: PBO or BKZ 16 mg, 64 mg, 160 mg or 320 mg Q4W. After week 12, study participants who were in the PBO, BKZ 16 mg and BKZ 64 mg groups were randomised 1:1 to BKZ 160 mg or 320 mg, patients originally randomised in the BKZ 160 mg or 320 mg groups remained on their initially assigned treatment.

Study participants who completed the 48-week AS0008 study were eligible to enter the open label extension study **AS0009** which has a 4-year duration, investigating long term safety, tolerability and efficacy of bimekizumab.

AS0010 was a 52-week multicenter, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active nonradiographic axial spondyloarthritis (nr-axSpA).

To be eligible to participate in this study, study participants must have had active adult-onset nr-axSpA (BASDAI ≥4 and spinal pain ≥4 on a 0 to 10 NRS meeting ASAS classification criteria, with inflammatory back pain for at least 3 months prior to the Screening Visit and an age at symptom onset of <45 years. Study participants must have had objective inflammation, defined by sacroiliitis on the Screening MRI according to ASAS/OMERACT scoring and/or elevated CRP. Study participants must not have had radiographic sacroiliitis as defined by mNY criteria.

The primary objective of AS0010 was to demonstrate the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) compared with placebo in the treatment of subjects with active nr-axSpA. The primary efficacy variable for this study was ASAS40 response at Week 16. This endpoint is in concordance with the EMA guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis. A series of secondary endpoints (all week 16) were investigated through a hierarchical testing strategy to account for multiplicity. While a rationale for the order of endpoints in the testing hierarchy was not provided, the CHMP considers that all the secondary enpoints are justifiable from a clinical perspective. Following week 16, all PBO patients were switched to active treatment.

AS0011 was a 52-week multicenter, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with active ankylosing spondylitis (AS), a

subtype of axial spondyloarthritis (axSpA) with radiographic evidence of disease (also known as radiographic axSpA [r-axSpA]).

To be eligible to participate in this study, study participants must have been adults with AS as per the mNY criteria (1984) including documented radiologic evidence (x-ray) based on central reading and at least 3 months of symptoms with age at symptom onset <45 years. In addition, study participants must have had moderate to severe active disease as defined by both BASDAI ≥4 AND spinal pain ≥4 on a 0 to 10 numeric rating scale (NRS) (from BASDAI Item 2).

The primary objective of AS0011 was to demonstrate the efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) compared with placebo in the treatment of subjects with active AS. The primary efficacy variable for this study is the Assessment of SpondyloArthritis International Society 40% response criteria (ASAS 40) response at Week 16. This endpoint is in concordance with the current EMA guideline on the Clinical Investigation of Medicinal Products for the Treatment of Axial Spondyloarthritis. A series of secondary endpoints (all week 16) were investigated through a hierarchical testing strategy to account for multiplicity. While a rationale for the order of endpoints in the testing hierarchy was not provided, the CHMP considers that all the secondary enpoints are justifiable from a clinical perspective. Following week 16, all PBO patients were switched to active treatment.

These primary and secondary endpoints are in line with EMA guidance on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis.

Efficacy data and additional analyses

In dose finding study **AS0008**, across the bimekizumab (BKZ) doses included in the Cochran-Mantel-Haenszel test, a statistically significant dose response was observed in ASAS40 responder rates at Week 12 ($p<0.001$). According to the MAH, this dose response was linear at bimekizumab doses up to 160mg, with ASAS40 responder rates at Week 12 ranging from 29.5% (bimekizumab 16mg) to 46.7% (bimekizumab 160mg), and 13.3% for PBO. However, from the clinical efficacy data presented in study AS0008 it appeared that the overall 64 mg Q4W response was already very comparable to the 160 mg Q4W response at week 12. In study AS0008, the outcome primary analysis of the primary endpoint was supported by the results of the secondary analyses and sensitivity analyses. In addition, the results of all 5 secondary endpoints were consistent and in favour of BKZ treatment thus supporting the primary endpoint findings.

The 160 mg Q4W and 320 mg Q4W responses were maintained and increased even further up to week 48. Unfortunately, no 48-week analysis was foreseen for the 64 mg Q4W dosing and in the subsequent phase 3 studies, only the 160 mg Q4W dose was further investigated. Further, in the phase 3 studies, the primary endpoint was analysed at week 16 instead of week 12. Nevertheless, the following proposed dose recommendation was considered acceptable by the CHMP: 160 mg (given as 1 subcutaneous injection) every 4 weeks.

Interim data up to week 104 from study **AS0009**, i.e. 3 year after start of therapy/PBO, suggested the BKZ treatment response was stable and remained high over time. Confirmation however was needed from long term phase 3 study data, this is further discussed below.

In phase III study **AS0010**, 254 patients were randomised. Study participant demographics and baseline characteristics were well balanced between treatment groups. Median time since first diagnosis of axSpa was less than 2 years. Only about 10% of patients had used biological anti TNF treatment in the past, and about 75% of patients were using NSAID at the start of the study.

The primary and key secondary efficacy endpoints were evaluated using a fixed-sequence testing procedure to account for multiplicity. Bimekizumab treatment resulted in statistically significant and

clinically meaningful differences over placebo for the primary endpoint (ASAS40 response at week 16, BKZ 47.7% vs PBO 21.4%) and in all week 16, key secondary endpoints of the predefined sequential testing sequence ($p<0.001$), demonstrating significant and clinically relevant effects on different components and symptoms of active non-radiographic axSpa. Secondary endpoints included assessments of BASDAI score, nocturnal spinal pain, ASQOL, SF-36 and enthesitis-free state.

Subgroup analysis showed that treatment response differences were observed according to age, gender and BMI. For the ASAS40 endpoint at week 16, treatment response was 60% in under 45 years and 24% in those 45 year and older; treatment response was 58% in males compared to 34% in females. In those patients presenting with a BMI of 30 or more, treatment response was only 28%.

Response to therapy (e.g ASAS40) was maintained up to week 52, with 78 of 128 patients (60.9%) who received 160mg Q4W having a positive outcome on ASAS40 assessment.

In phase III study **AS0011**, 332 patients were randomised. Demographics and baseline characteristics were well balanced between treatment groups except for a slight imbalance of study participants ≥45 years which had no significant effect on the clinical outcome of the study. Median time to diagnosis was 3.6 years, i.e. two years more than in study AS0010, which is considered logical because of the different patient population. In study AS0011, patients had to have radiographic evidence of disease in contrast to study AS0010 participants. 16% of patients had used prior anti-TNF therapy, and 80% was using NSAIDs at the start of the study.

The primary and key secondary efficacy endpoints were evaluated using a fixed-sequence testing procedure to account for multiplicity. Bimekizumab treatment resulted in statistically significant and clinically meaningful differences over placebo for the primary endpoint (ASAS40 response at week 16, BKZ 44.8% vs PBO 22.5%) and all 16-week key secondary endpoints included in the predefined sequential testing sequence, demonstrating significant and clinically relevant effects on different components and symptoms of active ankylosing spondylitis. Secondary endpoints included assessments of BASDAI score, nocturnal spinal pain, ASQOL, SF-36 and enthesitis-free state.

Subgroup analysis showed that treatment response differences were observed according to age and BMI, but not gender. For ASAS40 at week 16, treatment response was 49% in under 45 years and 29% in those 45 year and older; treatment response was 43% in males compared to 38% in females. In those patients presenting with a BMI of 30 or more, treatment response was only 26%.

Response to therapy (e.g. ASAS40) was maintained up to week 52 with 129 of 221 patients (58.4%) who received 160mg Q4W having a positive outcome on ASAS40 assessment.

Considering that in both study AS0010 and AS0011 large and potentially clinically relevant treatment effect differences were observed in subgroups based on age (younger than 45 years or 45 years and older) and based on BMI (BMI over 30 compared to BMI under 30), the MAH was requested to discuss whether these treatment effect differences should be highlighted in the SmPC as they can be considered of relevance to the prescriber. Overall, bimekizumab treatment showed a consistent trend towards greater clinical efficacy than placebo across subgroups in the full spectrum of axSpA; this is acknowledged. With regard to age, in pool EA1, the ASAS40 response at Week 16 was 54.5% vs 24.0%, respectively, for study participants <45 years old and 28.4% vs 17.1%, respectively, for study participants ≥45 years old (BKZ vs PBO). Although the treatment effect was more pronounced in the younger participants (<45 years old), there was no evidence of an interaction between age and treatment according to the MAH. In addition, pooled efficacy data at Week 52 (Pool EA2) indicate that in both age subgroup categories, the response rate improves substantially in the older study participants during the Maintenance Period up to 65.2% for participants <45 years old vs 47.4% for participants ≥45 years old. With regard to BMI, the MAH provided support for the use of bimekizumab 160mg every 4 weeks (Q4W) in higher-weight (≥120kg) patients in axial spondyloarthritis (axSpA). While it is acknowledged that

exposure is lower in higher-weight study participants, a dose of bimekizumab 160mg Q4W is at or near the plateau of the dose-response relationship, and weight-driven differences in exposure are not predicted to translate into clinically meaningful changes in the ASAS response rates. AxSpA clinical studies in the bimekizumab program showed that the observed ASAS40 response rate for higher-weight study participants (>100kg) approached that of the overall population. This is agreed. Update of SmPC was not considered warranted by the CHMP.

Receipt of rescue and/or prohibited medication was not identified as an intercurrent event and thus was implicitly handled using a treatment policy strategy. The MAH presented additional analyses of the primary endpoint in studies AS0010 and AS0011 in which receipt of rescue and/or prohibited medication was treated as a second intercurrent event to be handled using the same strategy as discontinuation of study treatment, i.e. using a composite strategy. This had no impact on the study conclusions.

Upon CHMP's request, the MAH provided results from the open-label extension trial, AS0014; these did not have an impact on the assessment of the clinical efficacy data.

2.4.4. Conclusions on the clinical efficacy

In the phase 3 studies AS0010 and AS0011, bimekizumab 160 mg Q4W resulted in a highly significant and clinically relevant ASAS40 response at week 16 (primary endpoint). In both trials, the primary endpoint result was corroborated by the outcomes of the secondary endpoints which included assessments of BASDAI score, nocturnal spinal pain, ASQOL, SF-36 and enthesitis-free state. Based on the clinical efficacy data provided, it can be concluded that bimekizumab has a beneficial effect on the symptoms and progression of non-radiographic axSpa and AS. The main analyses were done at 16 weeks of treatment, with evidence in phase 3 trials that efficacy is maintained up to week 52. The proposed dosing regimen of 160 mg (given as 1 subcutaneous injection) every 4 weeks was also supported by the CHMP.

2.5. Clinical safety

Introduction

For the currently approved plaque psoriasis indication, the most notable identified safety concern related to infections, the majority of which were upper respiratory and mucocutaneous candida and tinea infections. These were for the main part resolvable and did not impact on treatment compliance. The incidence rate of serious infections in bimekizumab-treated study participants was low. No particular patterns of serious infection were identified. Similar to other IL_17 inhibitors, clinically active important infections were included as a contraindication. Warnings were included in section 4.4 regarding use in patients with a chronic infection or a history of recurrent infection, IBD, hypersensitivity reactions, need for pre-treatment evaluation for TB and vaccinations. For the serious identified risk of serious infections and the serious potential risks of hypersensitivity, malignancies, IBD and MACE, an open-label, long-term study in adult study participants with moderate-to-severe chronic plaque PSO is ongoing (PS0014) to detect late developing ADRs, increased incidences to an already increased background rate of comorbidities and low-frequency adverse drug reactions. A bimekizumab real-world outcomes study is ongoing for long-term surveillance in larger and real-world patient populations with PSO.

The spondyloarthritis program included two pivotal phase 3 studies and one phase 3 open label extension study. Phase 2 studies were conducted in participants with AS and not in participants with nr-axSpA. Phase 3 studies included participants with nr-axSpA or AS to address the efficacy and safety profile in both subpopulations (AS0010 and AS0011, respectively, and their OLE AS0014).

Safety evaluation

The safety evaluation for bimekizumab mainly utilised 3 pools (see Table 62 below):

- Pool SA1 is the primary safety pool used to summarise the safety of bimekizumab vs placebo treatment in axSpA through Week 16 in Phase 3 studies AS0010 and AS0011.
- Pool SA2 provides the most comprehensive overview of safety in axSpA by including all Phase 2 and Phase 3 data from nr-axSpA and AS studies.
- Pool S3 provides an overview of safety across the BKZ development program.

Safety data from study participants with nr-axSpA or AS were combined for the purpose of the integrated pooled safety analyses. Combining the 2 subpopulations allowed to increase the sample size and was medically relevant by the MAH considering that nr-axSpA and AS belong to the same disease spectrum of axial spondyloarthritis. Selected summaries were also repeated by nr-axSpA and AS subpopulations.

Table 62: Overview of safety pools

Pool name	Studies included in pool	Treatment groups included in pool	Treatment periods included in pool	Purpose of pool
SA1	AS0010 AS0011	Participants exposed to: BKZ 160mg Q4W PBO	Initial Treatment Period (Weeks 0-16)	Primary study pool to summarize safety of BKZ compared to PBO through Week 16 in the combined nr-axSpA and AS population
SA2	AS0008 AS0009 AS0010 AS0011 AS0013 AS0014	Study participants exposed to: Phase 3 BKZ 160mg Q4W Phase 2/3 BKZ 160mg Q4W BKZ total[a]	Initial Treatment Period, Maintenance Treatment Period, OLE Treatment Period	Provide the most comprehensive overview of safety data on BKZ in the combined nr-axSpA and AS population
S3	AS0010 AS0011 PA0010 PA0011 PS0009 PS0013	Study participants exposed to: Rheumatology[b]: PBO BKZ 160mg Q4W Dermatology[c]: PBO BKZ 320mg Q4W Overall: PBO BKZ total	Initial Treatment Period (Weeks 0-16)	Summarize safety of BKZ compared to PBO through Week 16 across the BKZ development program for Phase 3 PBO-controlled studies in rheumatology (PsA and axSpA), and dermatology (PSO); this pooling is used to update the tabulated list of adverse reactions.

Patient exposure

T patient exposure to bimekizumab is estimated as approximately 588 patient-years cumulatively from 01 August 2021 to 31 January 2022.

As per PSUR (19 february2022) overall, 6875 study participants have received an investigational medicinal product during the bimekizumab development program since the Development International Birth Date (DIBD) up to the DLP. Out of this, a total of 5401 study participants were exposed to bimekizumab in ongoing unblinded, ongoing open-label and completed studies.

A total of 928 adult study participants with active axSpA have received bimekizumab during the axSpA development program.

Pool SA1 consisted of a total of 586 study participants; 349 participants (128 participants with nr-axSpA [AS0010] and 221 with AS [AS0011]) were exposed to bimekizumab and 237 participants (126 with nr-axSpA [AS0010] and 111 with AS [AS0011]) were exposed to placebo, with the total times at risk accounting for 108.6 participant-years in the bimekizumab 160mg Q4W group and 73.0 participant-years in the placebo group.

Pool SA2 consisted of a total of 928 study participants; 574 participants with nr-axSpA (244 participants) or AS (330 participants) from the Phase 3 program of which 351 participants had entered the OLE AS0014 at the cut-off date, and 354 participants with AS from the Phase 2 program (303 participants from AS0008 of which 255 had entered the OLE AS0009 at the cut-of date, and 51 participants from AS0013), with 588 study participants in the bimekizumab Total group exposed to bimekizumab for at least 12 months, and a total time at risk accounting for 1907.5 participant-years.

Phase 2 studies (AS0008, AS0009, and AS0013) were all conducted in study participants with active AS, while Phase 3 studies were conducted in participants with active AS (AS0011 and AS0014) and nr-axSpA (AS0010 and AS0014). The total study medication duration in Phase 3 was 284.3 and 441.4 participant-years for participants with nr-axSpA and AS, respectively, and the total time at risk was 292.6 and 454.3 participant-years for participants with nr-axSpA and AS, respectively.

Table 63: Study medication duration and participant-years of time at risk during the combined Initial, Maintenance, and OLE Treatment Period (Pool SA2)

	Phase 3 BKZ 160mg Q4W N=574	Phase 2/3 BKZ 160mg Q4W N=848	BKZ Total N=928
Study medication duration (days)			
n	574	848	928
Mean (SD)	461.8 (236.68)	717.0 (503.03)	727.2 (554.04)
Median	478.0	626.0	617.0
Min, Max	28, 894	17, 1770	5, 1800
Duration of exposure (months)			
>0	574 (100)	848 (100)	928 (100)
≥4	534 (93.0)	796 (93.9)	871 (93.9)
≥8	443 (77.2)	692 (81.6)	764 (82.3)
≥12	335 (58.4)	576 (67.9)	588 (63.4)
≥16	286 (49.8)	520 (61.3)	528 (56.9)
≥20	246 (42.9)	477 (56.3)	483 (52.0)
≥24	117 (20.4)	342 (40.3)	349 (37.6)
≥36	0	216 (25.5)	220 (23.7)
≥48	0	112 (13.2)	213 (23.0)
≥60	0	0	1 (0.1)

Subject Disposition

AS0010 (BE MOBILE 1)

A total of 254 study participants were randomised and started the Double-Blind Treatment Period as follows: 128 study participants in the bimekizumab 160mg Q4W group and 126 study participants in the placebo group.

The percentages of study participants who completed the Double-Blind Treatment Period were similar in the bimekizumab 160mg Q4W group (98.4%) and the placebo group (93.7%).

Table 64: Disposition and study discontinuation reasons – Double-Blind Treatment Period (RS)

Disposition	PBO N=126 n (%)	BKZ 160mg Q4W N=128 n (%)	All Study Participants N=254 n (%)
Started Double-Blind Treatment Period	126 (100)	128 (100)	254 (100)
Completed Double-Blind Treatment Period	118 (93.7)	126 (98.4)	244 (96.1)
Completed Double-Blind Treatment Period not on Randomized Treatment	0	0	0
Discontinued during Double-Blind Treatment Period	8 (6.3)	2 (1.6)	10 (3.9)
Primary reason for study discontinuation			
AE	3 (2.4)	1 (0.8)	4 (1.6)
Lack of efficacy	1 (0.8)	0	1 (0.4)
Protocol violation	0	0	0
Lost to follow-up	0	0	0
Withdrawal by study participant	4 (3.2)	0	4 (1.6)
Other	0	1 (0.8)	1 (0.4)

AS0011 (BE MOBILE 2)

A total of 332 study participants were randomized and started the Double-Blind Treatment Period as follows: 221 study participants in the bimekizumab 160mg Q4W group and 111 study participants in the placebo group.

The percentages of study participants who completed the Double-Blind Treatment Period were similar in the bimekizumab 160mg Q4W group (96.4%) and the placebo group (98.2%). The frequency of study discontinuation during the Double-Blind Treatment Period was low between the treatment groups (3.6% and 1.8% in the bimekizumab 160mg and the placebo groups, respectively).

Table 65: Disposition and study discontinuation reasons – Double-Blind Treatment Period (RS)

Disposition	PBO N=111 n (%)	BKZ 160mg Q4W N=221 n (%)	All Study Participants N=332 n (%)
Started Double-Blind Treatment Period	111 (100)	221 (100)	332 (100)
Completed Double-Blind Treatment Period	109 (98.2)	213 (96.4)	322 (97.0)
Completed Double-Blind Treatment Period not on randomized treatment	0	0	0
Discontinued during Double-Blind Treatment Period	2 (1.8)	8 (3.6)	10 (3.0)
Primary reason for study discontinuation			
AE	0	3 (1.4)	3 (0.9)
Lack of efficacy	0	1 (0.5)	1 (0.3)
Protocol violation	0	0	0
Lost to follow up	0	0	0
Withdrawal by study participant	1 (0.9)	3 (1.4)	4 (1.2)
Other	1 (0.9)	1 (0.5)	2 (0.6)

Pool SA1:

Table 66: Disposition and discontinuation reasons during the initial Treatment Period (Pool SA1)

Parameter	Placebo N=237 n (%)	BKZ 160mg Q4W N=349 n (%)	All study participants N=586 n (%)
Started Initial Period	237 (100)	349 (100)	586 (100)
Completed Initial Period	227 (95.8)	339 (97.1)	566 (96.6)
Discontinued Initial Period	10 (4.2)	10 (2.9)	20 (3.4)
Primary reason for study discontinuation			
Adverse event	3 (1.3)	4 (1.1)	7 (1.2)
Lack of efficacy	1 (0.4)	1 (0.3)	2 (0.3)
Protocol violation	0	0	0
Lost to follow-up	0	0	0
Consent withdrawn	5 (2.1)	3 (0.9)	8 (1.4)
Other	1 (0.4)	2 (0.6)	3 (0.5)

Pool SA2:

Table 67: Disposition and discontinuation reasons as of the clinical cut-off date (Pool SA2)

Disposition	Phase 3 BKZ 160mgQ4W N=574 n (%)	Phase 2/3 BKZ 160mgQ4W N=848 n (%)	BKZ Total N=928 n (%)
Treated with BKZ	574 (100)	848 (100)	928 (100)
Ongoing as of the clinical cut-off date	493 (85.9)	703 (82.9)	703 (75.8)
Completed as of the clinical cut-off date	16 (2.8)	19 (2.2)	72 (7.8)
Discontinued as of the clinical cut-off date	65 (11.3)	126 (14.9)	153 (16.5)
Primary reason for study discontinuation			
Adverse event	23 (4.0)	46 (5.4)	64 (6.9)
Lack of efficacy	8 (1.4)	12 (1.4)	12 (1.3)
Protocol violation	0	0	0
Lost to follow-up	3 (0.5)	8 (0.9)	11 (1.2)
Consent withdrawn	28 (4.9)	53 (6.3)	56 (6.0)
Other	3 (0.5)	7 (0.8)	10 (1.1)

Demographics

Demographic and Baseline characteristic variables are presented by treatment group for Pool SA1 and Pool SA2.

Pool SA1

The mean age of study participants was 39.5 years (range: 18 to 79 years), with most of the study participants (68.3%) in the age category <45 years of age. The proportion of participants aged 65 to <85 years of age was small (2.9%) and no participants were ≥85 years of age.

There were more male than female participants (64.5% vs 35.5%), which is in line with the higher prevalence of AS in men than in women.

Table 68: Demographics (Pool SA1)

Variable	Statistic	Placebo N=237	BKZ 160mg Q4W N=349	All study participants N=586
Age (years)	n	237	349	586
	Mean	38.8	40.0	39.5
	SD	12.1	11.8	11.9
	Median	38.0	39.0	39.0
	Min, Max	18, 75	19, 79	18, 79
Gender				
Male	n (%)	145 (61.2)	233 (66.8)	378 (64.5)
Female	n (%)	92 (38.8)	116 (33.2)	208 (35.5)

Variable	Statistic	Placebo N=237	BKZ 160mg Q4W N=349	All study participants N=586
Weight (kg)	n	237	349	586
	Mean	81.50	80.06	80.64
	SD	17.88	18.76	18.41
	Median	80.50	78.20	79.20
	Min	41.2	37.0	37.0
	Max	130.3	159.0	159.0
Height (cm)	n	237	349	586
	Mean	172.46	172.26	172.34
	SD	10.81	9.59	10.09
	Median	173.00	172.00	172.55
	Min	135.0	140.1	135.0
	Max	204.0	198.0	204.0
BMI (kg/m^2)	n	237	349	586
	Mean	27.38	26.91	27.10
	SD	5.65	5.85	5.77
	Median	26.33	26.18	26.27
	Min	17.3	15.2	15.2
	Max	45.7	56.0	56.0
Racial Group 2				
White	n (%)	200 (84.4)	286 (81.9)	486 (82.9)
Black	n (%)	2 (0.8)	2 (0.6)	4 (0.7)
Asian		33 (13.9)	52 (14.9)	85 (14.5)
Other	n (%)	2 (0.8)	9 (2.6)	11 (1.9)
Geographical Region				
Asia	n (%)	34 (14.3)	55 (15.8)	89 (15.2)
Eastern Europe	n (%)	126 (53.2)	181 (51.9)	307 (52.4)
North America	n (%)	12 (5.1)	15 (4.3)	27 (4.6)
Western Europe	n (%)	65 (27.4)	98 (28.1)	163 (27.8)

Variable	Statistic	Placebo N=237	BKZ 160mg Q4W N=349	All study participants N=586
Time since first diagnosis of axSpA (years)	Mean	4.56	5.60	5.18
	SD	6.21	7.72	7.16
	Median	1.95	2.22	2.12
Time since first symptoms of axSpA (years)	Mean	10.34	12.35	11.54
	SD	8.89	10.52	9.94
	Median	7.71	9.71	8.82
Age at first diagnosis of axSpA (years)	Mean	35.31	35.42	35.38
	SD	11.46	10.80	11.06
	Median	33.53	34.60	34.24
Age at first symptoms of axSpA (years)	Mean	29.54	28.67	29.02
	SD	8.53	8.40	8.46
	Median	28.58	28.00	28.00
HLA-B27				
Positive	n (%)	187 (78.9)	294 (84.2)	481 (82.1)
Negative	n (%)	50 (21.1)	55 (15.8)	105 (17.9)
Prior anti-TNF Therapy				
Yes	n (%)	34 (14.3)	47 (13.5)	81 (13.8)
No	n (%)	203 (85.7)	302 (86.5)	505 (86.2)
Baseline synthetic csDMARD[a]				
Yes	n (%)	51 (21.5)	77 (22.1)	128 (21.8)
No	n (%)	186 (78.5)	272 (77.9)	458 (78.2)
Baseline corticosteroid use[a,b]				
Yes	n (%)	22 (9.3)	22 (6.3)	44 (7.5)
No	n (%)	215 (90.7)	327 (93.7)	542 (92.5)
Baseline analgesic/opioid therapies[a]				
Yes	n (%)	37 (15.6)	50 (14.3)	87 (14.8)
No	n (%)	200 (84.4)	299 (85.7)	499 (85.2)

Table 69: Key concomitant medications of study participants in either treatment group (Pool SA1)

WHO-DD (Mar 2021) Anatomical Main Group (Level 1) Pharmacological subgroup (Level 3) Preferred Term (PT)	Placebo N=237 n (%)	BKZ 160mg Q4W N=349 n (%)
Any concomitant medication	223 (94.1)	332 (95.1)
Antineoplastic and immunomodulating agents	18 (7.6)	23 (6.6)
Immunosuppressants	18 (7.6)	23 (6.6)
Methotrexate	12 (5.1)	21 (6.0)
Musculo-skeletal system	189 (79.7)	291 (83.4)
Intestinal antiiflamatory agents	1 (0.4)	4 (1.1)
Sulfasalazine	0	3 (0.9)
Antiinflammatory and antirheumatic products, non-steroids	185 (78.1)	285 (81.7)
Meloxicam	29 (12.2)	51 (14.6)
Sulfasalazine	34 (14.3)	51 (14.6)
Etoricoxib	38 (16.0)	47 (13.5)
Celecoxib	18 (7.6)	33 (9.5)
Diclofenac sodium	20 (8.4)	32 (9.2)
Diclofenac	12 (5.1)	23 (6.6)
Naproxen	12 (5.1)	21 (6.0)
Ibuprofen	14 (5.9)	17 (4.9)
Aceclofenac	17 (7.2)	10 (2.9)

WHO-DD (Mar 2021) Anatomical Main Group (Level 1) Pharmacological subgroup (Level 3) Preferred Term (PT)	Placebo N=237 n (%)	BKZ 160mg Q4W N=349 n (%)
Nervous system	52 (21.9)	80 (22.9)
Other analgesic and antipyretics	22 (9.3)	28 (8.0)
Paracetamol	13 (5.5)	9 (2.6)
Systemic hormonal preparations, excl. sex hormones and insulins	36 (15.2)	37 (10.6)
Corticosteroids for systemic use, plain	25 (10.5)	26 (7.4)
Methylprednisolone	14 (5.9)	14 (4.0)

Pool SA2

Baseline characteristics were comparable between Pool SA1 and Pool SA2.

Table 70 from the integrated summary of safety demonstrates the characteristics of participants in studies included in SA2. The demographic and baseline characteristics with a differences >5% between the groups were:

- A higher proportion of Eastern European participants in Phase 2/3 bimekizumab 160mg Q4W group (64.0%) as compared to Phase 3 bimekizumab 160mg Q4W (52.4%) group.
- A higher proportion of Asian participants in Phase 3 studies than in Phase 2/3 studies (14.6% vs 9.9%) and a lower proportion of White participants in Phase 3 studies than in Phase 2/3 studies (82.9% vs 88.0%) due to the participation of Asian clinical study sites in Phase 3 studies.
- A higher proportion of women in Phase 3 than in Phase 2/3 studies (35.2% vs 28.5%) resulting from the nr-axSpA study AS0010 in Phase 3 (while all Phase 2 studies were in the AS population) and a higher prevalence of AS in men than in women and a balanced prevalence of nr-axSpA between men and women.

Table 70: Demographics and Baseline Characteristics Analysis Set: Pool SA2

Variable	Statistic	Phase 3 BKZ 160mg Q4W N=574	Phase 2/3 BKZ 160mg Q4W N=848	BKZ Total N=928
Age (years)	n	574	848	928
	Mean	39.6	40.3	40.5
	SD	11.9	11.9	12.0
	Median	39.0	39.0	39.0
	Min	18	18	18
	Max	79	79	79
Age (years) [a]				
18 to <65	n (%)	557 (97.0)	820 (96.7)	895 (96.4)
65 to <85	n (%)	17 (3.0)	28 (3.3)	33 (3.6)
>=85	n (%)	0	0	0
Age (years)				
<40	n (%)	303 (52.8)	431 (50.8)	472 (50.9)
40 to <65	n (%)	254 (44.3)	389 (45.9)	423 (45.6)
>=65	n (%)	17 (3.0)	28 (3.3)	33 (3.6)
Age (years)				
<45	n (%)	391 (68.1)	561 (66.2)	612 (65.9)
>=45	n (%)	183 (31.9)	287 (33.8)	316 (34.1)
Age (years) [b]				
<=18	n (%)	1 (0.2)	1 (0.1)	1 (0.1)
19 to <65	n (%)	556 (96.9)	819 (96.6)	894 (96.3)
>=65	n (%)	17 (3.0)	28 (3.3)	33 (3.6)
Age (years)				
<75	n (%)	569 (99.1)	842 (99.3)	922 (99.4)
>=75	n (%)	5 (0.9)	6 (0.7)	6 (0.6)
Gender				
Male	n (%)	372 (64.8)	606 (71.5)	672 (72.4)
Female	n (%)	202 (35.2)	242 (28.5)	256 (27.6)

Variable	Statistic	Phase 3 BKZ 160mg Q4W N=574	Phase 2/3 BKZ 160mg Q4W N=848	BKZ Total N=928
Weight (kg)	n	574	848	928
	Mean	80.67	80.68	80.63
	SD	18.50	17.87	17.72
	Median	79.20	79.15	79.15
	Min	37.0	37.0	37.0
	Max	159.0	159.0	159.0
Weight (kg)				
<=100	n (%)	490 (85.4)	732 (86.3)	803 (86.5)
>100	n (%)	84 (14.6)	116 (13.7)	125 (13.5)
Weight (kg)				
<70	n (%)	178 (31.0)	254 (30.0)	273 (29.4)
>=70 to <95	n (%)	260 (45.3)	407 (48.0)	456 (49.1)
>=95 to <115	n (%)	112 (19.5)	153 (18.0)	161 (17.3)
>=115	n (%)	24 (4.2)	34 (4.0)	38 (4.1)
Height (cm)	n	574	848	928
	Mean	172.41	172.67	172.68
	SD	10.03	9.71	9.67
	Median	173.00	173.00	173.00
	Min	135.0	135.0	135.0
	Max	204.0	204.0	204.0
BMI (kg/m2)	n	574	848	928
	Mean	27.09	27.01	27.00
	SD	5.81	5.53	5.51
	Median	26.24	26.26	26.24
	Min	15.2	15.2	15.2
	Max	56.0	56.0	56.0
BMI (kg/m2)				
<25	n (%)	237 (41.3)	340 (40.1)	372 (40.1)
>=25 to <30	n (%)	181 (31.5)	291 (34.3)	321 (34.6)
>=30	n (%)	156 (27.2)	217 (25.6)	235 (25.3)

BMI (kg/m2)				
<24	n (%)	197 (34.3)	274 (32.3)	300 (32.3)
>=24 to <28	n (%)	165 (28.7)	261 (30.8)	287 (30.9)
>=28	n (%)	212 (36.9)	313 (36.9)	341 (36.7)
Racial Group 1				
American Indian/Alaskan Native	n (%)	0	1 (0.1)	1 (0.1)
Asian	n (%)	84 (14.6)	84 (9.9)	84 (9.1)
Black	n (%)	3 (0.5)	3 (0.4)	3 (0.3)
Native Hawaiian or Other Pacific Islander	n (%)	0	0	0
White	n (%)	476 (82.9)	746 (88.0)	825 (88.9)
Other/Mixed	n (%)	5 (0.9)	8 (0.9)	9 (1.0)
Missing	n (%)	6 (1.0)	6 (0.7)	6 (0.6)

Variable	Statistic	Phase 3 BKZ 160mg Q4W N=574	Phase 2/3 BKZ 160mg Q4W N=848	BKZ Total N=928
Racial Group 2				
White	n (%)	476 (82.9)	746 (88.0)	825 (88.9)
Black	n (%)	3 (0.5)	3 (0.4)	3 (0.3)
Asian	n (%)	84 (14.6)	84 (9.9)	84 (9.1)
Other	n (%)	11 (1.9)	15 (1.8)	16 (1.7)
Ethnicity				
Hispanic or Latino	n (%)	7 (1.2)	9 (1.1)	9 (1.0)
Not Hispanic or Latino	n (%)	564 (98.3)	836 (98.6)	916 (98.7)
Missing	n (%)	3 (0.5)	3 (0.4)	3 (0.3)
Geographical Region				
Asia	n (%)	88 (15.3)	88 (10.4)	88 (9.5)
Eastern Europe	n (%)	301 (52.4)	543 (64.0)	610 (65.7)
North America	n (%)	25 (4.4)	37 (4.4)	40 (4.3)
Western Europe	n (%)	160 (27.9)	180 (21.2)	190 (20.5)
Time since first diagnosis of axSpA (years)	n	574	848	928
	Mean	5.26	6.05	6.22
	SD	7.21	7.75	7.81
	Median	2.20	2.72	2.86
	Min	0.1	0.0	0.0
	Max	41.0	41.0	41.0
Time since first diagnosis of axSpA (years)				
<2	n (%)	276 (48.1)	369 (43.5)	393 (42.3)
>=2	n (%)	298 (51.9)	479 (56.5)	535 (57.7)
Time since first symptoms of axSpA (years)	n	574	848	928
	Mean	11.58	12.42	12.67
	SD	9.96	9.93	10.05
	Median	8.86	10.24	10.34
	Min	0.4	0.2	0.2
	Max	59.1	59.1	59.1

Age at first diagnosis of axSpA (years)	n	574	848	928
	Mean	35.35	35.09	35.09
	SD	11.03	10.79	10.82
	Median	34.24	33.90	33.65
	Min	13.0	13.0	13.0
	Max	76.0	76.0	76.0
Age at first symptoms of axSpA (years)	n	574	848	928
	Mean	29.03	28.72	28.64
	SD	8.44	8.41	8.39
	Median	28.00	28.00	27.91
	Min	11.0	10.8	10.0
	Max	47.3	65.5	65.5
HLA-B27				
Positive	n (%)	471 (82.1)	717 (84.6)	788 (84.9)
Negative	n (%)	103 (17.9)	125 (14.7)	134 (14.4)
Missing	n (%)	0	6 (0.7)	6 (0.6)

Variable	Statistic	Phase 3 BKZ 160mg Q4W N=574	Phase 2/3 BKZ 160mg Q4W N=848	BKZ Total N=928
Prior anti-TNF Therapy				
Yes	n (%)	79 (13.8)	108 (12.7)	113 (12.2)
No	n (%)	495 (86.2)	740 (87.3)	815 (87.8)
Prior biologic therapy other than anti-TNF				
Yes	n (%)	21 (3.7)	21 (2.5)	21 (2.3)
No	n (%)	553 (96.3)	827 (97.5)	907 (97.7)
Baseline NSAID therapies [c]				
Yes	n (%)	446 (77.7)	689 (81.3)	742 (80.0)
No	n (%)	128 (22.3)	159 (18.8)	186 (20.0)
Baseline NSAID therapies [c]				
0	n (%)	128 (22.3)	159 (18.8)	186 (20.0)
1	n (%)	435 (75.8)	675 (79.6)	727 (78.3)
2	n (%)	11 (1.9)	14 (1.7)	15 (1.6)
>=3	n (%)	0	0	0
Baseline synthetic DMARD [c]				
Yes	n (%)	127 (22.1)	198 (23.3)	209 (22.5)
No	n (%)	447 (77.9)	650 (76.7)	719 (77.5)
Baseline synthetic DMARD type [c]				
Methotrexate	n (%)	32 (5.6)	51 (6.0)	56 (6.0)
Sulfasalazine	n (%)	86 (15.0)	131 (15.4)	137 (14.8)
Hydroxychloroquine	n (%)	2 (0.3)	3 (0.4)	3 (0.3)
Apremilast	n (%)	0	0	0
Leflunomide	n (%)	2 (0.3)	2 (0.2)	2 (0.2)
More than one	n (%)	5 (0.9)	11 (1.3)	11 (1.2)
Baseline corticosteroid use [c]				
Yes	n (%)	44 (7.7)	70 (8.3)	71 (7.7)
No	n (%)	530 (92.3)	778 (91.7)	857 (92.3)
Baseline analgesic/opioid therapies [c]				
Yes	n (%)	85 (14.8)	98 (11.6)	107 (11.5)
No	n (%)	489 (85.2)	750 (88.4)	821 (88.5)

Adverse events

Pool SA1

Pool SA1 is the primary safety pool used to summarise the safety of bimekizumab compared with placebo through Week 16 of the Double-Blind Treatment Period in Phase 3 studies AS0010 and AS0011.

TEAEs were reported at a higher incidence in the bimekizumab 160mg Q4W group compared with the placebo group (57.3% vs 50.2%). The incidence of serious TEAEs was low overall and similar in the bimekizumab 160mg Q4W group (1.1%) compared with the placebo group (0.8%).

The incidence of study discontinuations due to TEAEs was low overall and similar in the bimekizumab 160mg Q4W group (2.3%) compared with the placebo group (2.1%).

Drug-related TEAEs (as assessed by the Investigator) were reported at a higher incidence in the bimekizumab 160mg Q4W group compared with the placebo group (27.8% vs 15.6%).

There were no deaths reported in Pool SA1.

Table 71: Overview of TEAEs during the Initial Treatment Period (Pool SA1)

	Placebo N=237 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=349 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)
Any TEAEs	119 (50.2) [268] 237.5 (196.8, 284.2)	200 (57.3) [510] 304.2 (263.5, 349.4)
Serious TEAEs	2 (0.8) [3] 2.8 (0.3, 9.9)	4 (1.1) [4] 3.7 (1.0, 9.5)
Study participant discontinuations due to TEAEs	5 (2.1) [5] 6.9 (2.2, 16.1)	8 (2.3) [8] 7.4 (3.2, 14.6)
Permanent withdrawal of study medication due to TEAEs	5 (2.1) [5] 6.9 (2.2, 16.1)	9 (2.6) [9] 8.4 (3.8, 15.9)
Drug-related TEAEs	37 (15.6) [81] 56.5 (39.8, 77.9)	97 (27.8) [214] 109.5 (88.8, 133.6)
Severe TEAEs	1 (0.4) [1] 1.4 (0.0, 7.6)	3 (0.9) [4] 2.8 (0.6, 8.1)
All deaths (AEs leading to death)	0 -	0 -
Deaths (TEAEs leading to death)	0 -	0 -

AE=adverse event; BKZ=bimekizumab; CI=confidence interval; EAIR=exposure-adjusted incidence rate; ISS=Integrated Summary of Safety; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event; yrs=years
Note: n=number of study participants reporting at least 1 TEAE in that category.
Note: [#] is the number of individual occurrences of the TEAE in that category.
Note: EAIR=incidence of new cases per 100 participant-years and associated 95% CI.

Pool SA2

Pool SA2 provided the most comprehensive overview of safety in axSpA by including all Phase 2 and Phase 3 data from nr-axSpA and AS studies. This included TEAEs during the combined Initial, Maintenance, and OLE Treatment Periods.

In Pool SA2, the majority of study participants in the bimekizumab Total group (85.6%; EAIR:

155.6/100 participant-years) reported a TEAE.

Almost half of study participants (45.4%; EAIR: 33.7/100 participant-years) had TEAEs that were considered drug-related.

At the time of the safety update (52-week data) there was one further death reported meaning that there were 3 deaths, in total reported in Pool SA2; all occurred in the Phase 2 program.

Table 72: Overview of TEAEs during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SA2)

Parameter	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any TEAEs	465 (81.0) [2100] 166.8 (152.0, 182.7)	720 (84.9) [3528] 142.4 (132.1, 153.1)	794 (85.6) [4168] 155.6 (145.0, 166.8)	495 (86.2) [2750] 155.7 (142.2, 170.0)	752 (88.7) [4287] 136.9 (127.3, 147.0)	826 (89.0) [4927] 149.7 (139.7, 160.3)
Serious TEAEs	39 (6.8) [42] 5.4 (3.9, 7.4)	88 (10.4) [104] 5.5 (4.4, 6.8)	100 (10.8) [125] 5.6 (4.6, 6.8)	47 (8.2) [52] 4.9 (3.6, 6.5)	97 (11.4) [117] 5.1 (4.1, 6.2)	109 (11.7) [138] 5.2 (4.3, 6.3)
Study participant discontinuations due to TEAEs	23 (4.0) [23] 3.1 (2.0, 4.7)	47 (5.5) [50] 2.8 (2.0, 3.7)	64 (6.9) [69] 3.4 (2.6, 4.3)	26 (4.5) [26] 2.6 (1.7, 3.8)	54 (6.4) [57] 2.7 (2.0, 3.5)	71 (7.7) [76] 3.2 (2.5, 4.0)
Permanent withdrawal of study medication due to TEAEs	27 (4.7) [27] 3.7 (2.4, 5.3)	52 (6.1) [58] 3.1 (2.3, 4.0)	69 (7.4) [77] 3.7 (2.8, 4.6)	30 (5.2) [30] 3.0 (2.0, 4.3)	59 (7.0) [65] 2.9 (2.2, 3.8)	76 (8.2) [84] 3.4 (2.7, 4.3)
Drug-related TEAEs	239 (41.6) [702] 43.8 (38.5, 49.8)	365 (43.0) [1039] 31.1 (28.0, 34.5)	421 (45.4) [1235] 33.7 (30.5, 37.0)	265 (46.2) [906] 38.4 (33.9, 43.3)	393 (46.3) [1253] 28.9 (26.1, 31.9)	450 (48.5) [1449] 31.4 (28.6, 34.4)
Severe TEAEs	29 (5.1) [35] 4.0 (2.7, 5.7)	59 (7.0) [76] 3.6 (2.7, 4.6)	66 (7.1) [88] 3.6 (2.8, 4.6)	34 (5.9) [44] 3.5 (2.4, 4.9)	66 (7.8) [91] 3.4 (2.6, 4.3)	73 (7.9) [103] 3.4 (2.7, 4.3)
All deaths (AEs leading to death)[c]	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Deaths (TEAEs leading to death)	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)

Parameter	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)

Serious adverse event/deaths/other significant events

Deaths

At the time of the safety update, a total of 3 bimekizumab-treated study participants experienced a TEAE with fatal outcome in the bimekizumab development program for axSpA. Both deaths occurred in the phase 2 studies AS0008 and AS0009 and were not considered related to the IMP.

In the updated safety data, there was one further death reported in study AS009. This event was assessed as unrelated to bimekizumab.

Serious SAEs

Pool SA1

In Pool SA1, incidences of serious TEAEs were low and similar in the bimekizumab 160mg Q4W group (1.1%) and in the placebo group (0.8%) during the Initial Treatment Period. By PT, all serious TEAEs by PT were reported by 1 study participant in any treatment group.

Table 73: Incidence of serious TEAEs per 100 participant-years by SOC and PT during the Initial Treatment Period (Pool SA1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=237 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=349 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)
Any Serious TEAE	2 (0.8) [3] 2.8 (0.3, 9.9)	4 (1.1) [4] 3.7 (1.0, 9.5)
Endocrine disorders	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Goitre	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Gastrointestinal disorders	1 (0.4) [1] 1.4 (0.0, 7.6)	2 (0.6) [2] 1.8 (0.2, 6.7)
Colitis ulcerative	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Crohn's disease	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Abdominal adhesions	1 (0.4) [1] 1.4 (0.0, 7.6)	0
Infections and infestations	1 (0.4) [1] 1.4 (0.0, 7.6)	1 (0.3) [1] 0.9 (0.0, 5.1)
Hepatitis A	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Viral infection	1 (0.4) [1] 1.4 (0.0, 7.6)	0
Psychiatric disorders	1 (0.4) [1] 1.4 (0.0, 7.6)	0
Depression	1 (0.4) [1] 1.4 (0.0, 7.6)	0

Pool SA2

During the combined Initial, Maintenance, and OLE Treatment Period, the incidence of serious TEAEs was 10.8% (EAIR=5.6/100 participant-years [95% CI: 4.6, 6.8]) of study participants in the bimekizumab Total group. Serious TEAEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (3.0%), Injury, poisoning and procedural complications (1.5%), Gastrointestinal disorders (1.4%).

Treatment-emergent serious TEAEs reported in at least 3 study participants by PT in Pool SA2 during the combined Initial, Maintenance, and OLE Treatment Period are presented below.

Table 74: Incidence of serious TEAEs per 100 participant-years in >3 study participants by PT in BKZ Total group during the Combined Initial, Maintenance, and OLE Treatment Period analysis set (Pool SA2)

	Data in original submission[a]			Data in Safety Update[b]		
MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any Serious TEAE	39 (6.8) [42] 5.4 (3.9, 7.4)	88 (10.4) [104] 5.5 (4.4, 6.8)	100 (10.8) [125] 5.6 (4.6, 6.8)	47 (8.2) [52] 4.9 (3.6, 6.5)	97 (11.4) [117] 5.1 (4.1, 6.2)	109 (11.7) [138] 5.2 (4.3, 6.3)
Gastrointestinal disorders	5 (0.9) [6] 0.7 (0.2, 1.6)	10 (1.2) [11] 0.6 (0.3, 1.1)	13 (1.4) [15] 0.7 (0.4, 1.2)	4 (0.7) [5] 0.4 (0.1, 1.0)	9 (1.1) [10] 0.4 (0.2, 0.8)	12 (1.3) [14] 0.5 (0.3, 0.9)
Colitis ulcerative	1 (0.2) [1] 0.1 (0.0, 0.7)	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	1 (0.2) [1] 0.1 (0.0, 0.6)	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Crohn's disease	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.2 (0.0, 0.5)	1 (0.2) [1] 0.1 (0.0, 0.6)	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Hepatobiliary disorders	1 (0.2) [1] 0.1 (0.0, 0.7)	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	3 (0.5) [3] 0.3 (0.1, 0.9)	5 (0.6) [5] 0.2 (0.1, 0.6)	5 (0.5) [5] 0.2 (0.1, 0.5)
Cholelithiasis	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.3) [2] 0.2 (0.0, 0.7)	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Infections and infestations	11 (1.9) [12] 1.5 (0.7, 2.7)	26 (3.1) [30] 1.6 (1.0, 2.3)	28 (3.0) [34] 1.5 (1.0, 2.2)	13 (2.3) [13] 1.3 (0.7, 2.2)	29 (3.4) [32] 1.5 (1.0, 2.1)	31 (3.3) [36] 1.4 (1.0, 2.0)
Appendicitis	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.5) [3] 0.3 (0.1, 0.9)	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Pneumonia	0	3 (0.4) [3] 0.2 (0.0, 0.5)	4 (0.4) [5] 0.2 (0.1, 0.5)	0	3 (0.4) [3] 0.1 (0.0, 0.4)	4 (0.4) [5] 0.2 (0.0, 0.5)
Erysipelas	2 (0.3) [2] 0.3 (0.0, 1.0)	3 (0.4) [4] 0.2 (0.0, 0.5)	3 (0.3) [4] 0.2 (0.0, 0.5)	2 (0.3) [2] 0.2 (0.0, 0.7)	3 (0.4) [4] 0.1 (0.0, 0.4)	3 (0.3) [4] 0.1 (0.0, 0.4)
Corona virus infection	0	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	0	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Musculoskeletal and connective tissue disorders	2 (0.3) [2] 0.3 (0.0, 1.0)	7 (0.8) [8] 0.4 (0.2, 0.9)	8 (0.9) [9] 0.4 (0.2, 0.8)	5 (0.9) [5] 0.5 (0.2, 1.2)	10 (1.2) [12] 0.5 (0.2, 0.9)	11 (1.2) [13] 0.5 (0.2, 0.9)
Bursitis	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.3) [2] 0.2 (0.0, 0.7)	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Osteoarthritis	1 (0.2) [1] 0.1 (0.0, 0.7)	3 (0.4) [3] 0.2 (0.0, 0.5)	4 (0.4) [4] 0.2 (0.1, 0.5)	2 (0.3) [2] 0.2 (0.0, 0.7)	4 (0.5) [4] 0.2 (0.1, 0.5)	5 (0.5) [5] 0.2 (0.1, 0.5)
Nervous system disorders	4 (0.7) [4] 0.5 (0.1, 1.4)	6 (0.7) [6] 0.4 (0.1, 0.8)	7 (0.8) [7] 0.4 (0.1, 0.8)	7 (1.2) [7] 0.7 (0.3, 1.5)	9 (1.1) [9] 0.4 (0.2, 0.8)	10 (1.1) [10] 0.4 (0.2, 0.8)
Syncope	3 (0.5) [3] 0.4 (0.1, 1.2)	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	4 (0.7) [4] 0.4 (0.1, 1.0)	4 (0.5) [4] 0.2 (0.1, 0.5)	4 (0.4) [4] 0.2 (0.0, 0.5)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	 Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	 BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	 Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	 BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)

Severe TEAEs

Pool SA1

In Pool SA1, during the Initial Treatment Period, the majority of TEAEs were mild or moderate in intensity in both treatment groups. The incidence of severe TEAEs was low overall and similar between the bimekizumab 160mg Q4W group (0.9%) and placebo group (0.4%) group. No severe TEAEs, by PT, were reported by >1 study participant. None of the severe TEAEs led to discontinuation.

Table 75: Incidence of Severe TEAEs per 100 subject-years during the Initial Treatment Period Analysis Set: Pool SA1

MedDRA v19.0 System Organ Class High Level Term Preferred Term	Placebo N=237 100 subject-yrs=0.73 n (%) [#] Incidence (95% CI) Event Rate	BKZ 160mg Q4W N=349 100 subject-yrs=1.09 n (%) [#] Incidence (95% CI) Event Rate
Any Severe TEAE	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	3 (0.9) [4] 2.8 (0.6, 8.1) 3.7
Gastrointestinal disorders	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	2 (0.6) [2] 1.8 (0.2, 6.7) 1.8
Colitis (excl infective)	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Colitis ulcerative	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Dental pain and sensation disorders	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Toothache	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Peritoneal and retroperitoneal fibrosis and adhesions	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	0
Abdominal adhesions	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	0

MedDRA v19.0 System Organ Class High Level Term Preferred Term	Placebo N=237 100 subject-yrs=0.73 n (%) [#] Incidence (95% CI) Event Rate	BKZ 160mg Q4W N=349 100 subject-yrs=1.09 n (%) [#] Incidence (95% CI) Event Rate
Investigations	0	1 (0.3) [2] 0.9 (0.0, 5.1) 1.8
Liver function analyses	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Aspartate aminotransferase increased	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Skeletal and cardiac muscle analyses	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Blood creatine phosphokinase increased	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9

Pool SA2

In Pool SA2, the incidence of severe TEAEs was low overall. A total of 7.1% of study participants in the bimekizumab Total group reported severe TEAEs during the combined Initial, Maintenance, and OLE Treatment Period. Severe TEAEs in the bimekizumab Total group were most frequently reported in the SOC of Infections and infestations (1.6%). Most severe TEAE were isolated cases. A total of 11 severe TEAEs were reported more than once in the bimekizumab Total group. These TEAEs include colitis ulcerative, toothache, diarrhoea, cholelithiasis, erysipelas, meniscus injury, humerus fracture, syncope,

and suicidal ideation, each accounting for 0.2% of the study participants, and osteoarthritis accounting for 0.3% of the study participants.

When adjusting for exposure for severe TEAEs in the Phase 3 bimekizumab group in Pool SA2 (EAIR: 4.0/100 participant-years [95% CI: 2.7, 5.7]), there was a small numerical increase (with overlapping CI) in incidence rate with longer exposure compared to Pool SA1 (EAIR: 2.8/100 participant-years [95% CI: 0.6, 8.1]).

At the time of the safety update, when adjusting for exposure, the EAIRs of severe TEAEs in the bimekizumab Total group were slightly lower (3.4/100 participant-years) compared with the original submission (3.6/100 participant-years).

For Pool SA2, severe TEAEs in ≥1 study participant by PT in the Phase 3 bimekizumab treatment group during the combined Initial, Maintenance, and OLE Treatment Periods are provided in the following Table 76.

Table 76: Incidence of severe TEAEs per 100 participant-years in ≥1 study participant by PT in the Phase 3 bimekizumab treatment group during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SA2)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Any severe TEAE	29 (5.1) [35] 4.0 (2.7, 5.7)	59 (7.0) [76] 3.6 (2.7, 4.6)	66 (7.1) [88] 3.6 (2.8, 4.6)
Cardiac disorders	0	3 (0.4) [4] 0.2 (0.0, 0.5)	3 (0.3) [4] 0.2 (0.0, 0.5)
Gastrointestinal disorders	4 (0.7) [4] 0.5 (0.1, 1.4)	6 (0.7) [7] 0.4 (0.1, 0.8)	7 (0.8) [8] 0.4 (0.1, 0.8)
Colitis ulcerative	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Toothache	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Diarrhoea	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Hepatobiliary disorders	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Cholelithiasis	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Infections and infestations	9 (1.6) [9] 1.2 (0.6, 2.3)	13 (1.5) [13] 0.8 (0.4, 1.3)	15 (1.6) [16] 0.8 (0.4, 1.3)
Erysipelas	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Injury, poisoning and procedural complications	3 (0.5) [3] 0.4 (0.1, 1.2)	9 (1.1) [9] 0.5 (0.2, 1.0)	10 (1.1) [13] 0.5 (0.3, 1.0)
Meniscus injury	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Humerus fracture	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Tendon injury	0	0	1 (0.1) [2] 0.1 (0.0, 0.3)
Musculoskeletal and connective tissue disorders	4 (0.7) [4] 0.5 (0.1, 1.4)	7 (0.8) [7] 0.4 (0.2, 0.9)	8 (0.9) [8] 0.4 (0.2, 0.8)
Osteoarthritis	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.2 (0.0, 0.5)
Nervous system disorders	7 (1.2) [7] 0.9 (0.4, 1.9)	8 (0.9) [8] 0.5 (0.2, 0.9)	8 (0.9) [8] 0.4 (0.2, 0.8)
Syncope	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Migraine	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Bipolar disorder	0	1 (0.1) [3] 0.1 (0.0, 0.3)	1 (0.1) [3] 0.1 (0.0, 0.3)
Suicidal ideation	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Vascular disorders	0	2 (0.2) [4] 0.1 (0.0, 0.4)	2 (0.2) [4] 0.1 (0.0, 0.4)
Subclavian steal syndrome	0	1 (0.1) [2] 0.1 (0.0, 0.3)	1 (0.1) [2] 0.1 (0.0, 0.3)

Trends in the types of SAEs reported were GI disorders, infections, musculoskeletal disorders and injury, poisoning or procedural complications.

Common AEs

Common TEAEs are defined as those TEAEs occurring in ≥2% of study participants in any treatment group for the pool being summarised.

Pool SA1

Treatment-emergent AEs were most frequently reported in the SOCs of Infections and infestations for both the bimekizumab 160mg Q4W and the placebo groups (30.4% and 23.6%, respectively). The incidences of nasopharyngitis were higher in the bimekizumab 160mg Q4W group compared with the placebo group (8.3% vs 4.2%, respectively). Rates of oral candidiasis were higher in the bimekizumab group (3.7% vs 0 participant). The incidences of uveitis and upper respiratory tract infection were lower in the bimekizumab 160mg Q4W group compared with the placebo group (0.6% vs 3.4%).

Table 77: Incidence of TEAEs per 100 participant-years in >2% of participants by PT in any treatment group during the Initial Treatment Period (Pool SA1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=237 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=349 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)
Any TEAE at or above 2% threshold	44 (18.6) [64]	92 (26.4) [132]
Gastrointestinal disorders	27 (11.4) [33] 39.4 (26.0, 57.4)	42 (12.0) [56] 42.0 (30.3, 56.8)
Diarrhoea	3 (1.3) [3] 4.1 (0.9, 12.1)	10 (2.9) [11] 9.4 (4.5, 17.3)
General disorders and administration site conditions	10 (4.2) [15] 14.1 (6.8, 26.0)	22 (6.3) [36] 21.3 (13.4, 32.3)
Injection site pain	3 (1.3) [4] 4.1 (0.9, 12.1)	8 (2.3) [14] 7.5 (3.2, 14.8)
Infections and infestations	56 (23.6) [78] 89.1 (67.3, 115.7)	106 (30.4) [163] 119.4 (97.7, 144.4)
Oral candidiasis	0	13 (3.7) [15] 12.2 (6.5, 20.8)
Nasopharyngitis	10 (4.2) [10] 14.0 (6.7, 25.8)	29 (8.3) [33] 28.1 (18.8, 40.3)
Upper respiratory tract infection	16 (6.8) [19] 22.9 (13.1, 37.1)	15 (4.3) [15] 14.2 (7.9, 23.4)
Pharyngitis	1 (0.4) [1] 1.4 (0.0, 7.7)	9 (2.6) [11] 8.4 (3.8, 15.9)
Rhinitis	6 (2.5) [6] 8.3 (3.1, 18.1)	4 (1.1) [5] 3.7 (1.0, 9.5)
Nervous system disorders	10 (4.2) [13] 14.2 (6.8, 26.1)	27 (7.7) [36] 26.4 (17.4, 38.3)
Headache	7 (3.0) [10] 9.8 (3.9, 20.2)	12 (3.4) [15] 11.4 (5.9, 19.9)
Skin and subcutaneous tissue disorders	13 (5.5) [18] 18.3 (9.7, 31.2)	34 (9.7) [42] 33.0 (22.9, 46.2)
Rash	1 (0.4) [1] 1.4 (0.0, 7.6)	8 (2.3) [10] 7.4 (3.2, 14.7)
Eye disorders	15 (6.3) [20] 21.2 (11.8, 34.9)	8 (2.3) [9] 7.5 (3.2, 14.7)
Uveitis	8 (3.4) [10] 11.1 (4.8, 22.0)	2 (0.6) [3] 1.8 (0.2, 6.7)

Pool SA2

Treatment-emergent AEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (67.1%), Gastrointestinal disorders (28.4 %), Skin and subcutaneous tissue disorders (25.9%), and Respiratory, thoracic and mediastinal disorders (11.7%). The most frequently reported TEAEs by PT were nasopharyngitis (18%), upper respiratory tract infection (14.3%), oral candidiasis (11.4%), and corona virus infection (8.7%).

The axSpA studies were conducted during the COVID-19 pandemic and more corona virus infections were reported in SA2, which covers a longer period and larger participant pool during the pandemic (7.0/100 participant-years in the Phase 3 bimekizumab group in Pool SA2 vs 1.9/100 participant-years in the bimekizumab 160mg Q4W group in Pool SA1.

Table 78: Incidence of TEAEs per 100 participant-years in at least 2% of participants by PT in any treatment group during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SA2)

	Data in original submission[a]			Data in Safety Update[b]		
MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any TEAE	465 (81.0) [2100] 166.8 (152.0, 182.7)	720 (84.9) [3528] 142.4 (132.1, 153.1)	794 (85.6) [4168] 155.6 (145.0, 166.8)	495 (86.2) [2750] 155.7 (142.2, 170.0)	752 (88.7) [4287] 136.9 (127.3, 147.0)	826 (89.0) [4927] 149.7 (139.7, 160.3)
Gastrointestinal disorders	122 (21.3) [199] 19.0 (15.7, 22.6)	203 (23.9) [325] 14.4 (12.4, 16.5)	231 (24.9) [377] 14.8 (13.0, 16.9)	148 (25.8) [247] 17.6 (14.9, 20.7)	236 (27.8) [385] 14.2 (12.4, 16.1)	264 (28.4) [437] 14.6 (12.9, 16.5)
Diarrhoea	29 (5.1) [35] 4.0 (2.7, 5.8)	40 (4.7) [49] 2.4 (1.7, 3.3)	43 (4.6) [52] 2.3 (1.7, 3.1)	36 (6.3) [42] 3.7 (2.6, 5.2)	48 (5.7) [57] 2.4 (1.8, 3.2)	51 (5.5) [60] 2.4 (1.8, 3.1)
Dyspepsia	10 (1.7) [10] 1.4 (0.7, 2.5)	19 (2.2) [19] 1.1 (0.7, 1.8)	19 (2.0) [19] 1.0 (0.6, 1.6)	12 (2.1) [12] 1.2 (0.6, 2.1)	21 (2.5) [21] 1.1 (0.7, 1.6)	21 (2.3) [21] 1.0 (0.6, 1.5)
Abdominal pain	14 (2.4) [14] 1.9 (1.0, 3.2)	16 (1.9) [16] 0.9 (0.5, 1.5)	18 (1.9) [18] 1.0 (0.6, 1.5)	18 (3.1) [19] 1.8 (1.1, 2.9)	20 (2.4) [21] 1.0 (0.6, 1.5)	22 (2.4) [23] 1.0 (0.6, 1.5)
Abdominal pain upper	10 (1.7) [10] 1.3 (0.6, 2.5)	14 (1.7) [14] 0.8 (0.5, 1.4)	15 (1.6) [15] 0.8 (0.4, 1.3)	14 (2.4) [15] 1.4 (0.8, 2.4)	18 (2.1) [19] 0.9 (0.5, 1.4)	19 (2.0) [20] 0.9 (0.5, 1.3)
Gastrooesophageal reflux disease	11 (1.9) [11] 1.5 (0.7, 2.7)	15 (1.8) [16] 0.9 (0.5, 1.5)	15 (1.6) [16] 0.8 (0.4, 1.3)	14 (2.4) [14] 1.4 (0.8, 2.4)	19 (2.2) [20] 0.9 (0.6, 1.5)	19 (2.0) [20] 0.9 (0.5, 1.3)
Nausea	13 (2.3) [14] 1.8 (0.9, 3.0)	16 (1.9) [17] 1.0 (0.5, 1.5)	18 (1.9) [20] 1.0 (0.6, 1.5)	17 (3.0) [18] 1.7 (1.0, 2.8)	20 (2.4) [21] 1.0 (0.6, 1.5)	22 (2.4) [24] 1.0 (0.6, 1.5)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
General disorders and administration site conditions	58 (10.1) [101] 8.3 (6.3, 10.7)	72 (8.5) [116] 4.5 (3.5, 5.6)	89 (9.6) [140] 5.0 (4.0, 6.2)	70 (12.2) [123] 7.6 (5.9, 9.6)	86 (10.1) [142] 4.5 (3.6, 5.5)	103 (11.1) [166] 5.0 (4.1, 6.0)
Fatigue	14 (2.4) [18] 1.9 (1.0, 3.2)	18 (2.1) [22] 1.1 (0.6, 1.7)	21 (2.3) [25] 1.1 (0.7, 1.7)	15 (2.6) [19] 1.5 (0.9, 2.5)	20 (2.4) [24] 1.0 (0.6, 1.5)	23 (2.5) [27] 1.0 (0.7, 1.6)
Injection site pain	13 (2.3) [28] 1.8 (0.9, 3.0)	13 (1.5) [28] 0.8 (0.4, 1.3)	14 (1.5) [29] 0.7 (0.4, 1.2)	13 (2.3) [32] 1.3 (0.7, 2.2)	13 (1.5) [32] 0.6 (0.3, 1.1)	14 (1.5) [33] 0.6 (0.3, 1.1)
Hepatobiliary disorders	13 (2.3) [18] 1.8 (0.9, 3.0)	31 (3.7) [42] 1.9 (1.3, 2.7)	36 (3.9) [48] 2.0 (1.4, 2.7)	22 (3.8) [30] 2.3 (1.4, 3.4)	41 (4.8) [55] 2.1 (1.5, 2.8)	46 (5.0) [61] 2.1 (1.6, 2.8)
Hepatic steatosis	7 (1.2) [7] 0.9 (0.4, 2.0)	14 (1.7) [14] 0.8 (0.5, 1.4)	15 (1.6) [15] 0.8 (0.4, 1.3)	9 (1.6) [11] 0.9 (0.4, 1.7)	18 (2.1) [20] 0.9 (0.5, 1.4)	19 (2.0) [21] 0.9 (0.5, 1.3)
Infections and infestations	312 (54.4) [693] 68.3 (61.0, 76.4)	493 (58.1) [1246] 53.7 (49.0, 58.6)	563 (60.7) [1476] 58.6 (53.9, 63.7)	369 (64.3) [933] 66.1 (59.5, 73.2)	558 (65.8) [1535] 53.4 (49.1, 58.1)	623 (67.1) [1765] 57.6 (53.1, 62.3)
Gastroenteritis	13 (2.3) [15] 1.8 (0.9, 3.0)	20 (2.4) [23] 1.2 (0.7, 1.8)	23 (2.5) [26] 1.2 (0.8, 1.8)	16 (2.8) [19] 1.6 (0.9, 2.6)	23 (2.7) [27] 1.1 (0.7, 1.7)	26 (2.8) [30] 1.2 (0.8, 1.7)
Conjunctivitis	13 (2.3) [15] 1.8 (0.9, 3.0)	27 (3.2) [32] 1.6 (1.1, 2.4)	33 (3.6) [40] 1.8 (1.2, 2.5)	19 (3.3) [22] 1.9 (1.2, 3.0)	33 (3.9) [39] 1.7 (1.1, 2.3)	39 (4.2) [47] 1.8 (1.3, 2.5)
Oral fungal infection	9 (1.6) [10] 1.2 (0.6, 2.3)	25 (2.9) [42] 1.5 (1.0, 2.2)	30 (3.2) [53] 1.6 (1.1, 2.3)	11 (1.9) [13] 1.1 (0.6, 2.0)	28 (3.3) [47] 1.4 (0.9, 2.1)	33 (3.6) [58] 1.5 (1.1, 2.1)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Fungal skin infection	13 (2.3) [17] 1.8 (0.9, 3.0)	21 (2.5) [26] 1.3 (0.8, 1.9)	29 (3.1) [34] 1.6 (1.0, 2.2)	13 (2.3) [18] 1.3 (0.7, 2.3)	20 (2.4) [26] 1.0 (0.6, 1.5)	28 (3.0) [34] 1.3 (0.8, 1.8)
Oral herpes	5 (0.9) [11] 0.7 (0.2, 1.6)	14 (1.7) [21] 0.8 (0.5, 1.4)	16 (1.7) [25] 0.9 (0.5, 1.4)	8 (1.4) [15] 0.8 (0.3, 1.6)	17 (2.0) [25] 0.8 (0.5, 1.4)	19 (2.0) [29] 0.9 (0.5, 1.3)
Respiratory tract infection	4 (0.7) [4] 0.5 (0.1, 1.4)	15 (1.8) [19] 0.9 (0.5, 1.5)	22 (2.4) [26] 1.2 (0.7, 1.8)	7 (1.2) [7] 0.7 (0.3, 1.4)	19 (2.2) [23] 1.0 (0.6, 1.5)	26 (2.8) [30] 1.2 (0.8, 1.7)
Bronchitis	11 (1.9) [13] 1.5 (0.7, 2.7)	35 (4.1) [39] 2.1 (1.5, 3.0)	51 (5.5) [55] 2.8 (2.1, 3.7)	14 (2.4) [16] 1.4 (0.8, 2.4)	39 (4.6) [43] 2.0 (1.4, 2.7)	55 (5.9) [59] 2.6 (2.0, 3.4)
Oral candidiasis	45 (7.8) [62] 6.3 (4.6, 8.5)	64 (7.5) [91] 4.0 (3.1, 5.1)	75 (8.1) [110] 4.2 (3.3, 5.2)	50 (8.7) [75] 5.3 (3.9, 7.0)	70 (8.3) [106] 3.7 (2.9, 4.6)	81 (8.7) [125] 3.9 (3.1, 4.8)
Nasopharyngitis	64 (11.1) [85] 9.4 (7.2, 12.0)	116 (13.7) [162] 7.7 (6.4, 9.3)	137 (14.8) [199] 8.3 (7.0, 9.8)	92 (16.0) [126] 10.3 (8.3, 12.6)	146 (17.2) [208] 8.2 (6.9, 9.6)	167 (18.0) [245] 8.7 (7.4, 10.1)
Upper respiratory tract infection	44 (7.7) [49] 6.3 (4.6, 8.4)	75 (8.8) [100] 4.8 (3.8, 6.0)	87 (9.4) [115] 5.0 (4.0, 6.2)	59 (10.3) [70] 6.3 (4.8, 8.2)	94 (11.1) [125] 5.0 (4.1, 6.1)	106 (11.4) [140] 5.2 (4.3, 6.3)
Pharyngitis	23 (4.0) [27] 3.2 (2.0, 4.8)	49 (5.8) [62] 3.0 (2.3, 4.0)	60 (6.5) [74] 3.3 (2.6, 4.3)	32 (5.6) [36] 3.3 (2.3, 4.7)	57 (6.7) [70] 3.0 (2.2, 3.8)	68 (7.3) [82] 3.2 (2.5, 4.1)
Tonsillitis	17 (3.0) [19] 2.3 (1.4, 3.7)	36 (4.2) [44] 2.2 (1.5, 3.0)	39 (4.2) [49] 2.1 (1.5, 2.9)	18 (3.1) [20] 1.8 (1.1, 2.9)	37 (4.4) [45] 1.9 (1.3, 2.6)	40 (4.3) [50] 1.9 (1.3, 2.5)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Rhinitis	17 (3.0) [18] 2.3 (1.3, 3.7)	32 (3.8) [36] 1.9 (1.3, 2.7)	41 (4.4) [45] 2.2 (1.6, 3.0)	23 (4.0) [24] 2.3 (1.5, 3.5)	38 (4.5) [42] 1.9 (1.4, 2.6)	47 (5.1) [51] 2.2 (1.6, 2.9)
Sinusitis	15 (2.6) [19] 2.0 (1.1, 3.4)	30 (3.5) [36] 1.8 (1.2, 2.6)	31 (3.3) [37] 1.7 (1.1, 2.4)	19 (3.3) [24] 1.9 (1.2, 3.0)	36 (4.2) [44] 1.8 (1.3, 2.5)	37 (4.0) [45] 1.7 (1.2, 2.3)
Urinary tract infection	21 (3.7) [29] 2.9 (1.8, 4.4)	28 (3.3) [37] 1.7 (1.1, 2.4)	29 (3.1) [39] 1.6 (1.0, 2.2)	23 (4.0) [35] 2.4 (1.5, 3.5)	32 (3.8) [45] 1.6 (1.1, 2.3)	33 (3.6) [47] 1.5 (1.0, 2.1)
Corona virus infection	50 (8.7) [51] 7.0 (5.2, 9.2)	70 (8.3) [72] 4.2 (3.3, 5.3)	70 (7.5) [72] 3.8 (2.9, 4.8)	97 (16.9) [103] 10.3 (8.4, 12.6)	133 (15.7) [141] 6.8 (5.7, 8.1)	133 (14.3) [141] 6.2 (5.2, 7.3)
Investigations	78 (13.6) [131] 11.2 (8.9, 14.0)	130 (15.3) [244] 8.5 (7.1, 10.1)	158 (17.0) [311] 9.5 (8.1, 11.1)	106 (18.5) [185] 11.6 (9.5, 14.1)	165 (19.5) [311] 9.1 (7.8, 10.7)	192 (20.7) [378] 10.0 (8.6, 11.5)
Alanine aminotransferase increased	10 (1.7) [12] 1.4 (0.6, 2.5)	29 (3.4) [43] 1.8 (1.2, 2.5)	36 (3.9) [59] 2.0 (1.4, 2.7)	9 (1.6) [14] 0.9 (0.4, 1.7)	29 (3.4) [46] 1.5 (1.0, 2.1)	36 (3.9) [62] 1.7 (1.2, 2.3)
Aspartate aminotransferase increased	18 (3.1) [21] 2.4 (1.4, 3.9)	32 (3.8) [40] 1.9 (1.3, 2.7)	37 (4.0) [51] 2.0 (1.4, 2.7)	17 (3.0) [24] 1.7 (1.0, 2.8)	32 (3.8) [45] 1.6 (1.1, 2.3)	37 (4.0) [56] 1.7 (1.2, 2.3)
Gamma-glutamyltransferase increased	7 (1.2) [10] 0.9 (0.4, 1.9)	20 (2.4) [29] 1.2 (0.7, 1.9)	30 (3.2) [44] 1.6 (1.1, 2.3)	9 (1.6) [11] 0.9 (0.4, 1.7)	22 (2.6) [31] 1.1 (0.7, 1.7)	32 (3.4) [46] 1.5 (1.0, 2.1)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Coronavirus test positive	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	14 (2.4) [16] 1.4 (0.8, 2.4)	17 (2.0) [19] 0.8 (0.5, 1.3)	17 (1.8) [19] 0.8 (0.4, 1.2)
Metabolism and nutrition disorders	31 (5.4) [37] 4.3 (2.9, 6.1)	62 (7.3) [83] 3.9 (3.0, 4.9)	74 (8.0) [109] 4.2 (3.3, 5.2)	51 (8.9) [61] 5.3 (4.0, 7.0)	84 (9.9) [111] 4.4 (3.5, 5.4)	96 (10.3) [137] 4.6 (3.7, 5.6)
Hypercholesterolaemia	12 (2.1) [13] 1.6 (0.8, 2.8)	31 (3.7) [35] 1.9 (1.3, 2.7)	37 (4.0) [46] 2.0 (1.4, 2.8)	17 (3.0) [20] 1.7 (1.0, 2.8)	36 (4.2) [42] 1.8 (1.3, 2.5)	42 (4.5) [53] 2.0 (1.4, 2.6)
Musculoskeletal and connective tissue disorders	118 (20.6) [201] 18.1 (15.0, 21.7)	179 (21.1) [313] 12.3 (10.5, 14.2)	208 (22.4) [360] 12.9 (11.2, 14.8)	137 (23.9) [253] 16.2 (13.6, 19.1)	200 (23.6) [370] 11.7 (10.1, 13.4)	228 (24.6) [417] 12.2 (10.7, 13.9)
Arthralgia	28 (4.9) [31] 3.8 (2.5, 5.5)	45 (5.3) [51] 2.7 (2.0, 3.7)	50 (5.4) [60] 2.7 (2.0, 3.6)	30 (5.2) [39] 3.1 (2.1, 4.4)	47 (5.5) [59] 2.4 (1.8, 3.2)	52 (5.6) [68] 2.4 (1.8, 3.2)
Back pain	23 (4.0) [26] 3.1 (2.0, 4.7)	28 (3.3) [31] 1.7 (1.1, 2.4)	31 (3.3) [36] 1.7 (1.1, 2.4)	30 (5.2) [34] 3.1 (2.1, 4.4)	35 (4.1) [39] 1.8 (1.2, 2.4)	38 (4.1) [44] 1.7 (1.2, 2.4)
Musculoskeletal pain	8 (1.4) [9] 1.1 (0.5, 2.1)	15 (1.8) [18] 0.9 (0.5, 1.5)	18 (1.9) [21] 1.0 (0.6, 1.5)	10 (1.7) [11] 1.0 (0.5, 1.9)	17 (2.0) [20] 0.9 (0.5, 1.4)	20 (2.2) [23] 0.9 (0.6, 1.4)
Ankylosing spondylitis	12 (2.1) [14] 1.6 (0.8, 2.8)	25 (2.9) [30] 1.5 (1.0, 2.2)	29 (3.1) [34] 1.6 (1.0, 2.2)	13 (2.3) [16] 1.3 (0.7, 2.3)	26 (3.1) [32] 1.3 (0.9, 1.9)	30 (3.2) [36] 1.4 (0.9, 2.0)
Nervous system disorders	70 (12.2) [105] 10.3 (8.0, 13.0)	112 (13.2) [159] 7.3 (6.0, 8.7)	130 (14.0) [190] 7.7 (6.4, 9.1)	89 (15.5) [131] 9.9 (8.0, 12.2)	132 (15.6) [186] 7.2 (6.1, 8.6)	150 (16.2) [217] 7.6 (6.4, 8.9)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Headache	33 (5.7) [45] 4.6 (3.2, 6.5)	51 (6.0) [67] 3.1 (2.3, 4.1)	58 (6.3) [80] 3.2 (2.4, 4.1)	38 (6.6) [51] 4.0 (2.8, 5.4)	56 (6.6) [73] 2.9 (2.2, 3.7)	63 (6.8) [86] 3.0 (2.3, 3.8)
Respiratory, thoracic and mediastinal disorders	54 (9.4) [76] 7.6 (5.7, 10.0)	82 (9.7) [108] 5.1 (4.1, 6.3)	97 (10.5) [127] 5.4 (4.4, 6.6)	63 (11.0) [91] 6.7 (5.2, 8.6)	94 (11.1) [128] 4.9 (4.0, 6.0)	109 (11.7) [147] 5.2 (4.3, 6.3)
Cough	13 (2.3) [14] 1.8 (0.9, 3.0)	17 (2.0) [18] 1.0 (0.6, 1.6)	20 (2.2) [21] 1.1 (0.6, 1.6)	14 (2.4) [16] 1.4 (0.8, 2.4)	19 (2.2) [21] 0.9 (0.6, 1.5)	22 (2.4) [24] 1.0 (0.6, 1.5)
Oropharyngeal pain	14 (2.4) [17] 1.9 (1.0, 3.2)	22 (2.6) [25] 1.3 (0.8, 2.0)	28 (3.0) [31] 1.5 (1.0, 2.2)	16 (2.8) [19] 1.6 (0.9, 2.6)	25 (2.9) [28] 1.2 (0.8, 1.8)	31 (3.3) [34] 1.4 (1.0, 2.0)
Skin and subcutaneous tissue disorders	119 (20.7) [194] 18.5 (15.3, 22.2)	185 (21.8) [292] 12.9 (11.1, 14.9)	216 (23.3) [337] 13.7 (11.9, 15.7)	141 (24.6) [246] 16.8 (14.2, 19.8)	209 (24.6) [349] 12.4 (10.7, 14.2)	240 (25.9) [394] 13.1 (11.5, 14.9)
Acne	9 (1.6) [9] 1.2 (0.6, 2.3)	12 (1.4) [14] 0.7 (0.4, 1.2)	13 (1.4) [15] 0.7 (0.4, 1.2)	12 (2.1) [13] 1.2 (0.6, 2.1)	15 (1.8) [18] 0.7 (0.4, 1.2)	16 (1.7) [19] 0.7 (0.4, 1.2)
Eczema	13 (2.3) [18] 1.8 (0.9, 3.0)	22 (2.6) [29] 1.3 (0.8, 2.0)	29 (3.1) [39] 1.6 (1.0, 2.2)	20 (3.5) [32] 2.0 (1.2, 3.1)	30 (3.5) [44] 1.5 (1.0, 2.2)	37 (4.0) [54] 1.7 (1.2, 2.3)
Pruritus	11 (1.9) [12] 1.5 (0.7, 2.7)	14 (1.7) [15] 0.8 (0.5, 1.4)	16 (1.7) [17] 0.9 (0.5, 1.4)	14 (2.4) [15] 1.4 (0.8, 2.4)	17 (2.0) [19] 0.8 (0.5, 1.4)	19 (2.0) [21] 0.9 (0.5, 1.3)
Psoriasis	10 (1.7) [11] 1.4 (0.6, 2.5)	20 (2.4) [24] 1.2 (0.7, 1.9)	20 (2.2) [24] 1.1 (0.7, 1.6)	14 (2.4) [16] 1.4 (0.8, 2.4)	26 (3.1) [33] 1.3 (0.9, 1.9)	26 (2.8) [33] 1.2 (0.8, 1.7)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Rash	20 (3.5) [24] 2.7 (1.7, 4.2)	29 (3.4) [33] 1.7 (1.2, 2.5)	31 (3.3) [37] 1.7 (1.1, 2.4)	21 (3.7) [25] 2.1 (1.3, 3.3)	30 (3.5) [34] 1.5 (1.0, 2.2)	32 (3.4) [38] 1.5 (1.0, 2.1)
Vascular disorders	33 (5.7) [35] 4.6 (3.1, 6.4)	57 (6.7) [66] 3.5 (2.7, 4.6)	68 (7.3) [78] 3.8 (2.9, 4.8)	40 (7.0) [44] 4.2 (3.0, 5.7)	65 (7.7) [76] 3.4 (2.6, 4.3)	76 (8.2) [88] 3.6 (2.8, 4.5)
Hypertension	24 (4.2) [25] 3.3 (2.1, 4.9)	41 (4.8) [45] 2.5 (1.8, 3.4)	48 (5.2) [53] 2.6 (1.9, 3.5)	28 (4.9) [31] 2.9 (1.9, 4.2)	45 (5.3) [51] 2.3 (1.7, 3.1)	52 (5.6) [59] 2.4 (1.8, 3.2)

Treatment-related adverse events

Pool SA1

The incidence of treatment-related TEAEs was higher in the bimekizumab 160mg Q4W group (27.8%) compared with the placebo group (15.6%). Treatment-related TEAEs in the bimekizumab 160mg Q4W group were primarily reported in the SOC of Infections and infestations (14.0%), and the incidence was higher compared with placebo (8.9%). The most frequently reported treatment-related TEAE by PT was oral candidiasis, which was only reported in the bimekizumab 160mg Q4W group (3.4%). In addition to oral candidiasis, the other frequently reported treatment-related TEAEs reported in the bimekizumab 160mg Q4W group were headache (2.9% vs 1.7% in the placebo group), nasopharyngitis (2.6% vs 1.3% in placebo group), injection site pain (2.3% vs 0.8% in the placebo group), and upper respiratory tract infection (1.7% vs 2.5% in the placebo group).

Table 79: Incidence of drug-related TEAEs per 100 participant-years in >1% of study participants by PT in any treatment group during the Initial Treatment Period (Pool SA1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=234 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=357 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)
Any drug-related TEAE	37 (15.6) [81] 56.5 (39.8, 77.9)	97 (27.8) [214] 109.5 (88.8, 133.6)
Gastrointestinal disorders	5 (2.1) [6] 7.0 (2.3, 16.2)	18 (5.2) [23] 17.2 (10.2, 27.2)
Diarrhoea	0	4 (1.1) [5] 3.7 (1.0, 9.5)
Nausea	1 (0.4) [1] 1.4 (0.0, 7.7)	5 (1.4) [5] 4.7 (1.5, 10.9)
Injection site pain	2 (0.8) [3] 2.8 (0.3, 10.0)	8 (2.3) [14] 7.5 (3.2, 14.8)
Infections and infestation	21 (8.9) [35] 30.5 (18.9, 46.6)	49 (14.0) [72] 48.8 (36.1, 64.5)
Oral candidiasis	0	12 (3.4) [14] 11.2 (5.8, 19.6)
Vulvovaginal mycotic infection	0	4 (1.1) [4] 3.7 (1.0, 9.5)
Bronchitis	3 (1.3) [3] 4.1 (0.9, 12.1)	0
Nasopharyngitis	3 (1.3) [3] 4.1 (0.9, 12.1)	9 (2.6) [12] 8.5 (3.9, 16.1)
Upper respiratory tract infection	6 (2.5) [9] 8.4 (3.1, 18.2)	6 (1.7) [6] 5.6 (2.0, 12.1)
Nervous system disorders	4 (1.7) [4] 5.5 (1.5, 14.2)	14 (4.0) [19] 13.4 (7.3, 22.4)
Headache	4 (1.7) [4] 5.5 (1.5, 14.2)	10 (2.9) [13] 9.4 (4.5, 17.4)
Respiratory, thoracic and mediastinal disorders	2 (0.8) [2] 2.8 (0.3, 9.9)	10 (2.9) [10] 9.4 (4.5, 17.2)
Oropharyngeal pain	0	4 (1.1) [4] 3.7 (1.0, 9.5)

Pool SA2

treatment-related TEAEs during the combined Initial, Maintenance, and OLE Treatment Period were experienced by 45.4% (EAIR: 33.7/100 participant-years) of study participants in the bimekizumab Total group; treatment-related TEAEs were primarily reported in the SOC of Infections and infestations (28.1%; EAIR: 17.1/100 participant-years).

A total of 23 PTs were reported as drug-related TEAEs in at least 1% of study participants in the bimekizumab Total group; the most common were oral candidiasis (6.8%), nasopharyngitis (4.0%), upper respiratory tract infection (2.5%), oral fungal infection (2.4%), ALT increased and AST increased (2.3% each), and fungal skin infection (2.2%).

Table 80: Incidence of drug-related TEAEs per 100 participant-years in ≥1% of study participants by PT in any treatment group during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SA2)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Any drug-related TEAE	239 (41.6) [702] 43.8 (38.5, 49.8)	365 (43.0) [1039] 31.1 (28.0, 34.5)	421 (45.4) [1235] 33.7 (30.5, 37.0)
Gastrointestinal disorders	45 (7.8) [67] 6.3 (4.6, 8.4)	69 (8.1) [98] 4.3 (3.3, 5.4)	80 (8.6) [114] 4.4 (3.5, 5.5)
Diarrhoea	10 (1.7) [13] 1.3 (0.6, 2.5)	14 (1.7) [17] 0.8 (0.5, 1.4)	14 (1.5) [17] 0.7 (0.4, 1.2)
Nausea	7 (1.2) [7] 0.9 (0.4, 1.9)	8 (0.9) [8] 0.5 (0.2, 0.9)	8 (0.9) [8] 0.4 (0.2, 0.8)
General disorders and administration site conditions	29 (5.1) [61] 4.0 (2.7, 5.8)	34 (4.0) [66] 2.0 (1.4, 2.9)	41 (4.4) [76] 2.2 (1.6, 3.0)
Injection site pain	13 (2.3) [28] 1.8 (0.9, 3.0)	13 (1.5) [28] 0.8 (0.4, 1.3)	13 (1.4) [28] 0.7 (0.4, 1.2)
Infections and infestations	158 (27.5) [300] 25.6 (21.8, 29.9)	228 (26.9) [477] 16.6 (14.5, 18.9)	261 (28.1) [555] 17.1 (15.1, 19.4)
Oral candidiasis	39 (6.8) [55] 5.5 (3.9, 7.5)	55 (6.5) [80] 3.4 (2.6, 4.4)	63 (6.8) [91] 3.5 (2.7, 4.4)
Otitis media	7 (1.2) [8] 0.9 (0.4, 1.9)	7 (0.8) [8] 0.4 (0.2, 0.9)	7 (0.8) [8] 0.4 (0.1, 0.8)
Conjunctivitis	4 (0.7) [4] 0.5 (0.1, 1.4)	9 (1.1) [10] 0.5 (0.2, 1.0)	10 (1.1) [12] 0.5 (0.3, 1.0)
Oral fungal infection	8 (1.4) [9] 1.1 (0.5, 2.1)	18 (2.1) [30] 1.1 (0.6, 1.7)	22 (2.4) [38] 1.2 (0.7, 1.8)
Fungal skin infection	11 (1.9) [13] 1.5 (0.7, 2.7)	15 (1.8) [18] 0.9 (0.5, 1.5)	20 (2.2) [23] 1.1 (0.6, 1.6)
Oral herpes	4 (0.7) [9] 0.5 (0.1, 1.4)	9 (1.1) [14] 0.5 (0.2, 1.0)	9 (1.0) [15] 0.5 (0.2, 0.9)
Nasopharyngitis	21 (3.7) [32] 2.9 (1.8, 4.4)	33 (3.9) [56] 2.0 (1.4, 2.8)	37 (4.0) [65] 2.0 (1.4, 2.8)
Upper respiratory tract infection	20 (3.5) [22] 2.7 (1.7, 4.2)	23 (2.7) [25] 1.4 (0.9, 2.1)	23 (2.5) [25] 1.2 (0.8, 1.8)
Pharyngitis	5 (0.9) [6] 0.7 (0.2, 1.6)	14 (1.7) [18] 0.8 (0.5, 1.4)	17 (1.8) [21] 0.9 (0.5, 1.5)
Sinusitis	2 (0.3) [2] 0.3 (0.0, 1.0)	9 (1.1) [10] 0.5 (0.2, 1.0)	10 (1.1) [11] 0.5 (0.3, 1.0)
Rhinitis	8 (1.4) [8] 1.1 (0.5, 2.1)	9 (1.1) [9] 0.5 (0.2, 1.0)	10 (1.1) [10] 0.5 (0.3, 1.0)
Urinary tract infection	6 (1.0) [11] 0.8 (0.3, 1.8)	6 (0.7) [11] 0.4 (0.1, 0.8)	6 (0.6) [11] 0.3 (0.1, 0.7)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Investigations	32 (5.6) [64] 4.4 (3.0, 6.2)	53 (6.3) [122] 3.3 (2.4, 4.3)	64 (6.9) [156] 3.5 (2.7, 4.5)
Alanine aminotransferase increased	5 (0.9) [7] 0.7 (0.2, 1.6)	17 (2.0) [27] 1.0 (0.6, 1.6)	21 (2.3) [36] 1.1 (0.7, 1.7)
Aspartate aminotransferase increased	10 (1.7) [12] 1.3 (0.6, 2.5)	19 (2.2) [25] 1.1 (0.7, 1.8)	21 (2.3) [32] 1.1 (0.7, 1.7)
Gamma-glutamyltransferase increased	5 (0.9) [8] 0.7 (0.2, 1.6)	13 (1.5) [22] 0.8 (0.4, 1.3)	18 (1.9) [30] 1.0 (0.6, 1.5)
Nervous system disorders	19 (3.3) [30] 2.6 (1.6, 4.1)	25 (2.9) [37] 1.5 (1.0, 2.2)	31 (3.3) [47] 1.7 (1.1, 2.4)
Headache	12 (2.1) [18] 1.6 (0.8, 2.9)	15 (1.8) [22] 0.9 (0.5, 1.5)	18 (1.9) [27] 1.0 (0.6, 1.5)
Respiratory, thoracic and mediastinal disorders	16 (2.8) [25] 2.2 (1.2, 3.5)	18 (2.1) [27] 1.1 (0.6, 1.7)	19 (2.0) [28] 1.0 (0.6, 1.6)
Oropharyngeal pain	8 (1.4) [9] 1.1 (0.5, 2.1)	9 (1.1) [10] 0.5 (0.2, 1.0)	10 (1.1) [11] 0.5 (0.3, 1.0)
Skin and subcutaneous tissue disorders	53 (9.2) [80] 7.5 (5.6, 9.8)	71 (8.4) [99] 4.4 (3.4, 5.5)	84 (9.1) [117] 4.7 (3.7, 5.8)
Eczema	7 (1.2) [12] 0.9 (0.4, 1.9)	8 (0.9) [13] 0.5 (0.2, 0.9)	10 (1.1) [17] 0.5 (0.3, 1.0)
Pruritus	8 (1.4) [9] 1.1 (0.5, 2.1)	9 (1.1) [10] 0.5 (0.2, 1.0)	9 (1.0) [10] 0.5 (0.2, 0.9)
Rash	7 (1.2) [8] 0.9 (0.4, 1.9)	10 (1.2) [11] 0.6 (0.3, 1.1)	10 (1.1) [11] 0.5 (0.3, 1.0)

Adverse Events of Special Interest

Potential Hy's Law was the only AESI defined for the axSpA program. Potential Hy's Law, defined as ≥3x ULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical Abnormality.

A review of hepatic TEAEs in Pool SA1 and Pool SA2 was performed using the MedDRA SMQ 'Drug related hepatic disorder' (excluding sub-SMQs 'Liver neoplasms, benign [incl cysts and polyps'" and 'Liver neoplasms, malignant and unspecified').

Pool SA1

In pool SA1 one case met Hy's Law laboratory criteria but was not a confirmed as a Hy's Law case due to a clinical and serological diagnosis of viral hepatitis A infection.

The incidences of hepatic TEAEs were 4.9% in the bimekizumab 160mg Q4W group and 3.0% in the placebo group. Hepatic TEAEs reported in >1 study participant in the bimekizumab 160mg Q4W group were aspartate aminotransferase increased (1.7%), alanine aminotransferase increased, transaminases increased (1.4% each), hepatic steatosis (1.1%), and liver function test increased (0.6%).

Table 81: Treatment-emergent elevated and markedly abnormal liver function during the Initial Treatment Period (Pool SA1)

	Placebo N=237 n/Nsub (%)	BKZ 160mg Q4W N=349 n/Nsub (%)
AST		
>3xULN	2/236 (0.8)	5/349 (1.4)
>5xULN	1/236 (0.4)	2/349 (0.6)
>8xULN	1/236 (0.4)	2/349 (0.6)
>10xULN	1/236 (0.4)	2/349 (0.6)
>20xULN	0/236	1/349 (0.3)
ALT		
>3xULN	3/236 (1.3)	3/349 (0.9)
>5xULN	1/236 (0.4)	2/349 (0.6)
>8xULN	1/236 (0.4)	1/349 (0.3)
>10xULN	1/236 (0.4)	1/349 (0.3)
>20xULN	1/236 (0.4)	0/349
Either AST or ALT		
>3xULN	3/236 (1.3)	5/349 (1.4)
>5xULN	1/236 (0.4)	3/349 (0.9)
>8xULN	1/236 (0.4)	2/349 (0.6)
>10xULN	1/236 (0.4)	2/349 (0.6)
>20xULN	1/236 (0.4)	1/349 (0.3)
Total bilirubin		
>1.5xULN	1/236 (0.4)	3/349 (0.9)
>2xULN	0/236	2/349 (0.6)
ALP		
>1.5xULN	0/236	1/349 (0.3)
>2xULN	0/236	0/349

Pool SA2

In Pool SA2, the incidence of any hepatic TEAEs in the bimekizumab Total group was 12.4% (EAIR: 6.7/100 participant-years). When adjusted for exposure, no increased incidence rate of a hepatic TEAEs was observed in the Phase 3 bimekizumab 160mg Q4W group from Pool SA2 (EAIR: 7.2/100 participant-years) when compared with the bimekizumab 160mg Q4W group from Pool SA1 (EAIR: 16.2/100 participant-years).

Of the 115 study participants in the bimekizumab Total group with hepatic TEAEs, 1 participant had a serious event of hepatotoxicity, 5 participants had 7 TEAEs leading to study discontinuation (including protocol mandated withdrawal as per PDILI criteria), 52 participants had 128 TEAEs considered drug related, and 2 participants had 2 severe TEAEs (alanine aminotransferase increased and aspartate aminotransferase increased).

Serious event of hepatotoxicity

This event relates to a 35-year-old male participant . Medical history was significant for dyslipidemia and obesity. LFTs >2x ULN at baseline and hepatoprotection was given. Bloods at day 801 revealed ALP 77 (normal), ALT 277 (5xULN), AST 213 (6.3xULN), TBil 31.3 (1.5xULN) and GGT 683 (10.7xULN). The participant was asymptomatic, and US showed diffuse liver changes in the form of fatty hepatosis and a diagnosis of hepatic steatosis. The participant was withdrawn from the study and abnormal enzymes are resolving with AST/ALT are 2xULN 150 days after last bimekizumab dose.

Table 82: Treatment-emergent elevated and markedly abnormal liver function during the combined initial, Maintenance, and OLE Treatment Period (Pool SA2)

	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)
AST						
>3xULN	18/574 (3.1)	31/847 (3.7)	36/927 (3.9)	22/574 (3.8)	37/847 (4.4)	42/927 (4.5)
>5xULN	6/574 (1.0)	10/847 (1.2)	12/927 (1.3)	8/574 (1.4)	13/847 (1.5)	15/927 (1.6)
>8xULN	3/574 (0.5)	5/847 (0.6)	5/927 (0.5)	4/574 (0.7)	6/847 (0.7)	6/927 (0.6)
>10xULN	2/574 (0.3)	3/847 (0.4)	3/927 (0.3)	2/574 (0.3)	3/847 (0.4)	3/927 (0.3)
>20xULN	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)
ALT						
>3xULN	9/574 (1.6)	16/847 (1.9)	24/927 (2.6)	10/574 (1.7)	18/847 (2.1)	26/927 (2.8)
>5xULN	3/574 (0.5)	6/847 (0.7)	6/927 (0.6)	3/574 (0.5)	6/847 (0.7)	6/927 (0.6)
>8xULN	1/574 (0.2)	2/847 (0.2)	2/927 (0.2)	1/574 (0.2)	2/847 (0.2)	2/927 (0.2)
>10xULN	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)
>20xULN	0	0	0	0	0	0
Either AST or ALT						
>3xULN	20/574 (3.5)	36/847 (4.3)	45/927 (4.9)	25/574 (4.4)	43/847 (5.1)	52/927 (5.6)
>5xULN	7/574 (1.2)	12/847 (1.4)	14/927 (1.5)	9/574 (1.6)	15/847 (1.8)	17/927 (1.8)
>8xULN	3/574 (0.5)	6/847 (0.7)	6/927 (0.6)	4/574 (0.7)	7/847 (0.8)	7/927 (0.8)
>10xULN	2/574 (0.3)	3/847 (0.4)	3/927 (0.3)	2/574 (0.3)	3/847 (0.4)	3/927 (0.3)
>20xULN	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)

	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)
Total bilirubin						
>1.5xULN	22/574 (3.8)	39/847 (4.6)	42/927 (4.5)	25/574 (4.4)	43/847 (5.1)	46/927 (5.0)
>2xULN	4/574 (0.7)	7/847 (0.8)	7/927 (0.8)	5/574 (0.9)	8/847 (0.9)	8/927 (0.9)
ALP						
>1.5xULN	2/574 (0.3)	2/847 (0.2)	5/927 (0.5)	2/574 (0.3)	3/847 (0.4)	5/927 (0.5)
>2xULN	0/574	0/847	1/927 (0.1)	0/574	0/847	1/927 (0.1)

Other safety topics of interest

Infections

Interleukin-17A and IL-17F play a role in muco-epidermal immunity by protecting against a variety of pathogens, and inhibition of IL-17 may increase susceptibility of infection during the period of exposure, especially to Candida species. In the bimekizumab axSpA development program, in line with observations in the pivotal studies of the psoriasis development program, infections were the most frequently reported TEAEs.

The most frequently reported infections in the axSpA development program were nasopharyngitis, upper respiratory tract infection, and oral candidiasis. When adjusted for exposure, no increased incidence rate of infections TEAEs was observed in the Phase 3 bimekizumab 160mg Q4W group from Pool SA2 (EAIR: 68.3/100 participant-years) when compared with the Pool SA1 bimekizumab 160mg Q4W group (EAIR: 119.4/100 participant-years).

Infections are further broken down into serious infections, opportunistic infections and fungal infections.

Serious infections:

Pool SA1

In Pool SA1, incidences of serious infection TEAEs were similar in the bimekizumab 160mg Q4W group (0.3%; EAIR: 0.9/100 participant-years) and in the placebo group (0.4%; EAIR: 1.4/100 participant-years).

Table 83: Incidence of Serious Infection TEAEs per 100 subject-years during the Initial Treatment Period Analysis Set: Pool SA1

MedDRA v19.0 System Organ Class High Level Term Preferred Term	Placebo N=237 100 subject-yrs=0.73 n (%) [#] Incidence (95% CI) Event Rate	BKZ 160mg Q4W N=349 100 subject-yrs=1.09 n (%) [#] Incidence (95% CI) Event Rate
Any Serious Infection	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Infections and infestations	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Hepatitis viral infections	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Hepatitis A	0	1 (0.3) [1] 0.9 (0.0, 5.1) 0.9
Viral infections NEC	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	0
Viral infection	1 (0.4) [1] 1.4 (0.0, 7.6) 1.4	0

One study participant in the bimekizumab 160mg Q4W group met the laboratory criteria for Hy's Law (ALT or AST ≥3xULN and total bilirubin ≥2xULN in the absence of ALP ≥2xULN) and was clinically and serologically diagnosed with Hepatitis A. The participant contracted hepatitis A from contaminated food. The study drug was temporarily discontinued and once restarted there was no further elevation in hepatic enzymes.

Pool SA2

In Pool SA2, the incidence of serious infections in the combined Initial, Maintenance, and OLE Treatment Period was low overall (3.3%; EAIR: 1.5/100 participant-years) in the updated safety data for the bimekizumab Total group. When adjusted for exposure, a similar incidence rate was observed in the Phase 3 bimekizumab 160mg Q4W group from Pool SA2 (EAIR: 1.5/100 participant-years) when compared with the Pool SA1 bimekizumab 160mg Q4W group (EAIR: 0.9/100 participant years). The EAIR of serious infection TEAEs was similar in the Safety Update (1.4/100 participant-years).

Of the 28 study participants with serious infections, 9 had drug-related serious infections as assessed by the Investigator and 9 had serious infections that were reported as severe in intensity. Study drug was withdrawn in 3 participants who discontinued due to a serious infection TEAE (perirectal abscess, cellulitis, and pneumonia).

Overall, 27 of the 34 serious infections (79.4%) in the bimekizumab Total group were reported as resolved. Two participants had a total of 3 events (abscess limb and erysipelas in 1 participant and corona virus infection in the other) that recovered with sequelae. Three serious infections (corona virus infection, otitis media, fungal oesophagitis) were reported as not resolved at the time of the data cut. One serious infection of cellulitis (2.9%) was reported as resolving.

In the Safety Update, a total of 3 additional serious infections (appendicitis, perirectal abscess, and diverticulitis) were reported; 2 TEAEs (appendicitis and perirectal abscess) were considered severe, 1 TEAE (diverticulitis) was considered related to study medication, and all 3 TEAEs were resolved.

Table 84: Incidence of serious infections per 100 participant-years by HLT during the combined Initial, Maintenance, and OLE Treatment Period (Pool SA2)

	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01	BKZ total N=928 100 participant-yrs=19.07	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34	BKZ Total N=928 100 participant-yrs=22.41
MedDRA v19.0 High Level Term	n (%) [#] EAIR (95% CI)	n (%) [#] EAIR (95% CI)	n (%) [#] EAIR (95% CI)	n (%) [#] EAIR (95% CI)	n (%) [#] EAIR (95% CI)	n (%) [#] EAIR (95% CI)
Any serious infection	11 (1.9) [12] 1.5 (0.7, 2.7)	26 (3.1) [30] 1.6 (1.0, 2.3)	28 (3.0) [34] 1.5 (1.0, 2.2)	13 (2.3) [13] 1.3 (0.7, 2.2)	29 (3.4) [32] 1.5 (1.0, 2.1)	31 (3.3) [36] 1.4 (1.0, 2.0)
Abdominal and gastrointestinal infections	2 (0.3) [2] 0.3 (0.0, 1.0)	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	4 (0.7) [4] 0.4 (0.1, 1.0)	6 (0.7) [6] 0.3 (0.1, 0.6)	6 (0.6) [6] 0.3 (0.1, 0.6)
Bacterial infections NEC	3 (0.5) [3] 0.4 (0.1, 1.2)	4 (0.5) [4] 0.2 (0.1, 0.6)	4 (0.4) [4] 0.2 (0.1, 0.5)	3 (0.5) [3] 0.3 (0.1, 0.9)	4 (0.5) [4] 0.2 (0.1, 0.5)	4 (0.4) [4] 0.2 (0.0, 0.5)
Bone and joint infections	0	0	1 (0.1) [1] 0.1 (0.0, 0.3)	0	0	1 (0.1) [1] 0.1 (0.0, 0.2)
Ear infections	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.2) [1] 0.1 (0.0, 0.6)	1 (0.1) [1] 0.0 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Fungal infections NEC	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	0	0
Hepatitis viral infections	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.2) [1] 0.1 (0.0, 0.6)	1 (0.1) [1] 0.0 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Infections NEC	0	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	0	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Lower respiratory tract and lung infections	1 (0.2) [1] 0.1 (0.0, 0.7)	5 (0.6) [5] 0.3 (0.1, 0.7)	7 (0.8) [8] 0.4 (0.1, 0.8)	1 (0.2) [1] 0.1 (0.0, 0.6)	5 (0.6) [5] 0.2 (0.1, 0.6)	7 (0.8) [8] 0.3 (0.1, 0.6)
Skin structures and soft tissue infections	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	1 (0.2) [1] 0.1 (0.0, 0.6)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)

MedDRA v19.0 High Level Term	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Streptococcal infections	2 (0.3) [2] 0.3 (0.0, 1.0)	3 (0.4) [4] 0.2 (0.0, 0.5)	3 (0.3) [4] 0.2 (0.0, 0.5)	2 (0.3) [2] 0.2 (0.0, 0.7)	3 (0.4) [4] 0.1 (0.0, 0.4)	3 (0.3) [4] 0.1 (0.0, 0.4)
Upper respiratory tract infections	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Urinary tract infections	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)
Viral infections NEC	0	3 (0.4) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.2 (0.0, 0.5)	0	3 (0.4) [3] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)

Opportunistic infections:

Pool SA1

One study participant in AS0014 had a TEAE of fungal oesophagitis that was entered after the final DLP for UCB assessment as an opportunistic infection. Upon CHMP's request, it was clarified that the case had fully resolved.

Pool SA2

In Pool SA2, the incidence of any localised opportunistic infection in the combined Initial, Maintenance, and OLE Treatment Period was low overall in the bimekizumab Total group (1.1%; EAIR: 0.5/100 participant-years). Except for 1 case of herpes zoster, all opportunistic infections were localised mucocutaneous fungal infections.

In the updated safety data the incidence of any localised opportunistic infection was 1.3% in the bimekizumab Total group in the Safety Update; the EAIR in the Safety Update was consistent with the original submission (0.5/100 participant-years each) which is also consistent with the initial submission.

Opportunistic infections PTs reported in Pool SA2 in the bimekizumab Total group were oropharyngeal candidiasis (0.6%), oesophageal candidiasis, fungal oesophagitis, oropharyngitis fungal, and herpes zoster (0.1%, each).

Two participants discontinued the study due to an opportunistic infection (herpes zoster and oesophageal candidiasis).

Table 85: Incidence of opportunistic infection TEAEs per 100 participant-years during the combined Initial, Maintenance, and OLE Treatment Period (SA2)

MedDRA v19.0 System Organ Class High Level Term Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Any Opportunistic Infection	8 (1.4) [9] 1.1 (0.5, 2.1)	9 (1.1) [10] 0.5 (0.2, 1.0)	10 (1.1) [11] 0.5 (0.3, 1.0)
Infections and infestations	8 (1.4) [9] 1.1 (0.5, 2.1)	9 (1.1) [10] 0.5 (0.2, 1.0)	10 (1.1) [11] 0.5 (0.3, 1.0)
Candida infections	6 (1.0) [7] 0.8 (0.3, 1.8)	7 (0.8) [8] 0.4 (0.2, 0.9)	7 (0.8) [8] 0.4 (0.1, 0.8)
Oropharyngeal candidiasis	5 (0.9) [6] 0.7 (0.2, 1.6)	6 (0.7) [7] 0.4 (0.1, 0.8)	6 (0.6) [7] 0.3 (0.1, 0.7)
Oesophageal candidiasis	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)
Fungal infections NEC	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)
Fungal oesophagitis[a]	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)
Oropharyngitis fungal	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)
Herpes viral infections	0	0	1 (0.1) [1] 0.1 (0.0, 0.3)
Herpes zoster	0	0	1 (0.1) [1] 0.1 (0.0, 0.3)

Fungal infections:

Pool SA1

In Pool SA1, the incidence of any fungal infection in the Initial Treatment Period was higher in the bimekizumab 160mg Q4W (6.3%; EAIR: 20.8/100 participant-years) compared with the placebo group (none reported). Oral candidiasis was the most frequently reported (3.7%) PT, followed by vulvovaginal mycotic infection (1.7%). All other PTs were reported in <1% of study participants. Of the 28 fungal infections reported (in 22 study participants), 25 were reported as resolved at the time of the DLP.

Table 86: Incidence of Fungal Infection TEAEs during the Initial Treatment Period by Outcome Analysis Set: Pool SA1

MedDRA v19.0 System Organ Class High Level Term Preferred Term Outcome	Placebo N=237 n (%)	BKZ 160mg Q4W N=349 n (%)
Any Fungal Infection	0	28
Recovered/Resolved	0	25 (89.3)
Recovered/Resolved with Sequelae	0	0
Recovering/Resolving	0	0
Not Recovered/Not Resolved	0	3 (10.7)
Fatal	0	0

Pool SA2

In Pool SA2, the incidence of any fungal infection during the combined Initial, Maintenance, and OLE Treatment Period in the bimekizumab Total group was 18.6% (EAIR: 10.7/100 participant years). By PT, oral candidiasis (8.1%), oral fungal infection (3.2%), and fungal skin infection (3.1%) were reported with an incidence ≥2% in the bimekizumab Total group. At the DLP 14 participants were classified as 'recovering/resolving' and 25 were classified as 'not recovered/not resolved'.

In the Safety Update, the incidence of any fungal infection TEAE was 20.3% in the bimekizumab Total group; the EAIR was lower in the Safety Update (9.9/100 participant-years) compared with the original submission (10.7/100 participant-years), indicating no increased risk with longer exposure to bimekizumab.

Table 87: Incidence of fungal infection TEAEs per 100 participant-years with an incidence of at least 1% by PT in any treatment group during the combined Initial, Maintenance and OLE Treatment Period (Pool SA2)

MedDRA v19.0 High Level Term Preferred Term	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any Fungal Infection	90 (15.7) [142] 13.5 (10.9, 16.6)	146 (17.2) [242] 10.0 (8.4, 11.7)	173 (18.6) [295] 10.7 (9.1, 12.4)	104 (18.1) [173] 11.8 (9.7, 14.3)	161 (19.0) [279] 9.2 (7.9, 10.8)	188 (20.3) [332] 9.9 (8.5, 11.4)
Candida infections	55 (9.6) [77] 7.9 (5.9, 10.2)	78 (9.2) [114] 4.9 (3.9, 6.1)	90 (9.7) [134] 5.1 (4.1, 6.2)	61 (10.6) [97] 6.6 (5.0, 8.4)	85 (10.0) [136] 4.5 (3.6, 5.6)	97 (10.5) [156] 4.7 (3.8, 5.7)
Oral candidiasis	45 (7.8) [62] 6.3 (4.6, 8.5)	64 (7.5) [91] 4.0 (3.1, 5.1)	75 (8.1) [110] 4.2 (3.3, 5.2)	50 (8.7) [75] 5.3 (3.9, 7.0)	70 (8.3) [106] 3.7 (2.9, 4.6)	81 (8.7) [125] 3.9 (3.1, 4.8)
Oropharyngeal candidiasis	5 (0.9) [6] 0.7 (0.2, 1.6)	6 (0.7) [7] 0.4 (0.1, 0.8)	6 (0.6) [7] 0.3 (0.1, 0.7)	6 (1.0) [9] 0.6 (0.2, 1.3)	7 (0.8) [10] 0.3 (0.1, 0.7)	7 (0.8) [10] 0.3 (0.1, 0.6)
Fungal infections NEC	37 (6.4) [55] 5.2 (3.7, 7.2)	70 (8.3) [113] 4.4 (3.5, 5.6)	84 (9.1) [142] 4.8 (3.8, 5.9)	42 (7.3) [61] 4.4 (3.2, 6.0)	75 (8.8) [123] 4.0 (3.1, 5.0)	89 (9.6) [152] 4.3 (3.5, 5.3)
Oral fungal infection	9 (1.6) [10] 1.2 (0.6, 2.3)	25 (2.9) [42] 1.5 (1.0, 2.2)	30 (3.2) [53] 1.6 (1.1, 2.3)	11 (1.9) [13] 1.1 (0.6, 2.0)	28 (3.3) [47] 1.4 (0.9, 2.1)	33 (3.6) [58] 1.5 (1.1, 2.1)
Fungal skin infection	13 (2.3) [17] 1.8 (0.9, 3.0)	21 (2.5) [26] 1.3 (0.8, 1.9)	29 (3.1) [34] 1.6 (1.0, 2.2)	13 (2.3) [18] 1.3 (0.7, 2.3)	20 (2.4) [26] 1.0 (0.6, 1.5)	28 (3.0) [34] 1.3 (0.8, 1.8)
Tongue fungal infection	1 (0.2) [2] 0.1 (0.0, 0.7)	6 (0.7) [10] 0.4 (0.1, 0.8)	8 (0.9) [16] 0.4 (0.2, 0.8)	3 (0.5) [4] 0.3 (0.1, 0.9)	8 (0.9) [14] 0.4 (0.2, 0.8)	10 (1.1) [20] 0.5 (0.2, 0.8)
Vulvovaginal mycotic infection	9 (1.6) [15] 1.2 (0.6, 2.3)	9 (1.1) [15] 0.5 (0.2, 1.0)	10 (1.1) [16] 0.5 (0.3, 1.0)	10 (1.7) [16] 1.0 (0.5, 1.9)	10 (1.2) [16] 0.5 (0.2, 0.9)	11 (1.2) [17] 0.5 (0.2, 0.9)
Onychomycosis	4 (0.7) [4] 0.5 (0.1, 1.4)	10 (1.2) [10] 0.6 (0.3, 1.1)	10 (1.1) [10] 0.5 (0.3, 1.0)	4 (0.7) [4] 0.4 (0.1, 1.0)	11 (1.3) [11] 0.5 (0.3, 1.0)	11 (1.2) [11] 0.5 (0.2, 0.9)
Tinea infections	9 (1.6) [10] 1.2 (0.6, 2.3)	13 (1.5) [15] 0.8 (0.4, 1.3)	17 (1.8) [19] 0.9 (0.5, 1.4)	14 (2.4) [15] 1.4 (0.8, 2.4)	18 (2.1) [20] 0.9 (0.5, 1.4)	22 (2.4) [24] 1.0 (0.6, 1.5)
Tinea pedis	3 (0.5) [4] 0.4 (0.1, 1.2)	6 (0.7) [8] 0.4 (0.1, 0.8)	9 (1.0) [11] 0.5 (0.2, 0.9)	6 (1.0) [7] 0.6 (0.2, 1.3)	9 (1.1) [11] 0.4 (0.2, 0.8)	12 (1.3) [14] 0.5 (0.3, 0.9)

TB

No study participant developed confirmed active TB.

One participant experienced latent TB for which they received Isoniazid.

In the Safety Update, no study participants developed active TB.

Covid-19

Specific COVID-19 terms are not available in MedDRA version 19.0, therefore symptomatic, confirmed, or suspected COVID-19 was coded as PT 'corona virus infectio' and asymptomatic, confirmed COVID-19 was coded as PT "'coronavirus test positive'.

Pool SA1

In Pool SA1, COVID-19 TEAEs were reported in 2 study participants (0.6%; EAIR: 1.9/100 participant-years) in the bimekizumab 160mg Q4W group and 4 study participants (1.7%; EAIR: 5.5/100 participant-years) in the placebo group.

Pool SA2

In Pool SA2, COVID-19 TEAEs were reported in 72 study participants (7.8%; EAIR: 3.9/100 participant-years) in the bimekizumab Total group. The incidence of PT corona virus infection was higher in Pool SA2

than in Pool SA1 (7.8% vs 0.6%, respectively), likely reflecting the increased prevalence of COVID-19 infection over time during the conduct of the axSpA studies.

Overall, in the bimekizumab Total group, 3 study participants (0.3%) had a serious COVID-19.

TEAE (all PT corona virus infection), and 1 participant experienced a severe event of corona virus infection (1 of the serious events). No participant discontinued due to a COVID-19 TEAE. Three study participants (0.3%) with a COVID-19 TEAE had an event assessed as drug related by the Investigator. The majority of COVID-19 TEAEs were reported as resolved at the time of the DLP.

In the safety update, the incidence of COVID-19 TEAEs in the bimekizumab Total group was 16.2%. The EAIR was higher in the Safety Update (7.0/100 participant-years) compared with the original submission (3.9/100 participant-year). The EAIR of the PT of corona virus infection was also higher in the Safety Update (6.2/100 participant-years) compared with the original submission (3.8/100 participant-years), reflecting the increased prevalence of COVID-19 infection over time during the conduct of the axSpA studies.

Table 88: Incidence of COVID-19 TEAEs per 100 participant-years by preferred term during the Initial Treatment Period (Pool SA1) and in the bimekizumab Total group during the combined Initial, Maintenance, and OLE TREAtment Periods (Pool SA2)

MedDRA V19.0 Preferred Term	SA1		SA2
	Placebo N=237 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=349 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Any COVID-19 TEAE	4 (1.7) [4] 5.5 (1.5, 14.2)	2 (0.6) [2] 1.9 (0.2, 6.7)	72 (7.8) [74] 3.9 (3.0, 4.9)
Corona virus infection	4 (1.7) [4] 5.5 (1.5, 14.2)	2 (0.6) [2] 1.9 (0.2, 6.7)	70 (7.5) [72] 3.8 (2.9, 4.8)
Coronavirus test positive	0	0	2 (0.2) [2] 0.1 (0.0, 0.4)

Major adverse cardiovascular events (MACE)

Pool SA1

No adjudicated MACE or extended MACE were reported in the bimekizumab 160mg Q4W group or with placebo.

Pool SA2

In Pool SA2, the overall incidence of adjudicated MACE was low, occurring in 4 study participants (0.4%; EAIR: 0.2/100 participant-years). Adjudicated MACE included cardiac arrest, cerebrovascular accident, acute myocardial infarction, and coronary artery stenosis (0.1%; EAIR: 0.1/100 participant-years each). Of the 4 study participants with adjudicated MACE, all events were serious, 3 were severe, and none was assessed as drug related by the Investigator. One study participant experienced a MACE with fatal outcome (cardiac arrest). None of the 3 remaining MACE led to study discontinuation or permanent withdrawal of study medication. Other than the fatal cardiac arrest, all other adjudicated MACE (75%) were reported as resolved. For 25 participants there was not enough information available to adjudicate or determine whether or not they should be classified as MACE.

Table 89: Incidence of adjudicated MACE, extended MACE, and cardiovascular events per 100 participant-years (Pool SA2)

Category CV event type	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any adjudicated MACE[c]	0	3 (0.4) [3] 0.2 (0.0, 0.5)	4 (0.4) [4] 0.2 (0.1, 0.5)	0	4 (0.5) [6] 0.2 (0.1, 0.5)	5 (0.5) [7] 0.2 (0.1, 0.5)
Any adjudicated extended MACE[d]	0	6 (0.7) [6] 0.4 (0.1, 0.8)	7 (0.8) [7] 0.4 (0.1, 0.8)	0	7 (0.8) [10] 0.3 (0.1, 0.7)	8 (0.9) [11] 0.4 (0.2, 0.7)
Any adjudicated cardiovascular TEAE	12 (2.1) [18] 1.6 (0.8, 2.8)	29 (3.4) [45] 1.7 (1.2, 2.5)	37 (4.0) [55] 2.0 (1.4, 2.7)	14 (2.4) [21] 1.4 (0.8, 2.4)	31 (3.7) [54] 1.6 (1.1, 2.2)	39 (4.2) [64] 1.8 (1.3, 2.4)
Non-fatal myocardial infarction	0	1 (0.1) [1] 0.1 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	1 (0.1) [1] 0.0 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.3)
Non-fatal stroke: ischemic	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [1] 0.0 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Hospitalization or ER for unstable angina with urgent revascularization	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [1] 0.0 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Hospitalization or ER for unstable angina without urgent revascularization *	0	2 (0.2) [3] 0.1 (0.0, 0.4)	2 (0.2) [3] 0.1 (0.0, 0.4)	0	2 (0.2) [3] 0.1 (0.0, 0.4)	2 (0.2) [3] 0.1 (0.0, 0.3)
Hospitalization for heart failure	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [2] 0.0 (0.0, 0.3)	1 (0.1) [2] 0.0 (0.0, 0.2)

Category CV event type	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Coronary revascularization procedures (eg, percutaneous coronary intervention, coronary artery bypass grafting)	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.2)
Arrhythmia (not associated with ischemia) *	2 (0.3) [2] 0.3 (0.0, 1.0)	6 (0.7) [6] 0.4 (0.1, 0.8)	6 (0.6) [6] 0.3 (0.1, 0.7)	3 (0.5) [3] 0.3 (0.1, 0.9)	7 (0.8) [7] 0.3 (0.1, 0.7)	7 (0.8) [7] 0.3 (0.1, 0.6)
Peripheral arterial event *	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [2] 0.0 (0.0, 0.3)	1 (0.1) [2] 0.0 (0.0, 0.2)
Venous thromboembolic event: DVT *	0	0	0	1 (0.2) [1] 0.1 (0.0, 0.6)	1 (0.1) [1] 0.0 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Venous thromboembolic event: PE and DVT *	1 (0.2) [2] 0.1 (0.0, 0.7)	1 (0.1) [2] 0.1 (0.0, 0.3)	1 (0.1) [2] 0.1 (0.0, 0.3)	1 (0.2) [2] 0.1 (0.0, 0.6)	1 (0.1) [2] 0.0 (0.0, 0.3)	1 (0.1) [2] 0.0 (0.0, 0.2)
Other CV event *	4 (0.7) [5] 0.5 (0.1, 1.4)	5 (0.6) [6] 0.3 (0.1, 0.7)	7 (0.8) [8] 0.4 (0.1, 0.8)	5 (0.9) [6] 0.5 (0.2, 1.2)	6 (0.7) [7] 0.3 (0.1, 0.6)	8 (0.9) [9] 0.4 (0.2, 0.7)
Sudden cardiac death	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	2 (0.2) [4] 0.1 (0.0, 0.4)	2 (0.2) [4] 0.1 (0.0, 0.3)
Non-cardiovascular death *	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	0	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.2)

Category CV event type	Data in original submission[a] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Data in original submission[a] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	Data in original submission[a] BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	Data in Safety Update[b] BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Non-cardiovascular event [c]	8 (1.4) [9] 1.1 (0.5, 2.1)	16 (1.9) [20] 1.0 (0.5, 1.5)	22 (2.4) [27] 1.2 (0.7, 1.8)	8 (1.4) [9] 0.8 (0.3, 1.6)	17 (2.0) [21] 0.8 (0.5, 1.4)	23 (2.5) [28] 1.0 (0.7, 1.6)
Not enough information to adjudicate/not classified [c]	0	10 (1.2) [13] 0.6 (0.3, 1.1)	25 (2.7) [30] 1.4 (0.9, 2.0)	0	10 (1.2) [13] 0.5 (0.2, 0.9)	25 (2.7) [30] 1.2 (0.8, 1.7)

4 adjudicated MACE cases:

Table 90: Bimekizumab treated axSpA study participants with adjudicated MACE

Study[a]	Gender/ age range (yrs)	Treatment at the time of MACE	Days since 1st inj./ Days since 1st BKZ inj./ Days since most recent BKZ inj.	Preferred Term/ Reported term	Cardiovascular risk factors
Adjudicated MACE					
Sudden cardiac death					
AS0008	M/40-50	BKZ 160mg Q4W	10/ 10/ 10	Cardiac arrest/ sudden cardiac arrest	BMI >30kg/m^2, hypertension, family history of sudden cardiac death, alcohol use, tobacco use (autopsy findings were not available to confirm the cause of death).
Non-fatal stroke					
AS0008	F/60-70	BKZ 160mg Q4W	1368/ 1368/ 25	Cerebrovascular accident/ cerebrovascular event	hypertension, palpitations, alcohol use, and tobacco use (50 years of smoking; 10 cigarettes/day).
Non-fatal myocardial infarction					
AS0008	M/40-50	BKZ 160mg Q4W	293/ 293/ 10	Acute myocardial infarction/ ST-lengths elevation myocardial infarction	BMI >30kg/m^2, previous myocardial infarction, coronary artery disease, hypertension, hyperlipidemia, depression, sleep apnoea syndrome, myocardial infarction, alcohol use, and tobacco use.
AS0013	M/50-60	BKZ 160mg Q2W	26/ 26/ 14	Coronary artery stenosis/ coronary stenosis	BMI >30kg/m^2, previous myocardial infarction, coronary artery disease, peripheral edema, blood cholesterol increased, hypertension, diabetes mellitus, coronary stent, and tobacco use

The four participants who experienced MACE had significant medical histories with cardiac risk factors.

One study participant experienced a MACE with fatal outcome (cardiac arrest), which is discussed as part of the deaths that occurred during the study. None of the 3 remaining MACE led to study discontinuation or permanent withdrawal of study medication.

One additional participant in the Safety Update experienced 3 concurrent events adjudicated as MACE (sudden cardiac death): cardio-respiratory arrest, ventricular fibrillation, and dyspnoea (0.1%; EAIR: 0.0/100 participant-years each). This event was fatal and is included in the discussion on deaths during this study.

Extended MACE:

Extended MACE occurred in 7 study participants (0.8%; EAIR: 0.4/100 participant-years) and included the adjudicated MACE described above plus arteriosclerosis coronary artery, angina pectoris, and cardiac failure, in the bimekizumab total group.

Table 91: Incidence of Adjudicated Extended Major Adverse Cardiac Events (MACE) TEAEs during the Combined Initial, Maintenance and OLE Treatment Period by Outcome Analysis Set: Pool SA2

MedDRA v19.0 System Organ Class High Level Term Preferred Term Outcome	Phase 3 BKZ 160mg Q4W N=574 n (%)	Phase 2/3 BKZ 160mg Q4W N=848 n (%)	BKZ Total N=928 n (%)
Any Adjudicated Extended MACE event	0	6	7
Recovered/Resolved	0	3 (50.0)	4 (57.1)
Recovered/Resolved with Sequelae	0	1 (16.7)	1 (14.3)
Recovering/Resolving	0	0	0
Not Recovered/Not Resolved	0	1 (16.7)	1 (14.3)
Fatal	0	1 (16.7)	1 (14.3)

A recent meta-analysis suggests that the risk of atrial fibrillation and atrioventricular block is increased in patients with ankylosing spondylitis when compared to the general population. An increased risk of atrial fibrillation (RR: 1.85, 95%CI: 1.15-2.98) and atrioventricular block (OR: 3.46, 95%CI: 1.09-10.93) was found in AS subjects compared to the general population. In a subgroup analysis based on study design, a greater association between AS and atrioventricular block in cohort studies (RR: 5.14, 95%CI: 1.001-26.50) compared to cross-sectional ones was noted. However, no association between AS and any arrhythmia (OR=3.36, 95% CI: 0.93-12.15), or conduction disorders (OR: 0.64, 95%CI: 0.38-1.06) was found. (Morovatdar et al)

Based on a previous study, by Szabo et al, there is a 25% increased risk of cardiovascular disease (CVD) in valvular heart disease, ischemic heart disease, congestive heart failure and other cardiovascular diseases in AS patients.

Suicide

Pool SA1

In Pool SA1, there were no study participants with positive responses for suicidal ideation and/or behaviour during the Initial Treatment Period.

Pool SA2

Within Pool SA2, the incidence of treatment-emergent positive responses for suicidal ideation and/or behavior was low. Overall, 3 study participants had events adjudicated as SIB: suicidal ideation in 2 participants (0.2%) and intentional self-injury in another participant (0.1%). All events were serious and severe.

No completed suicides were observed in study participants.

The event of suicidal ideation that led to study discontinuation and was considered drug related by the Investigator occurred in a study participant who had a history of depression as well as cannabis and alcohol abuse. This resolved with antidepressants.

IBD

Pool SA1

In Pool SA1, in the bimekizumab 160mg Q4W group, 2 study participants (0.6%; EAIR: 1.8/100 participant-years) had TEAEs adjudicated as definite or probable IBD, which included 1 participant with an

event of definite IBD and 1 participant with an event of probable IBD (0.3%; EAIR: 0.9/100 participant-years, each).

Pool SA2

Overall, in the bimekizumab Total group of Pool SA2, 15 study participants (1.6%; EAIR: 0.8/100 participant-years) had TEAEs adjudicated as definite or probable IBD, which included 9 participants (1.0%; EAIR: 0.5/100 participant-years) with an event of definite IBD and 7 participants (0.8%; EAIR: 0.4/100 participant-years) with an event of probable IBD

One participant had multiple events in both categories. In the bimekizumab Total group, overall, 8 participants (0.9%; EAIR: 0.4/100 participant-years) had an event adjudicated as possible IBD; all events occurred in participants without a history of IBD.

Safety update:

The incidence for any definite or probable adjudicated IBD in the Safety Update was 1.8% in the bimekizumab Total group; the EAIR in the Safety Update was consistent with the original submission (0.8/100 participant-years each), indicating no increase in risk with longer exposure to bimekizumab.

Two additional participants had IBD TEAEs adjudicated as definite or probable. One study participant reported 1 TEAE of colitis and 1 TEAE of diarrhea that were both adjudicated as probable Crohn's disease; 1 study participant reported 1 TEAE of colitis ulcerative that was adjudicated as definite ulcerative colitis.

Neither study participant had a medical history of IBD; both study participants had risk factors for IBD, such as smoking, concomitant medications (ie, NSAIDs), and HLA-B27 positive at baseline.

Table 92: Incidence of adjudicated definite/probable IBD TEAES during the Initial Treatment Period (Pool SA1) and during the Combined Initial, Maintenance, and OLE Treatment Periods (Pool SA2)

Category Event Type classification	Data in original submission[a]			Data in Safety Update[b]
	SA1		SA2	SA2
	Placebo N=237 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=349 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any definite or probable adjudicated IBD TEAE	1 (0.4) [1] 1.4 (0.0, 7.6)	2 (0.6) [2] 1.8 (0.2, 6.7)	15 (1.6) [25] 0.8 (0.4, 1.3)	17 (1.8) [29] 0.8 (0.4, 1.2)
Definite IBD – Crohn's Disease	0	1 (0.3) [1] 0.9 (0.0, 5.1)	4 (0.4) [6] 0.2 (0.1, 0.5)	4 (0.4) [6] 0.2 (0.0, 0.5)
Definite IBD – Ulcerative Colitis	1 (0.4) [1] 1.4 (0.0, 7.6)	0	4 (0.4) [7] 0.2 (0.1, 0.5)	5 (0.5) [8] 0.2 (0.1, 0.5)
Definite IBD – Unclassified	0	0	2 (0.2) [4] 0.1 (0.0, 0.4)	2 (0.2) [4] 0.1 (0.0, 0.3)
Probable IBD - Crohn's Disease	0	0	3 (0.3) [4] 0.2 (0.0, 0.5)	4 (0.4) [7] 0.2 (0.0, 0.5)
Probable IBD - Ulcerative Colitis	0	1 (0.3) [1] 0.9 (0.0, 5.1)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.0 (0.0, 0.2)
Probable IBD - no further differentiation possible	0	0	3 (0.3) [3] 0.2 (0.0, 0.5)	3 (0.3) [3] 0.1 (0.0, 0.4)

Malignancy

Interleukin-17, with its pro-inflammatory properties, may play a dual role in cancer, serving either as a promoter or antitumor factor, possibly dependent on the cellular source. Thus, there is a theoretical risk that immunomodulators have carcinogenic potential.

A meta-analysis of published data showed that AS is associated with a 14% (pooled RR 1.14; 95% CI: 1.03-1.25) increase in the overall risk for malignancy. Compared to controls, patients with AS are at a specific increased risk for malignancy of the digestive system (pooled RR 1.20; 95% CI: 1.01- 1.42), multiple myelomas (pooled RR 1.92; 95% CI: 1.37-3.69) and lymphomas (pooled RR 1.32; 95% CI 1.11-1.57) (Deng et al, 2016). Overall, in a study including 22 countries, the prevalence of any type of cancer has been estimated at 3.0% (95% CI: 2.46-3.52) in patients with spondyloarthropathies (Molto et al, 2016).

According to the MAH, there is no evidence to suggest that the number of malignancies in AS subjects exposed to bimekizumab is higher than what was expected.

Pool SA1

In Pool SA1, no malignancy TEAE was reported in the bimekizumab 160mg Q4W group or in the placebo group.

Pool SA2

In Pool SA2, the overall incidence of malignancies was low, occurring in 6 study participants (0.6%; EAIR: 0.3/100 participant-years) in the bimekizumab Total group.

Excluding non-melanomic skin cancers, the incidence rate of malignancies was also low in the bimekizumab Total group (5 participants [0.5%; EAIR: 0.3/100 participant-years]). By PT, all malignant tumor TEAEs were reported only once: breast cancer, clear cell renal cell carcinoma, lung neoplasm malignant, superficial spreading melanoma stage I, basal cell carcinoma, and testicular seminoma (pure) ([0.1%; EAIR: 0.1/100 participants each]).

In the bimekizumab Total group, the TEAE of testicular seminoma (pure) was serious, severe, and led to study discontinuation; the TEAE of lung neoplasm malignant was serious and severe; and the TEAEs of clear cell renal cell carcinoma, breast cancer, and superficial spreading melanoma stage I were serious and mild or moderate in intensity.

Table 93: Incidence of Malignancy TEAEs per 100 subject-years during the Combined Initial, Maintenance, and OLE Treatment Period Analysis Set: Pool SA2

MedDRA v19.0 System Organ Class High Level Term Preferred Term	Phase 3 BKZ 160mg Q4W N=574 100 subject-yrs=7.47 n (%) [#] Incidence (95% CI) Event Rate	Phase 2/3 BKZ 160mg Q4W N=848 100 subject-yrs=17.01 n (%) [#] Incidence (95% CI) Event Rate	BKZ Total N=928 100 subject-yrs=19.07 n (%) [#] Incidence (95% CI) Event Rate
Any Malignancies	3 (0.5) [3] 0.4 (0.1, 1.2) 0.4	6 (0.7) [6] 0.4 (0.1, 0.8) 0.4	6 (0.6) [6] 0.3 (0.1, 0.7) 0.3
Any Malignancies (excluding non melanomic skin cancers)	3 (0.5) [3] 0.4 (0.1, 1.2) 0.4	5 (0.6) [5] 0.3 (0.1, 0.7) 0.3	5 (0.5) [5] 0.3 (0.1, 0.6) 0.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.5) [3] 0.4 (0.1, 1.2) 0.4	6 (0.7) [6] 0.4 (0.1, 0.8) 0.4	6 (0.6) [6] 0.3 (0.1, 0.7) 0.3
Breast and nipple neoplasms malignant	1 (0.2) [1] 0.1 (0.0, 0.7) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Breast cancer	1 (0.2) [1] 0.1 (0.0, 0.7) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Renal neoplasms malignant	1 (0.2) [1] 0.1 (0.0, 0.7) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Clear cell renal cell carcinoma	1 (0.2) [1] 0.1 (0.0, 0.7) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Respiratory tract and pleural neoplasms malignant cell type unspecified NEC	0	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1

Lung neoplasm malignant	0	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Skin melanomas (excl ocular)	1 (0.2) [1] 0.1 (0.0, 0.7) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Superficial spreading melanoma stage I	1 (0.2) [1] 0.1 (0.0, 0.7) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Skin neoplasms malignant and unspecified (excl melanoma)	0	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Basal cell carcinoma	0	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Testicular neoplasms malignant	0	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1
Testicular seminoma (pure)	0	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1	1 (0.1) [1] 0.1 (0.0, 0.3) 0.1

Hypersensitivity

Pool SA1

In Pool SA1, hypersensitivity reactions were reported at a higher incidence in the bimekizumab 160mg Q4W group (6.0%; EAIR: 19.9/100 participant-years) compared with the placebo group (2.1%; EAIR: 6.9/100 participant-years). The highest incidences of hypersensitivity reactions were reported in the SOC of Skin and subcutaneous tissue disorders (4.9% in the bimekizumab 160mg Q4W group vs 1.7% in the placebo group); mainly from the HLTs Rashes, eruptions and exanthems NEC (2.3% in the bimekizumab 160mg Q4W group and 0.4% in the placebo group) and Dermatitis and eczema (2.0% in the bimekizumab 160mg Q4W group and 0.4% in the placebo group). The most frequently reported TEAEs by PT in the SOC of Skin and subcutaneous tissue were rash (2.3%), dermatitis, eczema, and hand dermatitis (0.6% each). The majority of hypersensitivity reactions (92.3%) were reported as resolved.

Pool SA2

The incidence of hypersensitivity reactions in the combined Initial, Maintenance, and OLE Treatment Period was 13.5% (EAIR: 7.2/100 participant years) in the bimekizumab Total group. The majority of hypersensitivity reactions was reported in the SOC of Skin and subcutaneous tissue disorders (12.1%) in the bimekizumab Total group; mainly from the HLT Dermatitis and eczema (7.1%). The most frequently reported hypersensitivity reactions by PT were rash (3.3%), eczema (3.1%), and dermatitis (1.6%). The following additional hypersensitivity reactions by PT were reported in at least 5 study participants in the bimekizumab Total group: rash pustular, rhinitis allergic, dermatitis allergic, dermatitis contact, and dermatitis atopic. The majority of hypersensitivity reactions were reported as resolved (73.3%) or resolving (9.1%).

Table 94: Incidence of hypersensitivity reactions per 100 participant-years occurring in at least 5 study participants by HLT in BKZ Total group during the combined Initial, Maintenance, and OLE Treatment Period (Pool SA2)

MedDRA v19.0 High Level Term	Phase 3 BKZ 160mg Q4W N= 574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)
Any hypersensitivity reaction	71 (12.4) [104] 10.3 (8.0, 13.0)	106 (12.5) [149] 6.8 (5.5, 8.2)	125 (13.5) [176] 7.2 (6.0, 8.6)
Skin structures and soft tissue infections	6 (1.0) [7] 0.8 (0.3, 1.8)	6 (0.7) [7] 0.4 (0.1, 0.8)	6 (0.6) [7] 0.3 (0.1, 0.7)
Nasal congestion and inflammations	3 (0.5) [3] 0.4 (0.1, 1.2)	4 (0.5) [4] 0.2 (0.1, 0.6)	5 (0.5) [5] 0.3 (0.1, 0.6)
Dermatitis and eczema	34 (5.9) [44] 4.7 (3.3, 6.6)	53 (6.3) [71] 3.2 (2.4, 4.2)	66 (7.1) [87] 3.6 (2.8, 4.6)
Rashes, eruptions and exanthems NEC	24 (4.2) [28] 3.3 (2.1, 4.9)	33 (3.9) [37] 2.0 (1.4, 2.8)	37 (4.0) [43] 2.0 (1.4, 2.7)

No participants had a serious hypersensitivity reaction, 1 participant had a severe hypersensitivity reaction, 5 participants discontinued due to a hypersensitivity reaction, and 41 participants had a hypersensitivity reaction considered drug related by the Investigator.

The incidence for hypersensitivity reactions in the Safety Update was 15.6% in the bimekizumab Total group; the EAIR in the Safety Update (52-week data) was consistent with the original submission (7.2/100 participant-years), indicating no increased risk with longer exposure to bimekizumab.

The most frequently reported hypersensitivity reactions by PT in the bimekizumab Total group in the Safety Update were eczema (4.0%; EAIR: 1.7/100 participant-years), rash (3.4%; EAIR: 1.5/100 participant-years), and dermatitis (1.6%; EAIR: 0.8/100 participant-years) and were similar to the original submission.

Injection site reactions

Pool SA1

The incidence of injection site reactions by HLT was reported by 3.4% (EAIR: 11.4/100 participant-years) of study participants in the bimekizumab 160mg Q4W group and by 1.7% (EAIR: 5.5/100 participant-years) of study participants in the placebo group. By PT, injection site reaction TEAEs that occurred in >1 study participant in the bimekizumab 160mg Q4W group were injection site pain (2.3%) and injection site erythema (0.2%).

Pool SA2

In Pool SA2, the incidence of injection site reactions in the combined Initial, Maintenance, and OLE Treatment Period was low overall (2.8%; EAIR: 1.4/100 participant years in the bimekizumab Total group). By PT, the most frequently reported injection site reaction TEAE was injection site pain (1.5% of participants). All other PTs were reported in <1% of study participants.

All injections site reactions were nonserious and mild or moderate in intensity. One study participant discontinued due to a moderate TEAE of injection site reaction, which was considered drug related by the Investigator.

The incidence for administration and injection site reactions in the Safety Update was 2.9% in the bimekizumab Total group; the EAIR was similar in the Safety Update (1.2/100 participant-years) and the original submission (1.4/100 participant-years) and did not indicate an increase in risk with longer exposure to bimekizumab.

ADAb

Treatment-emergent AEs, hypersensitivity reactions, anaphylactic reactions, serious TEAEs, and TEAEs leading to discontinuation in Pool SA2 (study participants initially randomised to bimekizumab 160mg Q4W treatment, or initially randomised to placebo and initiating bimekizumab 160mg Q4W treatment at Week 16 in studies AS0010 and AS0011) were summarised by ADAb status. Study participants on bimekizumab 160mg Q4W treatment who were ADAb positive were further analysed for NAb. TEAEs were summarised by NAb status using the following categories:

- ADAb negative
- ADAb positive / NAb negative
- NAb positive

Pool SA1 and Pool SA2

In Pool SA1, the incidence of study participants who were ADAb positive at Baseline was low (4.8% [15/313]). Overall, by Week 16, 35.5% (111/313) of study participants had at least 1 ADAb-positive sample. Approximately half of these (14.7% [46/313]) had at least 2 ADAb-positive samples by Week 16.

Overall, by Week 24, 42.5% (133/313) of study participants in the bimekizumab 160mg Q4W group and 17.9% (36/201) of study participants in the placebo/bimekizumab 160mg Q4W group were ADAb positive. Overall, by Week 52 (based on all available data), 47.6% (149/313) of study participants in the bimekizumab 160mg Q4W group and 37.8% (76/201) of study participants in the placebo/bimekizumab 160mg Q4W group were ADAb positive. Of note, ADAb status up to Week 52 could not be derived for 34.5% (108/313) and 24.9% (50/201) of participants in the bimekizumab 160mg Q4W and placebo/bimekizumab 160mg Q4W groups, respectively, mainly due to missing scheduled samples from study participants who had not yet reached Week 52.

After the safety update:

Overall by Week 52, 49.2% (154/313) of study participants in the bimekizumab 160mg Q4W group and 38.8% (78/201) of study participants in the placebo/bimekizumab 160mg Q4W group had at least 1 ADAb-positive sample. By Week 52, 34.5% (108/313) of participants in the bimekizumab 160mg Q4W group and 19.4% (39/201) of participants in the placebo/bimekizumab 160mg Q4W group had at least 2 ADAb-positive samples.

Table 95: ADAb status by visit and overall up to SFU (Pool SA1 and Pool EA2)

Visit	Status	Placebo/BKZ 160mg Q4W N=201 n (%)	BKZ 160mg Q4W N=313 n (%)
Overall up to Week 16[a]	ADAb Positive	NA	111 (35.5)
	ADAb Negative	NA	194 (62.0)
	Total	NA	305 (97.4)
	ADAb Missing	NA	8 (2.6)
Overall up to Week 16 for efficacy subgroup analysis[b]	ADAb Positive	NA	46 (14.7)
	ADAb Negative	NA	259 (82.7)
	Total	NA	305 (97.4)
	ADAb Missing	NA	8 (2.6)
Overall up to Week 52[c]	ADAb Positive	78 (38.8)	154 (49.2)
	ADAb Negative	120 (59.7)	141 (45.0)
	Total	198 (98.5)	295 (94.2)
	ADAb Missing	3 (1.5)	18 (5.8)
Overall up to Week 52 for efficacy subgroup analysis[b]	ADAb Positive	39 (19.4)	108 (34.5)
	ADAb Negative	159 (79.1)	187 (59.7)
	Total	198 (98.5)	295 (94.2)
	ADAb Missing	3 (1.5)	18 (5.8)
Overall up to SFU[c]	ADAb Positive	78 (38.8)	155 (49.5)
	ADAb Negative	120 (59.7)	140 (44.7)
	Total	198 (98.5)	295 (94.2)
	ADAb Missing	3 (1.5)	18 (5.8)
Baseline	ADAb Positive	15 (7.5)	15 (4.8)
	ADAb Negative	183 (91.0)	296 (94.6)
	Total	198 (98.5)	311 (99.4)
	ADAb Missing	3 (1.5)	2 (0.6)
Week 4	ADAb Positive	NA	42 (13.4)
	ADAb Negative	NA	266 (85.0)
	Total	NA	308 (98.4)
	ADAb Missing	NA	5 (1.6)

Visit	Status	Placebo/BKZ 160mg Q4W N=201 n (%)	BKZ 160mg Q4W N=313 n (%)
Week 8	Positive	NA	38 (12.1)
	Negative	NA	263 (84.0)
	Total	NA	301 (96.2)
	ADAb Missing	NA	12 (3.8)
Week 12	ADAb Positive	NA	51 (16.3)
	ADAb Negative	NA	247 (78.9)
	Total	NA	298 (95.2)
	ADAb Missing	NA	15 (4.8)
Week 16	ADAb Positive	15 (7.5)	52 (16.6)
	ADAb Negative	183 (91.0)	250 (79.9)
	Total	198 (98.5)	302 (96.5)
	ADAb Missing	3 (1.5)	11 (3.5)
Week 20	ADAb Positive	20 (10.0)	67 (21.4)
	ADAb Negative	177 (88.1)	228 (72.8)
	Total	197 (98.0)	295 (94.2)
	ADAb Missing	4 (2.0)	18 (5.8)
Week 24	ADAb Positive	19 (9.5)	67 (21.4)
	ADAb Negative	178 (88.6)	225 (71.9)
	Total	197 (98.0)	292 (93.3)
	ADAb Missing	4 (2.0)	21 (6.7)
Week 36	ADAb Positive	45 (22.4)	60 (19.2)
	ADAb Negative	153 (76.1)	220 (70.3)
	Total	198 (98.5)	280 (89.5)
	ADAb Missing	3 (1.5)	33 (10.5)
Week 52	ADAb Positive	39 (19.4)	46 (14.7)
	ADAb Negative	151 (75.1)	221 (70.6)
	Total	190 (94.5)	267 (85.3)
	ADAb Missing	11 (5.5)	46 (14.7)
SFU	ADAb Positive	3 (1.5)	6 (1.9)
	ADAb Negative	8 (4.0)	24 (7.7)
	Total	11 (5.5)	30 (9.6)
	ADAb Missing	0	0

Pool SA2

Incidences of TEAEs by time of onset relative to ADAb status in Pool SA2 were 53.1% (TEAEs starting before the first ADAb-positive result), 59.2% (TEAEs starting on or after the first ADAb-positive result), and 70.5% (TEAEs for participants who were always ADAb negative). Exposure-adjusted incidence rates were 283.5/100 participant-years (95% CI: 233.0, 341.7), 217.8/100 participant-years (95% CI: 183.0, 257.3), and 167.8/100 participant-years (95% CI: 145.2, 192.9), respectively. The percentage of study participants reporting any TEAEs who were always ADAb negative was higher than the percentages of study participants reporting any TEAE starting before or starting on/after the first ADAb positive result; however, the EAIR was lower in the study participants who were always ADAb negative.

The TEAEs with an incidence difference of ≥2.5% between TEAEs starting on/after the first ADAb-positive result and TEAEs starting before the first ADAb-positive result by PT were oral candidiasis (7.7% vs 4.8%), otitis externa (2.6% vs 0), rhinitis (2.6% vs 0), and corona virus infection (4.3% vs 0.5%) in the Infections and infestations SOC, and arthralgia (4.3% vs 1.4%) and headache (2.1% vs 4.8%) from other SOCs, although the incidence of rhinitis, corona virus infection, and headache for TEAEs starting on/after the first ADAb-positive result was comparable with or lower than the incidence in participants who were always ADAb negative.

Table 96: Incidence of TEAEs by time of onset relative to ADAb status (reported by PT in >5% of study participants in any group and/or with an incidence difference of >2.5% between TEAEs starting before or on/after the first ADAb-positive result) (Pool SA2)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W by anti-BKZ antibody status		
	AEs starting before 1st anti-BKZ antibody positive result N=207 100 participant-yrs=0.69 n (%) [#] Incidence (95% CI)	AEs starting on or after 1st anti-BKZ antibody positive result N=233 100 participant-yrs=1.39 n (%) [#] Incidence (95% CI)	AEs for participants who are always anti-BKZ antibody negative N=281 100 participant-yrs=2.37 n (%) [#] Incidence (95% CI)
Any TEAE	110 (53.1) [278] 283.5 (233.0, 341.7)	138 (59.2) [500] 217.8 (183.0, 257.3)	198 (70.5) [747] 167.8 (145.2, 192.9)
Infections and infestations	62 (30.0) [85] 118.0 (90.5, 151.3)	92 (39.5) [191] 99.9 (80.6, 122.6)	122 (43.4) [220] 71.7 (59.5, 85.6)
PTs reported with an incidence difference of ≥2.5% between TEAEs starting before 1st ADAb-positive result and TEAEs starting on/after 1st ADAb-positive result			
Oral candidiasis	10 (4.8) [11] 14.9 (7.2, 27.5)	18 (7.7) [23] 14.0 (8.3, 22.1)	12 (4.3) [16] 5.2 (2.7, 9.1)
Otitis extema	0	6 (2.6) [6] 4.4 (1.6, 9.6)	4 (1.4) [8] 1.7 (0.5, 4.4)
Rhinitis	0	6 (2.6) [7] 4.4 (1.6, 9.6)	7 (2.5) [7] 3.0 (1.2, 6.2)
Corona virus infection	1 (0.5) [1] 1.5 (0.0, 8.1)	10 (4.3) [10] 7.4 (3.5, 13.5)	13 (4.6) [14] 5.6 (3.0, 9.5)
Arthralgia	3 (1.4) [3] 4.4 (0.9, 12.9)	10 (4.3) [13] 7.5 (3.6, 13.7)	7 (2.5) [11] 3.0 (1.2, 6.2)
Headache	10 (4.8) [11] 14.9 (7.1, 27.4)	5 (2.1) [6] 3.7 (1.2, 8.6)	17 (6.0) [20] 7.5 (4.4, 12.0)
Additional PTs reported in ≥5% of study participants for TEAEs in any group			
Nasopharyngitis	15 (7.2) [18] 23.3 (13.1, 38.5)	16 (6.9) [19] 12.2 (7.0, 19.8)	29 (10.3) [33] 13.2 (8.8, 19.0)
Upper respiratory tract infection	6 (2.9) [6] 9.0 (3.3, 19.5)	7 (3.0) [7] 5.2 (2.1, 10.8)	15 (5.3) [16] 6.6 (3.7, 10.8)

Incidences of TEAEs leading to study medication discontinuation by time of onset relative to ADAb status in Pool SA2 were 0.5% [1/207] for TEAEs starting before the first ADAb-positive result, 4.7% [11/233] for TEAEs starting on or after the first ADAb-positive result, and 3.6% [10/281] for TEAEs in participants who were always ADAb negative. When adjusted for exposure, the EAIR for TEAEs starting on or after the first ADAb-positive result (8.1/100 participant-years [95% CI: 4.1, 14.5] was higher than for TEAEs starting before the first ADAb-positive result (1.5/100 participant-years [95% CI: 0.0, 8.1]) and for TEAEs in participants who were always ADAb negative (4.3/100 participant-years [95% CI: 2.1, 7.9]).

No anaphylactic reactions were observed in the axSpA Phase 3 studies.

In Pool SA2, the HLT of Injection site reactions was reported at a low incidence in all groups (<5%). The EAIR for TEAEs starting on/after the first ADAb-positive result (EAIR: 5.2/100 participant-years [95% CI:

2.1, 10.7]) was lower than for TEAEs starting before the first ADAb-positive result (EAIR: 10.6/100 participant-years [95% CI: 4.3, 21.8) and slightly higher than for TEAEs in participants who were always ADAb negative (EAIR: 3.0/100 participant-years [95% CI: 1.2, 6.2]).

When adjusted for exposure, the incidence of hypersensitivity reaction TEAEs was slightly higher for TEAEs that started on/after the first ADAb-positive result (17.8/100 participant-years [95% CI: 11.3, 26.7], n=23/233) compared with TEAEs starting before the first ADAb-positive result (13.9/100 participant-years [95% CI: 6.4, 26.5], n=9/207) and was higher than in the group that was always ADAb negative (7.4/100 participant-years [95% CI: 4.3, 11.9], n=17/281). One study participant who was always ADAb negative experienced a TEAE of drug hypersensitivity.

Exposure-adjusted incidences for hypersensitivity reaction TEAEs were lower in NAb-positive (EAIR: 10.8/100 participant-years [95% CI: 4.9, 20.5]) than in ADAb positive/NAb-negative participants (EAIR: 20.4/100 participant-years [95% CI: 12.8, 30.8]) and was lowest in ADAb-negative participants (EAIR: 7.4/100 participant-years [95% CI: 4.3, 11.9]).

Laboratory findings

Parameters included are based on the set of biochemistry and haematology parameters routinely collected as part of the Phase 3 studies. Specific parameters summarised in Table 97 and Table 98 are as follows:

- Biochemistry: Calcium, chloride, magnesium, potassium, sodium, glucose, BUN, creatinine, ALP, AST, ALT, GGT, total bilirubin, LDH, and total cholesterol.
- Hematology: Basophils (absolute counts), eosinophils (absolute counts), lymphocytes (absolute counts), monocytes (absolute counts), neutrophils (absolute counts), hematocrit, hemoglobin, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, mean corpuscular volume, platelet count, RBC count, and WBC count.

Markedly abnormal values are defined as those with a severity of Grade 3 and above based on the CTCAE Version 4.03.

Haematology

Table 97: Markedly abnormal hematology data (Pool SA2)

	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)
Any TEMA hematology laboratory value	6/574 (1.0)	17/847 (2.0)	19/927 (2.0)
Hemoglobin low (<8.0g/dL)	0/574	2/847 (0.2)	2/927 (0.2)
Hemoglobin high (>40g/dL above ULN)	0/574	0/847	0/927
Lymphocytes low (<0.5x10^9/L)	2/574 (0.3)	4/847 (0.5)	4/927 (0.4)
Lymphocytes high (>20x10^9/L)	0/574	0/847	0/927
Neutrophils low (<1x10^9/L)	4/574 (0.7)	10/847 (1.2)	11/927 (1.2)
Platelets low (<50x10^9/L)	0/574	1/847 (0.1)	2/927 (0.2)
WBC count low (<2.0x10^9/L)	1/574 (0.2)	1/847 (0.1)	1/927 (0.1)
WBC count high (>100x10^9/L)	0/574	0/847	0/927

Neutropenia

Pool SA1

In Pool SA1, the incidence of neutropenia TEAEs reported in the bimekizumab 160mg Q4W group was low (0.6%; EAIR: 1.8/100 participant-years).

No study participant in the bimekizumab 160mg Q4W group had a TEMA neutrophil value (<1.0x10^9/L). One study participant (0.4%) in the placebo group had a TEMA neutrophil value (CTCAE Grade 3 low neutrophil value at Week 16).

Pool SA2

In Pool SA2, 11 study participants (1.2%) in the bimekizumab Total group had a TEMA neutrophils low count (<1.0x10^9/L). Of these 11 participants, 2 had confirmed pseudoneutropenia. Nine study participants had Grade 3 neutrophil values; all were transient and had resolved. Two study participants had reversible Grade 4 neutrophil values that returned to normal at subsequent visits.

A spike in low neutrophil counts was observed during January to March 2021. These phenomena were observed across several ongoing studies at the time and were investigated by the central laboratory (ICON) for possible causes, as this was not in line with previous bimekizumab safety data. Most of the samples with low neutropenia count during this period were processed at the central laboratory and were from a small number of countries, including Russia and Poland. Data indicated that the occurrence of low neutrophil laboratory findings peaked during February 2021 and dates coincided with very cold temperatures in those locations. Additionally, these study participants were retested within a few days up to 3 weeks and were reported to be normal, suggesting that it was more likely that the neutropenia detected was 'pseudoneutropenia'due to sample integrity issues (ie, exposure to cold temperatures during shipment) and not true neutropenia.

Biochemistry

Table 98: Markedly abnormal biochemistry data (Pool SA2)

	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)
Any TEMA clinical chemistry laboratory value	10/574 (1.7)	18/847 (2.1)	25/927 (2.7)
Creatinine (>3.0xULN or >3.0xbaseline)	0/574	0/847	0/927
Glucose low (<2.2mmol/L)	0/574	0/847	0/927
Glucose high (>13.9mmol/L)	5/574 (0.9)	7/847 (0.8)	11/927 (1.2)
Calcium low (<1.75mmol/L)	0/574	0/847	0/927
Calcium high (>3.1mmol/L)	0/574	0/847	0/927
Magnesium low (<0.4mmol/L)	0/574	0/847	0/927
Magnesium high (>1.23mmol/L)	1/574 (0.2)	2/847 (0.2)	2/927 (0.2)
Potassium low (<3.0mmol/L)	0/574	1/847 (0.1)	1/927 (0.1)
Potassium high (>6.0mmol/L)	4/574 (0.7)	7/847 (0.8)	7/927 (0.8)
Sodium low (<130mmol/L)	0/574	1/847 (0.1)	3/927 (0.3)
Sodium high (>155mmol/L)	0/574	0/847	0/927
Total cholesterol high (>10.34mmol/L)	0/574	0/847	1/927 (0.1)

Pool SA1

In Pool SA1, during the Initial Treatment Period, the incidence of TEMA biochemistry laboratory values was low and similar between the bimekizumab 160mg Q4W group (0.9%) and the placebo group (0.4%). Two study participants (0.6%) in the bimekizumab 160mg Q4W group and 1 study participant (0.4%) in the placebo group reported high glucose TEMA biochemistry values (>13.9 mmol/L). One study participant (0.3%) in the bimekizumab 160mg Q4W group reported a potassium high TEMA biochemistry value (>6.0 mmol/L).

Pool SA2

In Pool SA2, during the combined Initial, Maintenance, and OLE Treatment Period, 10 study participants (1.7%) in the Phase 3 bimekizumab 160mg Q4W group, 18 study participants (2.1%) in Phase 2/3 bimekizumab 160mg Q4W group, and 25 study participant (2.7%) in the bimekizumab Total group reported any TEMA biochemistry laboratory value. The most frequently reported TEMA biochemistry value was high glucose (1.2% in the bimekizumab Total group); note that fasting before blood sampling was not a requirement. The proportion of study participants who experienced other TEMA biochemistry laboratory values was low (<1%).

Vital signs and Physical examination

Pool SA1

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

Table 99: Markedly abnormal systolic and diastolic blood pressure during the Initial Treatment Period (SA1)

Visit	Variable Criteria	Placebo (N=237) n/Nsub (%)	BKZ 160mg Q4W (N=349) n/Nsub (%)
Any post-Baseline SBP value through Week 16	SBP (mmHg)		
	>180 and increase of ≥20	1/237 (0.4)	1/349 (0.3)
	<90 and decrease of ≥20	2/237 (0.8)	1/349 (0.3)
Any post-Baseline DBP value through Week 16	DBP (mmHg)		
	>105 and increase of ≥15	2/237 (0.8)	4/349 (1.1)
	<50 and decrease of ≥15	0/237	1/349 (0.3)

Pool SA2

The number of study participants with markedly abnormal SBP or DBP was generally low and observed in ≤2% of study participants in the Phase 3 bimekizumab 160mg Q4W, Phase 2/3 bimekizumab 160mg Q4W, and bimekizumab Total group.

Table 100: Markedly abnormal systolic and diastolic blood pressure during the combined Initial, Maintenance, and OLE Treatment Period (Pool SA2)

Visit	Variable Criteria	Phase 3 BKZ 160mg Q4W N=574 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/Nsub (%)	BKZ Total N=928 n/Nsub (%)
Any post-Baseline DBP value	<50 and decrease of ≥15	6/574 (1.0)	8/848 (0.9)	9/928 (1.0)

Physical examination findings

No safety concern was identified from physical examination findings including body weight over time. This remained unchanged in the updated safety data.

Electrocardiogram

QTcF increases

Pool SA1

In Pool SA1, the proportion of study participants with post-Baseline QTcF outliers was low, and no trends in QTcF increases were observed across treatment groups and no study participant had QTcF values >500ms.

Table 101: Post-Baseline QTcF Outliers (Pool SA1)

Visit	Outlier criteria	Placebo N=237 n/Nsub (%)	BKZ 160mg Q4W N=349 n/Nsub (%)
Any post-Baseline visit	QTcF >450ms	1/219 (0.5)	4/337 (1.2)
	QTcF >480ms	0/219	1/337 (0.3)
	QTcF >500ms	0/219	0/337
	QTcF increase from BL >30ms	6/218 (2.8)	12/337 (3.6)
	QTcF increase from BL >60ms	0/218	0/337
	QTcF increase from BL >90ms	0/218	0/337
	QTcF >450ms and increase from BL >30ms	0/218	2/337 (0.6)
	QTcF >500ms and increase from BL >60ms	0/218	0/337

Pool SA2

The proportion of study participants with post-Baseline QTcF outliers was low, and no clinically meaningful trends were observed in the 12-lead ECG during the combined Initial, Maintenance, and OLE Treatment Period.

Table 102: Post-Baseline QTcF outliers (Pool SA2)

Visit	Outlier criteria	Data in original submission[a]			Data in Safety Update[b]		
		Phase 3 BKZ 160mg Q4W N=574 n/N:ub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/N:ub (%)	BKZ Total N=928 n/N:ub (%)	Phase 3 BKZ 160mg Q4W N=574 n/N:ub (%)	Phase 2/3 BKZ 160mg Q4W N=848 n/N:ub (%)	BKZ Total N=928 n/N:ub (%)
Any post-Baseline visit	QTcF >450ms	6/558 (1.1)	28/830 (3.4)	37/904 (4.1)	8/562 (1.4)	31/834 (3.7)	40/908 (4.4)
	QTcF >480ms	1/558 (0.2)	8/830 (1.0)	9/904 (1.0)	1/562 (0.2)	8/834 (1.0)	9/908 (1.0)
	QTcF >500ms	0/558	4/830 (0.5)	4/904 (0.4)	0/562	4/834 (0.5)	4/908 (0.4)
	QTcF increase from BL >30ms	41/557 (7.4)	103/818 (12.6)	121/891 (13.6)	43/561 (7.7)	110/822 (13.4)	128/895 (14.3)
	QTcF increase from BL >60ms	1/557 (0.2)	26/818 (3.2)	29/891 (3.3)	1/561 (0.2)	26/822 (3.2)	29/895 (3.2)
	QTcF increase from BL >90ms	0/557	8/818 (1.0)	9/891 (1.0)	0/561	8/822 (1.0)	9/895 (1.0)
	QTcF >450ms and increase from BL >30ms	3/557 (0.5)	20/818 (2.4)	23/891 (2.6)	3/561 (0.5)	20/822 (2.4)	23/895 (2.6)
	QTcF >500ms and increase from BL >60ms	0/557	4/818 (0.5)	4/891 (0.4)	0/561	4/822 (0.5)	4/895 (0.4)

Adverse events related to ECG findings

A total of 11 study participants were identified experiencing 12 events (4 serious, 8 nonserious) coding to the PTs of cardiac arrest (1 study participant), ventricular fibrillation (1 study participant), syncope (8 study participants), and loss of consciousness (1 study participant).

Dose was not changed except for 1 event of syncope in which study medication was temporarily interrupted. None of the syncope events were associated with abnormal ECG findings.

Overall, Safety Update results were comparable to those of Pool SA2 in the original submission and the incidences of TEAEs (by PT) related to ECG measurements remained low. Syncope TEAEs increased from 8 to 9 events and 1 event each was reported for cardio-respiratory arrest and ventricular fibrillation. The new event of syncope was serious, mild, considered drug-related, and resolved without dose interruption.

The new event of cardio-respiratory arrest was serious, severe, considered not drug-related, and had a fatal outcome. The event of ventricular fibrillation was not serious, severe, considered not drug-related, and had an unknown outcome.

Both cardiac arrests were classified as not drug related.

Safety in special populations

Pregnancy and breastfeeding

There is a limited amount of data from the use of bimekizumab in pregnant women. Animal studies did not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/fetal development, parturition, or postnatal development. As a precautionary measure, it is preferable to avoid the use of bimekizumab in pregnancy. It is not known whether bimekizumab is excreted in human milk or absorbed systemically after ingestion. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for bimekizumab and any potential adverse effects on the breastfed infant from bimekizumab or from the underlying maternal condition. This is reflected in section 4.6 of the SmPC.

As of the clinical cut-off date (20 December 2021), no maternal bimekizumab exposure pregnancies were reported in the studies included in Pool SA2.

See RMP section regarding inclusion of axSpA patients in PASS PS0037.

Age

Pool SA1

The vast majority of bimekizumab-treated study participants were <65 years of age in Pool SA1 (<40 years: 51.0%, 40 to <65 years: 45.6%, and ⩾65 years: 3.4%). The subgroup analysis is limited by the number of participants ⩾65 years.

In Pool SA1, the incidences of TEAEs in the bimekizumab 160mg Q4W group were higher in the oldest age group (66.7% in the ⩾65 years age group) compared with the youngest age groups (54.5% and 59.7%, respectively, in the <40 and 40 to <65 years age groups) and the same trend was observed for the placebo group (60.0%, 52.3%, and 47.0%, respectively). The highest difference in incidence of TEAEs (⩾5%) in bimekizumab-treated study participants was observed in the SOC of Injury, poisoning, and procedural complications, which was mainly driven by the HLT Muscle, tendon and ligament injuries (<40 years, 40 to <65 years, and ⩾65 years: 0%, 0.6%, and 16.7%, respectively). A higher incidence of TEAEs (⩾5%) in the bimekizumab-treated study participants was also observed in the oldest age group compared with the youngest age groups in the SOCs of Musculoskeletal and connective tissue disorders and Nervous system disorders.

Pool SA2

In Pool SA2 the vast majority of bimekizumab-treated study participants were (<40 years: 50.9%, 40 to <65 years: 45.6%, and ⩾65 years: 3.6%, in the bimekizumab Total. The subgroup analysis is limited by the number of participants ⩾65 years.

When comparing all age groups with the oldest age group (⩾65 years), the highest differences in incidences of TEAEs (⩾5%) were in the SOCs of Musculoskeletal and connective tissue disorders (41.2% in the ⩾65 years age group compared with 18.8% and 21.3% in the <40 and 40 to <65 years age groups, respectively), Nervous system disorders (24.2% in the ⩾65 years age group compared with 10.6% and 17.0% in the <40 and 40 to <65 years age groups, respectively), and Vascular disorders (21.2% in the ⩾65 years age group compared with 4.2% and 9.7% in the <40 and 40 to <65 years age groups, respectively). Treatment-emergent AEs with a ⩾5% difference in incidence in the Musculoskeletal and connective tissue disorders (⩾5%) were in the HLTs Joint related signs and symptoms, Musculoskeletal and connective tissue pain and discomfort, and Spondyloarthropathies; these are conditions known to be more prevalent in the elderly population and, therefore, this difference is expected.

In the Safety Update (and in the original submission), the majority of bimekizumab-treated study participants in the bimekizumab Total group were <65 years of age (<40 years: 50.9%, 40 to <65 years: 45.6%, and ≥65 years: 3.6%).

The TEAEs by age group were consistent with the trends observed in the overall Pool SA2. When comparing the <40 years age group and ≥40 years to <65 years age group with the oldest age group (≥65 years), the highest differences in incidences of TEAEs (≥5%) were in the SOCs of Musculoskeletal and connective tissue disorders (22.9% and 24.3% vs 51.5%), Vascular disorders (4.9% and 10.9% vs 21.2%), and Injury, poisoning and procedural complications (13.8% and 13.0% vs 33.3%) (Table 103). Treatment-emergent AEs with a ≥5% difference in incidence in the Musculoskeletal and connective tissue disorders were in the HLTs of Joint related signs and symptoms (5.7% and 6.6% vs 15.2%) and Musculoskeletal and connective tissue pain and discomfort (8.1% and 6.9% vs 21.2%); these are conditions known to be more prevalent in the elderly population and, therefore, this difference is expected.

Table 103: TEAEs with ≥5% difference in incidence in SOC by age groups (Pool SA2)

MedDRA v19.0 System Organ Class	Data in original submission[a] BKZ Total <40 years N=472 n (%) [#]	40-<65 years N=423 n (%) [#]	≥65 years N=33 n (%) [#]	Data in Safety Update[b] BKZ Total <40 years N=472 n (%) [#]	40-<65 years N=423 n (%) [#]	≥65 years N=33 n (%) [#]
Any TEAE	387 (82.0) [1991]	377 (89.1) [1992]	30 (90.9) [185]	405 (85.8) [2415]	390 (92.2) [2304]	31 (93.9) [208]

MedDRA v19.0 System Organ Class	Data in original submission[a] BKZ Total <40 years N=472 n (%) [#]	40-<65 years N=423 n (%) [#]	≥65 years N=33 n (%) [#]	Data in Safety Update[b] BKZ Total <40 years N=472 n (%) [#]	40-<65 years N=423 n (%) [#]	≥65 years N=33 n (%) [#]
Cardiac disorders	7 (1.5) [8]	24 (5.7) [34]	4 (12.1) [8]	8 (1.7) [10]	28 (6.6) [42]	4 (12.1) [8]
Eye disorders	34 (7.2) [44]	38 (9.0) [49]	5 (15.2) [7]	41 (8.7) [55]	44 (10.4) [58]	6 (18.2) [8]
Gastrointestinal disorders	106 (22.5) [170]	113 (26.7) [185]	12 (36.4) [22]	121 (25.6) [204]	131 (31.0) [211]	12 (36.4) [22]
Hepatobiliary disorders	17 (3.6) [24]	16 (3.8) [20]	3 (9.1) [4]	25 (5.3) [35]	17 (4.0) [21]	4 (12.1) [5]
Infections and infestations	277 (58.7) [756]	264 (62.4) [675]	22 (66.7) [45]	313 (66.3) [931]	288 (68.1) [789]	22 (66.7) [45]
Injury, poisoning and procedural complications	53 (11.2) [70]	52 (12.3) [72]	8 (24.2) [10]	65 (13.8) [86]	55 (13.0) [80]	11 (33.3) [16]
Investigations	90 (19.1) [199]	63 (14.9) [106]	5 (15.2) [6]	109 (23.1) [245]	78 (18.4) [121]	5 (15.2) [12]
Metabolism and nutrition disorders	26 (5.5) [35]	43 (10.2) [67]	5 (15.2) [7]	34 (7.2) [47]	55 (13.0) [81]	7 (21.2) [9]
Musculoskeletal and connective tissue disorders	99 (21.0) [152]	94 (22.2) [176]	15 (45.5) [32]	108 (22.9) [178]	103 (24.3) [203]	17 (51.5) [36]
Nervous system disorders	50 (10.6) [76]	72 (17.0) [103]	8 (24.2) [11]	58 (12.3) [86]	84 (19.9) [119]	8 (24.2) [12]
Respiratory, thoracic and mediastinal disorders	47 (10.0) [64]	44 (10.4) [57]	6 (18.2) [6]	55 (11.7) [77]	48 (11.3) [64]	6 (18.2) [6]
Vascular disorders	20 (4.2) [20]	41 (9.7) [51]	7 (21.2) [7]	23 (4.9) [24]	46 (10.9) [57]	7 (21.2) [7]

BMI

Analysis of TEAEs by BMI was performed in Pool SA1 and Pool SA2 for the following categories: <25kg/m2, ⩾25 to <30kg/m2, and ⩾30kg/m2.

Pool SA1

In Pool SA1, 151 study participants (43.3%) had BMIs <25kg/m2, 108 study participants (30.9%) had BMIs ⩾25 to <30kg/m2, and 90 study participants (25.8%) had BMIs ⩾30kg/m2 in the bimekizumab 160mg Q4W group.

In Pool SA1, higher incidences of TEAEs were observed in the highest BMI group compared with the lower BMI groups in study participants treated with bimekizumab (⩾30kg/m2: 63.3%, <25kg/m2: 56.3%, and ⩾25 to <30kg/m2: 53.7%)

Pool SA2

In Pool SA2, 372 study participants (40.1%) had BMIs <25kg/m2, 321 study participants (34.6%) had BMIs ⩾25 to <30kg/m2, and 235 study participants (25.3%) had BMIs ⩾30kg/m2 in the bimekizumab Total group.

In pool SA2, slightly higher incidences of TEAEs in the highest BMI group compared with the lower BMIgroups were observed in the bimekizumab Total group.

These differences in incidence of TEAEs were most noticeable (⩾5%) in the HLTs Musculoskeletal and connective tissue pain and discomfort and Vascular hypertensive disorders NEC (9.5% vs 4.0% and 4.6%, in ⩾95kg vs <70kg and ⩾70 to <95kg weight groups, respectively). There was a tendency for more serious and severe TEAEs in heavier study participants driven by the Infections and infestations SOC without any clear pattern, and more drug-related TEAEs in lower body weight participants driven by the HLT Candida infections.

The Safety Update results for TEAEs by body weight were similar to the original submission. In the Safety Update (and in the original submission), 273 study participants (29.4%) weighed <70kg, 456 study participants (49.1%) weighed ≥70 to <95kg, and 199 study participants (21.4%) weighed ≥95kg in the bimekizumab Total group.

The heavier study participants (≥95kg weight group) had a higher incidence of TEAEs in the 5 SOCs of General disorders and administration site conditions (16.6% vs 8.8% and 10.1%, respectively); Injury, poisoning and procedural complications (18.6% vs 14.3% and 12.1%, respectively); Musculoskeletal and connective tissue disorders (30.7% vs 22.0% and 23.5%, respectively); Nervous system disorders (21.1% vs 16.1% and 14.0%, respectively); and Vascular disorders (13.1% vs 5.1% and 7.9%, respectively). These differences in incidence of TEAEs were most noticeable (≥5%) in the HLT of and Vascular hypertensive disorders NEC (10.1% vs 4.0% and 5.3%, respectively). Similar to the original submission, there was a tendency for more serious and severe TEAEs in heavier study participants, and more drug-related TEAEs in lower body weight participants. It is like that these TEAEs are BMI related and not related to bimekizumab.

Race

The majority of subjects in the study population were white, limiting the subgroup analyses by race.

Pool SA1

In Pool SA1, for the bimekizumab 160mg Q4W group, the incidences of TEAEs were 53.5% for White study participants, 100% for Black study participants, and 73.1% for Asian study Participants.

Table 104: Incidence of TEAEs by Race during the Initial Treatment Period Analysis Set: Pool SA1

	Placebo N=237		
MedDRA v19.0 System Organ Class High Level Term Preferred Term	White N=200 n (%) [#]	Black N=2 n (%) [#]	Asian N=33 n (%) [#]
Any TEAE	96 (48.0) [219]	1 (50.0) [1]	21 (63.6) [47]

Pool SA2

In Pool SA2, the incidences of TEAEs were 80.0% for White study participants, 100% for Black study participants, and 85.7% for Asian study participants.

Table 105: Incidence of TEAEs by Race during the Combined Initial, Maintenance, and OLE Treatment Period Analysis Set: Pool SA2

	Phase 3 BKZ 160mg Q4W N=563		
MedDRA v19.0 System Organ Class High Level Term Preferred Term	White N=476 n (%) [#]	Black N=3 n (%) [#]	Asian N=84 n (%) [#]
Any TEAE	381 (80.0) [1765]	3 (100) [13]	72 (85.7) [258]

Noticeable differences (>5% difference in incidence by SOC) in the incidence of TEAEs between White and Asian study participants are listed below (due to the low number of Black study participants [N=3], comparison between Black, White, and Asian study participants were not considered).

• Infections and infestations (62.2% and 44.0%, in White and Asian study participants, respectively)

  – HLTs >5% difference: Candida infections (10.5% and 2.4%, in White and Asian study participants, respectively); Fungal infections NEC (10.1% and 0%, in White and Asian study participants, respectively), Lower respiratory tract and lung infections (7.4% and 0%, in White and Asian study participants, respectively), Upper respiratory tract infections (34.9% and 21.4%, in White and Asian study participants, respectively), and Viral infections NEC (11.5% and 1.2%, in White and Asian study participants, respectively)

• Investigations (15.6% and 31.0%, in White and Asian study participants, respectively)

  – HLTs >5% difference: Liver function analyses (9.5% and 17.9%, in White and Asian study participants, respectively)

• Vascular disorders (8.2% and 0%, in White and Asian study participants, respectively)

  – HLTs >5% difference: Vascular hypertensive disorders NEC (6.2% and 0%, in White and Asian study participants, respectively)

In the other 3 SOCs, the differences in the incidence of TEAEs (⩾5% difference in groups) were not driven by a particular HLT:

• Eye disorders (7.8% and 13.1%, in White and Asian study participants, respectively)

• Musculoskeletal and connective tissue disorders (23.5% and 8.3%, in White and Asian study participants, respectively)

• Nervous system disorders (14.5% and 7.1%, in White and Asian study participants, respectively)

Incidences of the most frequently reported TEAEs by PT in White and Asian study participants were: nasopharyngitis (15.8% and 3.6%, respectively) and upper respiratory tract infection (9.2% and 10.7%, respectively).

In the Safety Update, 88.9% of study participants were White, 0.3% were Black, 9.1% were Asian, and 1.7% were 'Other' in the bimekizumab Total group.

Due to the small number of Black participants (N=3), comparisons between Black, White, and Asian study participants were not considered. Notable differences in incidence of TEAEs (≥5%) in White compared with Asian bimekizumab-treated study participants were observed in the SOCs of Infections and infestations (67.9% vs 58.3%, respectively); Blood and lymphatic system disorders (5.7% vs 11.9%, respectively); Eye disorders (9.1% vs 16.7%, respectively); Investigations (18.4% vs 42.9%, respectively); Musculoskeletal and connective tissue disorders (25.5% vs 13.1%, respectively); Nervous system disorders (16.6% vs 10.7%, respectively); Respiratory, thoracic and mediastinal disorders

(10.9% vs 19.0%, respectively); Skin and subcutaneous tissue disorders (25.0% vs 31.0%, respectively); and Vascular disorders (9.1% vs 1.2%, respectively). Treatment-emergent AEs with a ≥5% difference in incidence between White and Asian participants in the Infections and infestations SOC were in the HLTs of Abdominal and gastrointestinal infections (2.7% vs 9.5%, respectively), Candida infections (11.4% vs 2.4%, respectively), Fungal infections NEC (10.7% vs 0%, respectively), Lower respiratory tract and lung infections (8.1% vs 1.2%, respectively), Tinea infections (1.9% vs 7.1%, respectively), Upper respiratory tract infections (39.2% vs 31.0%, respectively), Urinary tract infections (5.3% vs 0%, respectively), and Viral infections NEC (19.2% vs 6.0%, respectively).

This is similar to the initial submission.

Gender

In Pool SA2, 672 study participants (72.4%) were male and 256 study participants (27.6%) were female in the bimekizumab Total group. The number of male study participants was more than twice as high as the number of female study participants; this was as expected due to higher male prevalence in AS.

Incidences of the most frequently reported TEAE by PT were similar in female and male study participants: nasopharyngitis (14.1% [EAIR: 9.3/100 participant-years] and 15.0% [EAIR: 8.0/100 participant-years], respectively). Incidences of the other most frequently reported TEAEs by PT were slightly higher in female compared with male study participants: oral candidiasis (10.9% [EAIR: 7.0/100 participant-years] vs 7.0% [EAIR: 3.4/100 participant-years], respectively) and upper respiratory tract infection (11.7% [EAIR: 7.7/100 participant-years] and 8.5% [EAIR: 4.2/100 participant-years], respectively).

There was no significant gender-based differences in TEAEs seen in the updated safety data.

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.

The Safety Update results for TEAEs by geographic region (North America, Western Europe, Eastern Europe, Asia) were similar to the original submission with no concerning findings seen.

Baseline DMARDs

Pool SA1

In Pool SA1, in the bimekizumab 160mg Q4W group, the incidence of TEAEs was higher in study participants who were using csDMARDs at Baseline compared with study participants who were not using csDMARDs at Baseline (62.3% vs 55.9%, respectively).

Table 106: Incidence of TEAEs by Baseline Synthetic DMARD Use during the Initial Treatment Period Analysis Set: Pool SA1

	Placebo N=237		BKZ 160mg Q4W N=349	
MedDRA v19.0 System Organ Class High Level Term Preferred Term	Yes N=51 n (%) [#]	No N=186 n (%) [#]	Yes N=77 n (%) [#]	No N=272 n (%) [#]
Any TEAE	23 (45.1) [38]	96 (51.6) [230]	48 (62.3) [128]	152 (55.9) [382]

Pool SA2

In Pool SA2, in the bimekizumab Total group, the incidence of TEAEs was lower in study participants who were using csDMARDs compared with study participants who were not using csDMARDs at Baseline (80.9% vs 86.9%, respectively).

Table 107: Incidence of TEAEs by Baseline Synthetic DMARD Use during the Combined Initial, Maintenance, and OLE Treatment Period Analysis Set: Pool SA2

	Phase 3 BKZ 160mg Q4W N=574	
MedDRA v19.0 System Organ Class High Level Term Preferred Term	Yes N=127 n (%) [#]	No N=447 n (%) [#]
Any TEAE	93 (73.2) [441]	372 (83.2) [1659]

Treatment-emergent AEs were summarized for study participants by csDMARD subgroup. The Safety Update results for TEAEs by csDMARD subgroup were similar to the original submission.

In the Safety Update, 208 of 928 study participants (22.4%) were using csDMARDs at Baseline in the bimekizumab Total group. The incidence of TEAEs was slightly lower in study participants who were using csDMARDs compared with study participants who were not using csDMARDs at Baseline (86.1% vs 89.9%, respectively).

Safety related to drug-drug interactions and other interactions

No DDI studies have been conducted with bimekizumab. Given the mode of action of bimekizumab and studies conducted with other IL-17 and IL-23 antibodies, minimal impact is expected on the exposure of drugs metabolized by the cytochrome P450 (CYP450) system. Population PK modeling found no evidence of a significant impact for use of medications concomitantly administered with bimekizumab in rheumatologic indications (MTX, corticosteroids, or csDMARDs) on bimekizumab.

Discontinuation due to adverse events

Pool SA1

In Pool SA1, the incidence of TEAEs leading to discontinuation was similar in the bimekizumab 160mg Q4W group (2.3%) compared with the placebo group (2.1%).

Table 108: Incidence of TEAEs leading to study discontinuation per 100 participant-years by SOC and PT during the Initial Treatment Period (Pool SA1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=237 100 participant-yrs=0.73 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=349 100 participant-yrs=1.09 n (%) [#] EAIR (95% CI)
Any TEAE leading to discontinuation	5 (2.1) [5] 6.9 (2.2, 16.1)	8 (2.3) [8] 7.4 (3.2, 14.6)
Blood and lymphatic system disorders	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Lymphoid tissue hyperplasia*	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Eye disorders	2 (0.8) [2] 2.8 (0.3, 9.9)	0
Uveitis	2 (0.8) [2] 2.8 (0.3, 9.9)	0
Gastrointestinal disorders	1 (0.4) [1] 1.4 (0.0, 7.6)	1 (0.3) [1] 0.9 (0.0, 5.1)
Crohn's disease	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Colitis ulcerative	1 (0.4) [1] 1.4 (0.0, 7.6)	0
Infections and infestations	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Oral candidiasis	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Investigations	2 (0.8) [2] 2.7 (0.3, 9.9)	3 (0.9) [3] 2.8 (0.6, 8.1)
Psychiatric evaluation abnormal	2 (0.8) [2] 2.7 (0.3, 9.9)	3 (0.9) [3] 2.8 (0.6, 8.1)
Nervous system disorders	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Dizziness	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Skin and subcutaneous tissue disorders	0	1 (0.3) [1] 0.9 (0.0, 5.1)
Rash	0	1 (0.3) [1] 0.9 (0.0, 5.1)

Pool SA2

In Pool SA2, the incidence of TEAEs leading to discontinuation was 6.9% (EAIR: 3.4/100 participant-years) in the bimekizumab Total group. The incidence of treatment-emergent AEs leading to study discontinuation per 100 participant years did not increase between the Initial Treatment Period (EAIR: 7.4/100 participant-years in the bimekizumab 160mg Q4W group in Pool SA1) and the longer-term combined Initial, Maintenance, and OLE Treatment Period (EAIR: 3.1/100 participant-years in the Phase 3 bimekizumab 160mg Q4W group in Pool SA2).

The incidence of TEAEs leading to discontinuation was 7.7% of study participants in the bimekizumab Total group in the Safety Update; the EAIR for TEAEs leading to discontinuation in the Safety Update (3.2/100 participant-years) was lower than in the original submission (3.4/100 participant-years), indicating no increase in TEAEs leading to discontinuation over time.

A total of 6 additional TEAEs leading to discontinuation were reported, including latent TB (2 events), cardio-respiratory arrest, skin infection, psychiatric evaluation abnormal, anxiety, and dermatitis allergic (1 event each); 1 TEAE PT of aphthous ulcer was updated to oral candidiasis in the Safety Update.

Table 109: Incidence of TEAEs leading to study discontinuation per 100 participant-years in at least 2 participants by PT during the Combined Initial, Maintenance, and OLE Treatment Periods (Pool SA2)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Any TEAE leading to discontinuation	23 (4.0) [23] 3.1 (2.0, 4.7)	47 (5.5) [50] 2.8 (2.0, 3.7)	64 (6.9) [69] 3.4 (2.6, 4.3)	26 (4.5) [26] 2.6 (1.7, 3.8)	54 (6.4) [57] 2.7 (2.0, 3.5)	71 (7.7) [76] 3.2 (2.5, 4.0)
Gastrointestinal disorders	3 (0.5) [3] 0.4 (0.1, 1.2)	10 (1.2) [10] 0.6 (0.3, 1.1)	16 (1.7) [16] 0.8 (0.5, 1.4)	2 (0.3) [2] 0.2 (0.0, 0.7)	9 (1.1) [9] 0.4 (0.2, 0.8)	15 (1.6) [15] 0.7 (0.4, 1.1)
Crohn's disease	2 (0.3) [2] 0.3 (0.0, 1.0)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.3) [2] 0.2 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)
Aphthous ulcer	1 (0.2) [1] 0.1 (0.0, 0.7)	3 (0.4) [3] 0.2 (0.0, 0.5)	5 (0.5) [5] 0.3 (0.1, 0.6)	0	2 (0.2) [2] 0.1 (0.0, 0.4)	4 (0.4) [4] 0.2 (0.0, 0.5)
Glossodynia	0	0	2 (0.2) [2] 0.1 (0.0, 0.4)	0	0	2 (0.2) [2] 0.1 (0.0, 0.3)
Tongue coated	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)
Infections and infestations	6 (1.0) [6] 0.8 (0.3, 1.7)	12 (1.4) [12] 0.7 (0.4, 1.2)	17 (1.8) [17] 0.9 (0.5, 1.4)	8 (1.4) [8] 0.8 (0.3, 1.6)	16 (1.9) [16] 0.8 (0.5, 1.3)	21 (2.3) [21] 0.9 (0.6, 1.4)
Oral candidiasis	4 (0.7) [4] 0.5 (0.1, 1.4)	4 (0.5) [4] 0.2 (0.1, 0.6)	5 (0.5) [5] 0.3 (0.1, 0.6)	5 (0.9) [5] 0.5 (0.2, 1.2)	5 (0.6) [5] 0.2 (0.1, 0.6)	6 (0.6) [6] 0.3 (0.1, 0.6)
Latent tuberculosis	0	0	0	0	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)

MedDRA v19.0 System Organ Class Preferred Term	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=7.47 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=17.01 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=19.07 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=574 100 participant-yrs=10.03 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=848 100 participant-yrs=20.34 n (%) [#] EAIR (95% CI)	BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR (95% CI)
Investigations	5 (0.9) [5] 0.7 (0.2, 1.6)	8 (0.9) [9] 0.5 (0.2, 0.9)	10 (1.1) [12] 0.5 (0.3, 1.0)	6 (1.0) [6] 0.6 (0.2, 1.3)	9 (1.1) [10] 0.4 (0.2, 0.8)	11 (1.2) [13] 0.5 (0.2, 0.9)
Alanine aminotransferase increased	0	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.2 (0.0, 0.5)	0	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.3) [3] 0.1 (0.0, 0.4)
Aspartate aminotransferase increased	0	1 (0.1) [1] 0.1 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	1 (0.1) [1] 0.0 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.3)
Hepatic enzyme increased	0	1 (0.1) [1] 0.1 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.4)	0	1 (0.1) [1] 0.0 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.3)
Psychiatric evaluation abnormal	5 (0.9) [5] 0.7 (0.2, 1.6)	5 (0.6) [5] 0.3 (0.1, 0.7)	5 (0.5) [5] 0.3 (0.1, 0.6)	6 (1.0) [6] 0.6 (0.2, 1.3)	6 (0.7) [6] 0.3 (0.1, 0.6)	6 (0.6) [6] 0.3 (0.1, 0.6)
Psychiatric disorders	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.3) [2] 0.2 (0.0, 0.7)	3 (0.4) [3] 0.1 (0.0, 0.4)	4 (0.4) [4] 0.2 (0.0, 0.5)
Suicidal ideation	1 (0.2) [1] 0.1 (0.0, 0.7)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.4)	1 (0.2) [1] 0.1 (0.0, 0.6)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)
Skin and subcutaneous tissue disorders	2 (0.3) [2] 0.3 (0.0, 1.0)	6 (0.7) [6] 0.4 (0.1, 0.8)	8 (0.9) [8] 0.4 (0.2, 0.8)	2 (0.3) [2] 0.2 (0.0, 0.7)	7 (0.8) [7] 0.3 (0.1, 0.7)	9 (1.0) [9] 0.4 (0.2, 0.8)
Dermatitis allergic	1 (0.2) [1] 0.1 (0.0, 0.7)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.1) [1] 0.1 (0.0, 0.3)	1 (0.2) [1] 0.1 (0.0, 0.6)	2 (0.2) [2] 0.1 (0.0, 0.4)	2 (0.2) [2] 0.1 (0.0, 0.3)

Post marketing experience

Cumulatively since the approval on 20 August 2021 up to the data lock point on 19 February 2022, the post-authorisation patient exposure outside of clinical studies to bimekizumab is estimated to be approximately 588 patient-years. During the interval of the Bimzelx PSUR (20 August 2021 to 19 February 2022), no safety related findings have been identified.

2.5.1. Discussion on clinical safety

The spondyloarthritis program included 2 pivotal phase 3 studies including participants with nr-axSpA or AS to address the efficacy and safety profile in both subpopulations (AS0010 and AS0011).and a phase 3 open label extension study (OLE AS0014). Phase 2 studies were conducted in participants with AS and not in participants with nr-axSpA.

The safety assessment focuses on integrated safety data in the following data pools:

- Pool SA1 is the primary safety pool used to summarise the safety of bimekizumab compared with placebo through Week 16 of the Double-Blind Treatment Period in Phase 3 studies AS0010 and AS0011.
- Pool SA2 provides the most comprehensive overview of safety in axSpA by including all Phase 2 and Phase 3 data from nr-axSpA and AS studies.
- Pool SA3 is provided as an overview of safety across the BKZ development program.

The full week 52 data set was made available upon CHMP's request and is further discussed below.

A total of 928 adult study participants with active axSpA received bimekizumab.

Pool SA1 consisted of a total of 586 study participants; 349 participants (128 participants with nr-axSpA [AS0010] and 221 with AS [AS0011]) were exposed to bimekizumab and 237 participants (126 with nr-axSpA [AS0010] and 111 with AS [AS0011]) were exposed to placebo, with the total time at risk accounting for 108.6 participant-years in the bimekizumab 160mg Q4W group and 73.0 participant-years in the placebo group.

Pool SA2 consisted of a total of 928 study participants; 574 participants with nr-axSpA (244 participants) or AS (330 participants) from the Phase 3 program of which 351 participants had entered the OLE AS0014 at the cut-off date, and 354 participants with AS from the Phase 2 program (303 participants from AS0008 of which 255 had entered the OLE AS0009 at the cut-of date, and 51 participants from AS0013), with 588 study participants in the bimekizumab Total group exposed to bimekizumab for at least 12 months, and a total time at risk accounting for 1907.5 participant-years.

The extent of exposure of all axSpA patients to BKZ complies with the requirements described in ICH E1 Population Exposure (300-600 exposed for 6 months and 100 patients exposed for a minimum of one year). Additional long-term data was considered necessary by the CHMP to detect late developing ADRs, increased incidences to an already increased background rate of comorbidities and low-frequency adverse drug reactions, thus the MAH was requested to submit the full week 52 safety data set.

Regarding long term exposure, an OLE study AS0014was ongoing. An update on available safety data was provided and did not negatively impact the safety of bimekizumab.

Demographic and Baseline characteristic variables were presented by treatment group for Pool SA1 and Pool SA2 and were generally well balanced. There was a larger proportion of male participants compared to female participants which reflects the disease in the population. The majority of subjects in SA1 (82.9%) in the study population were white, under representation of Black or African Americans in the AS

and nr-axSpA development program was raised as a concern. Nevertheless, this is accounted for by low HLA levels and lower disease rates in this population. Further, there is currently no evidence of a difference in safety between populations.

Regarding background disease characteristics, in Pool SA1, the majority of study participants (93.7% in the bimekizumab 160mg Q4W group and 91.1% in the placebo group) reported a previous or ongoing medical condition at baseline. The most frequently reported conditions/diseases at Baseline in all study participants were in the SOCs of Musculoskeletal and connective tissue disorders (64.5%).

The most frequently reported medical history conditions at Baseline ⩾5% by PT in All participants (bimekizumab 160mg Q4W or the placebo) were tendonitis (27.5%), arthritis (22.4%), hypertension (20.5%); peripheral arthritis (15.7%), uveitis (12.3%), vitamin D deficiency (8.2%), seasonal allergy (7.5%), psoriasis (7.0%), osteoarthritis (6.8%), gastro-oesophageal reflux disease (6.7%), dactylitis (6.5%), latent tuberculosis (6.3%), hypercholesterolaemia (6.0%), asthma (5.8%), obesity (5.6%), depression (5.5%), and drug hypersensitivity (5.1%). Previous or ongoing medical history conditions in Pool SA2 study participants were similar in the Safety Update and the original submission and are consistent with what is expected for this patient population.

Comorbidities at baseline reflect the peripheral and extra-articular manifestations in patients with axSpA as well as other frequent comorbidities like metabolic syndrome (hypertension and obesity) and hyperlipidemia (hypercholesterolaemia).

In pool SA1, TEAEs were reported at a higher incidence in the bimekizumab 160mg Q4W group compared with the placebo group (57.3% vs 50.2%). The incidence of serious TEAEs was low overall and similar in the bimekizumab 160mg Q4W group (1.1%) compared with the placebo group (0.8%).

In pool SA2, the majority of study participants in the bimekizumab Total group (85.6%; EAIR: 155.6/100 participant-years) reported a TEAE. Exposure-adjusted-incidence-rates of serious TEAEs were 10.8%; EAIR: 5.6/100 participant-years. When adjusted for exposure for serious TEAEs in the Phase 3 bimekizumab group in Pool SA2 (EAIR: 5.4/100 participant-years [95% CI: 3.9, 7.4]), there was a small numerical increase (with overlapping CI) in incidence rate with longer exposure compared to Pool SA1 (EAIR: 3.7/100 participant-years [95% CI: 1.0, 9.5]). When adjusting for exposure for severe TEAEs in the Phase 3 bimekizumab group in Pool SA2 (EAIR: 4.0/100 participant-years [95% CI: 2.7, 5.7]), there was a small numerical increase (with overlapping CI) in incidence rate with longer exposure compared to Pool SA1 (EAIR: 2.8/100 participant-years [95% CI: 0.6, 8.1])

The incidences of TEAEs were higher in this Safety Update (52-week data) compared with the original submission, which is expected given the longer treatment duration and resulting increased total time at risk in the bimekizumab Total group (2241.1 vs 1907.5 participant-years, respectively). However, the EAIRs for the TEAE categories in the Safety Update are similar to or lower than those in the original submission and therefore do not indicate an increase in risk with longer exposure to bimekizumab.

TEAEs were most frequently reported in the SOC of Infections and infestations. The most frequently reported TEAEs in bimekizumab-treated study participants in both pools were nasopharyngitis, upper respiratory tract infection, and oral candidiasis. These are known adverse events, throughout the development programme for bimekizumab, and are listed in section 4.8 of the SmPC. Upon CHMP's request, the warning on infections included in section 4.4 of the SmPC was updated to reflect that patients developing an infection should be carefully monitored that treatment should be discontinued if the infection becomes serious or is not responding to standard therapy until the infection resolves.

Potential Hy's Law was the only AESI defined for the axSpA program. Potential Hy's Law, defined as ≥3x ULN ALT or AST with coexisting ≥2xULN total bilirubin in the absence of ≥2xULN alkaline phosphatase (ALP), with no alternative explanation for the biochemical abnormality. A review of **hepatic TEAEs** in Pool SA1 and Pool SA2 was performed using the MedDRA SMQ "Drug related hepatic disorders"

(excluding sub-SMQs "Liver neoplasms, benign [incl cysts and polyps]" and "Liver neoplasms, malignant and unspecified"). When adjusted for exposure, no increased incidence rate of a hepatic TEAEs was observed in the Phase 3 bimekizumab 160mg Q4W group from Pool SA2 (EAIR: 7.2/100 participant-years) when compared with the bimekizumab 160mg Q4W group from Pool SA1 (EAIR: 16.2/100 participant-years).

The incidence of hepatic TEAEs in the Safety update was 13.6% in the bimekizumab Total group; the EAIRs were similar in the Safety Update (6.3/100 participant-years) and the original submission (6.7/100 participant-years), thus indicating no increase in risk with longer exposure to bimekizumab.

In pool SA1 One case met Hy's Law laboratory criteria but was not a confirmed as a Hy's Law case due to a clinical and serological diagnosis of viral hepatitis A infection.

The most frequently reported **infections** in the axSpA development program were nasopharyngitis, upper respiratory tract infection, and oral candidiasis. When adjusted for exposure, no increased incidence rate of infections TEAEs was observed in the Phase 3 bimekizumab 160mg Q4W group from Pool SA2 (EAIR: 68.3/100 participant-years) when compared with the Pool SA1 bimekizumab 160mg Q4W group (EAIR: 119.4/100 participant-years).

The incidences of fungal infections were lower compared to the incidences in the studies for the PSO indication in which a higher BKZ dose has been used.

Participants reported as having ongoing infection at the time of the original submission have either recovered or have persistent mild infection. Rates of vulvovaginal mycotic infection were similar between placebo and treatment arms and appear to be in keeping with rates in the general population.

Section 4.8 of the SmPC was updated to reflect that infections rates observed in axSpA (nr-axSpA and AS) phase 3 clinical studies were similar to those observed in plaque psoriasis apart from oral and oropharyngeal candidiasis rates in patients treated with bimekizumab at 3.7% and 0.3% respectively (0% in the placebo group).

In pool SA1, no adjudicated **MACE** or extended MACE were reported in the bimekizumab 160mg Q4W group or with placebo. In Pool SA2, the overall incidence of adjudicated MACE was low, occurring in 4 study participants (0.4%; EAIR: 0.2/100 participant-years). Adjudicated MACE included cardiac arrest, cerebrovascular accident, acute myocardial infarction, and coronary artery stenosis (0.1%; EAIR: 0.1/100 participant-years each).

The overall incidence of adjudicated MACE in the Safety Update was 0.5% in the bimekizumab Total group; the EAIR of adjudicated MACE in the Safety Update was consistent with the original submission (0.2/100 participant-years each).

One additional participant in the Safety Update experienced 3 concurrent events adjudicated as MACE (sudden cardiac death): cardio-respiratory arrest, ventricular fibrillation, and dyspnoea (0.1%; EAIR: 0.0/100 participant-years each. The event of cardio-respiratory arrest was serious, severe, assessed as not drug-related by the Investigator, and fatal. It is accepted that this was not drug related.

At the time of the DLP one participant was classified as experiencing MACE that was 'extended' This relates to a participant requiring PCI and stenting and has now resolved.

The incidence of **IBD** in pool SA2 (0.8/100 PY) was higher than that observed during the PSO development program (0.055/100 PY in the Pool S2 in the PSO MAA). Though, was not elevated beyond background rates reported in literature. IBD should continue to be closely monitored in future PSURs. The incidence for any definite or probable adjudicated IBD in the Safety Update was 1.8% in the bimekizumab Total group; the EAIR in the Safety Update was consistent with the original submission (0.8/100 participant-years each), indicating no increase in risk with longer exposure to bimekizumab.

In Pool SA1, no **malignancy** TEAE was reported in the bimekizumab 160mg Q4W group or in the placebo group. In Pool SA2, the overall incidence of malignancies was low, occurring in 6 study participants (0.6%; EAIR: 0.3/100 participant-years) in the bimekizumab Total group. No further malignancies were seen in the updated safety data.

In Pool SA1, **hypersensitivity** reactions were reported at a higher incidence in the bimekizumab 160mg Q4W group (6.0%; EAIR: 19.9/100 participant-years) compared with the placebo group (2.1%; EAIR: 6.9/100 participant-years). In Pool SA2, the incidence of hypersensitivity reactions in the combined Initial, Maintenance, and OLE Treatment Period was 13.5% (EAIR: 7.2/100 participant years) in the bimekizumab Total group.

The incidence for hypersensitivity reactions in the Safety Update was 15.6% in the bimekizumab Total group; the EAIR in the Safety Update was consistent with the original submission (7.2/100 participant-years), indicating no increased risk with longer exposure to bimekizumab.

One participant had a severe hypersensitivity reaction described as 'skin allergic rash' which was unresolved at the DLP. The study drug was discontinued for this participant, and they were referred to a dermatologist. No further information has been received on the participant since their Early Termination Visit in 2020.

The MAH was asked to discuss in more detail why rash (2.3% in the BKZ group in pool SA1 versus 0.4% in the placebo group) was not included in the list of adverse drug reactions in the SmPC. The majority of cases were considered unrelated to bimekizumab by the Investigator. Though, about 30% were considered related by the investigator. As requested, a detailed causality assessment was performed by the MAH and section 4.8 of the SmPC was updated with 'rash' included as a common ADR.

Regarding **Immunogenicity** to bimekizumab, the low number of participants does not allow definitive conclusions but a trend of increased incidence of hypersensitivity reaction TEAEs linked to ADAb positivity was observed. Therefore, the following sentence has been added to section 4.8 of the SmPC 'Across indications, no clinically meaningful impact on clinical response was associated with anti-bimekizumab antibodies development and an association between immunogenicity and treatment emergent adverse events has not been clearly established.'

In Pool SA1, the incidence of **neutropenia** TEAEs reported in the bimekizumab 160mg Q4W group was low (0.6%; EAIR: 1.8/100 participant-years). No study participant in the bimekizumab 160mg Q4W group had a TEMA neutrophil value ($<1.0x10^9$/L). In Pool SA2, 11 study participants (1.2%) in the bimekizumab Total group had a TEMA neutrophils low count ($<1.0x10^9$/L), 2 were reported as pseudoneutropenia.

A spike in neutropenia was noted between January and March 2021. This has been attributed to 'pseudoneutropenia' from exposure of samples to low temperatures. A plausible mechanism of action has been provided. There are no significant changes to rates of neutropenia in the updated safety data. It is accepted that those seen are likely 'pseudoneutropenia' and not drug related. The section 4.8 of the SmPC was updated to reflect that the frequency of neutropenia in axSpA (nr-axSpA and AS) clinical studies was similar to that observed in plaque psoriasis studies.

Upon CHMP's request, the MAH agreed to include PsA patients and axSpA patients in the PS0037 study. This will likely increase the sample size. See RMP section below.

Overall, the summary of the safety profile is consistent with the important identified risks mentioned in the **Safety Specification** of the Risk management plan. At this time, additional updates to the summary of safety concerns are not warranted.

2.5.2. Conclusions on clinical safety

The 52-week safety data is in line with what was presented in the original submission and uncertainties regarding the possibility of delayed or rare safety issues with long-term use of bimekizumab in an active axial spondyloarthiritis population have been alleviated. However, this population will be included in the ongoing PASS study to allow for long-erm monitoring of safety (see RMP section).

From the available safety data, the safety profile in the axial spondyloarthritis population is acceptable and was generally comparable with that established in the psoriasis population. Upon CHMP's request, the addition of rash as a common adverse drug reaction has been made in section 4.8 of the SmPC.

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 PRAC considered that the risk management plan version 1.8 is acceptable.

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, and axSpA patients compared to PSO, PsA, and axSpA patients exposed to other biologics (eg, anti-TNF, anti-IL-23, but not anti-IL-17).	Serious infections Serious hypersensitivity reactions MACE Malignancy IBD	Final protocol	Draft protocol submitted on 16 Dec 2022, final CHMP opinion received on 30 Mar 2023. Revised protocol to be submitted within 3 months after approval of PsA and axSpA indications in 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	Draft protocol submitted on 25 Nov 2021, final CHMP opinion received on 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

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
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; Revised protocol to be submitted within 3 months after approval of PsA and axSpA indications in EU.
			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	31 May 2023
			Submission of final clinical study report	31 Dec 2024
PS0015 (EudraCT Number: 2017-003784-35) A multicenter, randomized, double-blind, secukinumab-controlled, parallel-	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	Submission of interim clinical study report	31 Jan 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque PSO Ongoing		assessments. The study will also address missing information item of long-term safety	Submission of final clinical study report	31 Jul 2024
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

Risk minimisation measures

Safety concern	Routine risk minimization activities
Important identified risks	

Safety concern	Routine risk minimization activities
Serious infections	**Routine risk communication**: Use of bimekizumab is contraindicated in patients with clinically important active infections (eg, active tuberculosis) (SmPC Section 4.3). Risk of infections is discussed in SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Bimzelx) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendation for monitoring of infections are included in SmPC Section 4.4 (Special warnings and precautions for use) Instructions to look out for signs of serious infections are included in PL Section 2 (What you need to know before you use Bimzelx) Do not use Bimzelx if you have an infection, including tuberculosis (TB), which your doctor thinks is important (PL Section 2 What you need to know before you use Bimzelx) Recommendation to talk to the doctor, pharmacist or nurse for patients who have infections are included in PL Section 2 (What you need to know before you use Bimzelx) Serious infections are included in PL Section 4 (Possible side effects) **Other routine risk minimization measure beyond the Product Information:** 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).
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	**Routine risk communication**: SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) PL Section 2 (What you need to know before you use Bimzelx) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Recommendations for monitoring of inflammatory bowel disease are included in SmPC Section 4.4 (Special warnings and precautions for use) PL Section 2 (What you need to know before you use Bimzelx) **Other routine risk minimization measure beyond the Product Information:** 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)
Important potential risks	

Safety concern	Routine risk minimization activities
Serious hypersensitivity reactions	**Routine risk communication**: SmPC Section 4.3 (Contraindication) SmPC Section 4.4 (Warnings and Precautions) PL Section 2 (What you need to know before you use Bimzelx) PL Section 4 (Possible side effects) **Routine risk minimization activities recommending specific clinical measures to address the risk:** Serious hypersensitivity reactions are included in PL Section 4 (Possible side effects) Instructions to look out for allergic reactions are included in PL Section 2 (What you need to know before you use Bimzelx) Patients who are allergic to bimekizumab or any of the other ingredients of this medicine must not use Bimzelx (PL Section 2 What you need to know before you use Bimzelx) **Other routine risk minimization measure beyond the Product Information:** 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)
Major adverse cardiovascular events	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** 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)
Malignancies	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** 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)
Missing information	

Safety concern	Routine risk minimization activities
Use during pregnancy and lactation	**Routine risk communication**: SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) PL Section 2 (What you need to know before you use Bimzelx) **Routine risk minimization activities recommending specific clinical measures to address the risk:** SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) PL Section 2 (What you need to know before you use Bimzelx) **Other routine risk minimization measure beyond the Product Information:** 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)
Long-term safety	**Routine risk communication**: None **Routine risk minimization activities recommending specific clinical measures to address the risk:** None **Other routine risk minimization measure beyond the Product Information:** 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)

2.7. Update of the Product information

As a consequence of this new indication, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC have been updated. The Package Leaflet has been updated accordingly.

Changes were also made to the PI to bring it in line with the current Agency/QRD template which were reviewed and accepted by the CHMP.

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. 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

Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases (including axial spondyloarthritis [axSpA], psoriatic arthritis [PsA], reactive arthritis, the arthritis of inflammatory bowel disease [IBD], and undifferentiated SpA) that have features in common with each other and distinct from other inflammatory arthritides, particularly rheumatoid arthritis.

Axial spondyloarthritis (axSpA) comprises diseases with mainly axial involvement (sacroiliac [SI] joints and spine), including:

- Ankylosing spondylitis (AS; also known as radiographic axSpA [r-axSpA]) requires a diagnosis of definite radiographic damage of the SI joints, as demonstrated by radiographic evidence.
- Nonradiographic axSpA (nr-axSpA) where there is no definite radiographic damage on the SI joints.

3.1.2. Available therapies and unmet medical need

The goals of treatment of nr-axSpA and AS are to reduce symptom severity, maintain spinal flexibility and normal posture, reduce functional limitations, maintain work ability, decrease disease complications, and to slow progression of structural damage.

The mainstays of treatment have been nonsteroidal anti-inflammatory drugs (NSAIDs) as first line pharmacological treatment besides physical therapy, and exercise. Treatment with NSAIDs is effective for the symptoms (pain and stiffness) of axSpA, but many patients lose or never have a clinically meaningful response, and structural damage often progresses despite their use.

Therapy options for axSpA are limited because conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) eg, methotrexate and sulfasalazine or systemic glucocorticoids are not effective for the treatment of axial symptoms. Sulfasalazine may be considered in patients with peripheral arthritis. Intra-articular corticosteroids may be used for sacroiliac or peripheral joint inflammation whereas systemic corticosteroids in general are of little benefit.

Patients with active AS who are intolerant of or have inadequately responded to NSAIDs, or those in whom NSAIDs are contraindicated, have approved treatment options such as TNFα inhibitors. Additionally, the IL-17 cytokine family has been identified as a therapeutic target in axSpA. Janus kinase inhibitors have recently been approved for the treatment of patients with active axSpA.

Whilst those agents are effective in reducing core signs and symptoms of axSpA, many patients still do not achieve full control of disease including low disease activity/remission and EAMs. Suboptimal responses and residual inflammation drive disease activity and structural disease progression; thus, chronic untreated disease may limit the effectiveness of treatment.

In summary, spondyloarthritis is a degenerative musculo-skeletal condition for which many patients do not achieve relief through available therapies. As such, there is an unmet medical need for alternative therapies for this condition.

3.1.3. Main clinical studies

With this submission, the MAH seeks a new indication for bimekizumab for the treatment of axial spondylarthritis (nr-axSpA and AS). The recommended dose of bimekizumab is 160 mg every 4 weeks.

In support of the sought indication, the MAH is providing:

i) supportive data from study AS0008 and its long-term extension study AS0009;

ii) confirmatory evidence from two pivotal 52-week phase 3 studies AS0010 and AS0011.

and the ongoing open label extension study AS0014.

AS0008 was a Phase 2b, multicentre, randomised, double-blind, placebo-controlled, parallel-group, dose-ranging study to investigate the efficacy, safety, PK, and PD of bimekizumab compared with placebo in adult study participants with active AS. Study participants were randomised 1:1:1:1:1 to 1 of 5 groups; placebo or bimekizumab 16mg, 64mg, 160mg, or 320mg sc Q4W. Study participants who completed the 48-week AS0008 study were eligible to enter the open label extension study **AS0009** which has a 4-year duration, investigating long term safety, tolerability and efficacy of bimekizumab.

AS0010 was a multicentre, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in subjects with nr-axSpA. To be eligible to participate in this study, study participants must have had active adult-onset axSpA meeting ASAS classification criteria, with inflammatory back pain for at least 3 months prior to the Screening Visit and an age at symptom onset of <45 years. Study participants must have had objective inflammation, defined by sacroiliitis on the Screening MRI according to ASAS/Outcome Measures in Rheumatology Clinical Trials (OMERACT) scoring and/or elevated CRP. Study participants must not have had radiographic sacroiliitis as defined by modified New York (mNY) criteria.

AS0011 is a multicentre, Phase 3, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in study participants with active AS, a subtype of axSpA with radiographic sacroiliitis (r-axSpA). To be eligible to participate in this study, study participants must have been adults with a diagnosis of active AS (as defined), including at least 3 months of symptoms and age at symptom onset <45 years, and moderate to severe active disease at Baseline.

Study participants who completed Week 52 of AS0010 and AS0011 may be eligible for enrolment in an OLE study (AS0014) with bimekizumab.

The primary efficacy endpoint for both pivotal phase 3 studies (AS0010 and AS0011) was the ASAS40 response at Week 16.

3.2. Favourable effects

Bimekizumab dose of 160 mg Q4W selected for the phase 3 pivotal AS0010 and AS0011 studies comes from the phase 2 AS0008 study.

A statistically significant higher proportion (95% CI) of patients in the bimekizumab 160 mg Q4W group reached ASAS40 at week 16 in comparison to the placebo group: 47.7 (37.3, 57.7) % vs 21.4 (13.5, 29.7) % ($p<0.001$) in AS0010 study; and 44.8 (33.3, 50.3) % 22.5 (12.9, 29.2) % ($p<0.001$) in AS0011 study. The difference between treatment groups was observed as early as week 1 in AS0010 and week 2 in AS0011.

In the phase 3 studies AS0010 and AS0011, bimekizumab 160 mg Q4W resulted in a highly significant and clinically relevant ASAS40 response at week 16 (primary endpoint). In both trials, the primary endpoint result was corroborated by the outcomes of the secondary endpoints which included

assessments of BASDAI score, BASMI score, ASDAS score, nocturnal spinal pain, inflammation as measured by hs-CRP levels, SPARCC score, ASspiMRI-a (Berlin modifications) score, BASFI score, ASQOL, SF-36, FACIT-Fatigue score, enthesitis-free state assessed by MASES index and incidence of uveitis. These primary and secondary endpoints are in line with EMA guidance on the clinical investigation of medicinal products for the treatment of axial spondyloarthritis.

Efficacy, as demonstrated by e.g. ASAS40 response, was maintained up to week 52.

3.3. Uncertainties and limitations about favourable effects

It has been seen in trials investigating the use of bimekizumab in other conditions that there can be a difference in the pharmacokinetic profile of the product in patients with higher BMI levels. In both studies AS0010 and AS0011 large treatment response differences were observed based on age (younger than 45 years or 45 years and older) and based on BMI (BMI over 30 compared to BMI under 30). However, subgroup and post hoc analyses have shown that these differences did not have a significant effect on the outcome of the trials. As a result, no dose recommendation was warranted in these subgroups.

3.4. Unfavourable effects

Pool SA1 was the primary safety pool used to summarise the safety of bimekizumab vs placebo treatment in axSpA through Week 16 in Phase 3 studies AS0010 and AS0011. Pool SA2 provided the most comprehensive overview of safety in axSpA by including all Phase 2 and Phase 3 data from nr-axSpA and AS studies.

In pool SA1, TEAEs were reported at a higher incidence in the bimekizumab 160mg Q4W group compared with the placebo group (57.3% vs 50.2%). The incidence of serious TEAEs was low overall and similar in the bimekizumab 160mg Q4W group (1.1%) compared with the placebo group (0.8%).

TEAEs were most commonly reported in the SOCs of Infections and infestations for both the bimekizumab 160mg Q4W and the placebo groups (30.4% and 23.6%, respectively). The incidences of nasopharyngitis were higher in the bimekizumab 160mg Q4W group compared with the placebo group (8.3% vs 4.2%, respectively). Rates of oral candidiasis were higher in the bimekizumab group compared with the placebo group (3.7% vs 0 participant). The incidences of uveitis and upper respiratory tract infection were lower in the bimekizumab 160mg Q4W group compared with the placebo group (0.6% vs 3.4%).

In Pool SA1, during the Initial Treatment Period, the majority of TEAEs were mild or moderate in intensity in both treatment groups. The incidence of severe TEAEs was low overall and similar between the bimekizumab 160mg Q4W group (0.9%) and placebo group (0.4%) group.

In Pool SA1, incidences of serious TEAEs were low and similar in the bimekizumab 160mg Q4W group (1.1%) and in the placebo group (0.8%) during the Initial Treatment Period. By PT, all serious TEAEs by PT were reported by 1 study participant in any treatment group.

No severe TEAEs, by PT, were reported by >1 study participant.

In Pool SA2, the majority of study participants in the bimekizumab Total group (85.6%; EAIR: 155.6/100 participant-years) reported a TEAE.

Almost half of study participants 45.4%;(EAIR: 33.7/100 participant-years) had TEAEs that were considered drug-related.

Treatment-emergent AEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (60.7%), Gastrointestinal disorders (24.9%), Skin and subcutaneous tissue disorders (23.3%), and Respiratory, thoracic and mediastinal disorders (10.5%). The most frequently

reported TEAEs by PT were nasopharyngitis (14.8%), upper respiratory tract infection (9.4%), oral candidiasis (8.1%), and corona virus infection (7.5%).

During the combined Initial, Maintenance, and OLE Treatment Period, the incidence of serious TEAEs was 10.8% (EAIR=5.6/100 participant-years [95% CI: 4.6, 6.8]) of study participants in the bimekizumab Total group. Serious TEAEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (3.0%), Injury, poisoning and procedural complications (1.5%), Gastrointestinal disorders (1.4%).

In Pool SA2, the incidence of severe TEAEs was low overall. A total of 7.1% of study participants in the bimekizumab Total group reported severe TEAEs during the combined Initial, Maintenance, and OLE Treatment Period. Severe TEAEs in the bimekizumab Total group were most frequently reported in the SOC of Infections and infestations (1.6%). Most severe TEAE were isolated cases.

The incidences of TEAEs were higher in the 52-week Safety Update compared with the original submission, which is expected given the longer treatment duration and resulting increased total time at risk in the bimekizumab Total group (2241.1 vs 1907.5 participant-years, respectively). However, the EAIRs for the TEAE categories in the Safety Update are similar to or lower than those in the original submission and therefore do not indicate an increase in risk with longer exposure to bimekizumab.

In the bimekizumab Total group, TEAEs were most frequently reported in the SOCs of Infections and infestations (67.1%), Gastrointestinal disorders (28.4%), and Skin and subcutaneous tissue disorders (25.9%).

The most frequently reported TEAEs in the bimekizumab Total group by PT were nasopharyngitis (18.0%), corona virus infection (14.3%), upper respiratory tract infection (11.4%), and oral candidiasis (8.7%).

Other Safety topics of interest included malignancies, MACE, neutropenia, SIB, IBD, hypersensitivity reactions, and injection site reactions. No new safety concerns emerged from analyses of the remaining safety topics of interest based on the current axSpA submission.

In Pool SA1, in the bimekizumab 160mg Q4W group, the incidence of TEAEs was higher in study participants who were using csDMARDs at Baseline compared with study participants who were not using csDMARDs at Baseline (62.3% vs 55.9%, respectively).

In Pool SA2, in the bimekizumab Total group, the incidence of TEAEs was lower in study participants who were using csDMARDs compared with study participants who were not using csDMARDs at Baseline (80.9% vs 86.9%, respectively). This was also seen in the updated safety data to Week 52.

Approximately 57% of patients with nr-axSpA treated with bimekizumab up to 52 weeks at the recommended dosing regimen (160 mg every 4 weeks) had anti-drug antibodies. Of the patients with anti-drug antibodies, approximately 44% (25% of all patients treated with bimekizumab) had antibodies that were classified as neutralising. Approximately 44% of patients with AS treated with bimekizumab up to 52 weeks at the recommended dosing regimen (160 mg every 4 weeks) had anti-drug antibodies. Of the patients with anti-drug antibodies, approximately 44% (20% of all patients treated with bimekizumab) had antibodies that were classified as neutralising.

There is a numerical imbalance for the incidence of the PT rash in pool SA1: 2.3% in the BKZ group versus 0.4% in the placebo group. The imbalance in the incidence of the PT Rash between placebo and bimekizumab was less pronounced in the overall S3 pool combining 16-week data for the three indications (0.4% on placebo and 0.8% on bimekizumab). ‘Rash’ has been added to SmPC section 4.8 as a ‘common’ adverse reaction.

3.5. Uncertainties and limitations about unfavourable effects

Upon CHMP's request, the MAH agreed to include subjects with axSpA in the long-term PASS study (PSO038) for subjects with PSO to further characterise the long-term safety profile in this new indication post approval. In addition, the PASS on pregnancy will also include patients with axSpA.

Regarding immunogenicity, the low number of participants does not allow definitive conclusions but a trend of increased incidence of hypersensitivity reaction TEAEs linked to ADAb positivity was observed. Therefore, the section 4.8 of the SmPC was updated to reflect that an association between immunogenicity and treatment emergent events has not been clearly established.

A known risk for use of Bimekizumab is infection. All ongoing infections are considered mild or moderate and have not led to treatment discontinuation. The section 4.4 of the SmPC was updated to reflect that if a patient develops an infection, the patient should be carefully monitored and if the infection becomes serious or is not responding to standard therapy, treatment should be discontinuer until the infection resolves. This will also be monitored in the ongoing PASS study (see RMP).

3.6. Effects Table

Effects Table for Bimekizumab in AS and nr-AxSpA

Effect	Short description	Unit	Treatment BKZ 160mg Q4W vs Placebo	Uncertainties / Strength of evidence	References (Studies)
Favourable Effects					
ASAS40 at Week 16	Assessment of speed & depth of response on functional disease/pain at Week 16	%	**AS0010:** BKZ 47.7% (n=128) Placebo 21.4% (n=126)	P<0.001 for BKZ vs placebo (Pool EA1, AS0010, and AS0011)	AS0010: Initial treatment period (placebo-controlled) in Phase 3 study AS0010 AS0011: Initial treatment period (placebo-controlled) in Phase 3 study AS0011 Pool EA1: Pool of Initial treatment period (placebo-controlled) in Phase 3 studies AS0010 and AS0011
			AS0011: BKZ 44.8% (n=221) Placebo 22.5% (n=111)		
			Pool EA1: BKZ 45.8% (n=349) Placebo 21.9% (n=237)		
ASDAS LDA (ASDAS<2.1) at Week 16	Assessment of major response in disease activity ie, achieving low or inactive disease state	%	**AS0010:** BKZ 46.1% (n=128) Placebo 19.8% (n=126)	P<0.001 for BKZ vs placebo (Pool EA1, AS0010, and AS0011)	
			AS0011: BKZ 42.1% (n=221) Placebo 17.1% (n=111)		
			Pool EA1: BKZ 43.6% (n=349) Placebo 18.6% (n=237		
BASDAI 50 at Week 16	Improvement in disease activity	%	**AS0010:** BKZ 46.9% (n=128) Placebo 21.4% (n=126)	P<0.001 for BKZ vs placebo (Pool EA1, AS0010, and AS0011)	
			AS0011: BKZ 46.6% (n=221) Placebo 26.1% (n=111)		

			Pool EA1: BKZ 46.7% (n=349) Placebo 23.6% (n=237)		
BASFI at Week 16	Degree of functional improvements in patients	Decrease from Baseline	**AS0010**: BKZ 2.4 (n=128) Placebo 0.9 (n=126)	P<0.001 for BKZ vs placebo (Pool EA1, AS0010, and AS0011)	
			AS0011: BKZ 2.0 (n=221) Placebo 0.9 (n=111)		
			Pool EA1: BKZ 2.2 (n=349) Placebo 1.0 (n=237)		
ASQoL at Week 16	Validated 18-item questionnaire to measure health-related quality of life in patients with axSpA	Decrease from Baseline	**AS0010**: BKZ 4.9 (n=128) Placebo 2.3 (n=126)	P<0.001 for BKZ vs placebo (Pool EA1, AS0010, and AS0011)	
			AS0011: BKZ 4.6 (n=221) Placebo 3.0 (n=111)		
			Pool EA1: BKZ 4.8 (n=349) Placebo 2.7 (n=237)		
Unfavourable Effects					
Serious infections	Serious TEAEs under Infections and infestations SOC	%, EAIR	Pool SA1: BKZ 0.3% (n=349) Placebo 0.4% (n=237) Pool SA2: BKZ Total 3.3% (n=928) EAIR 1.4 (95% CI 1.0, 2.0)	In Pool SA1, incidences were comparable to placebo. Overall low incidence, majority resolved. Only a minor subset led to treatment discontinuation	Pool SA1 is pooled safety data of Initial treatment period (placebo-controlled) in Phase 3 studies AS0010 and AS0011. Pool SA2 consists of pooled safety data for the combined Initial, Maintenance, and OLE Treatment Periods with the available data at the time of the 52-week data cut-off. Includes study participants who received at least 1 dose of bimekizumab in the Phase 2 AS0008 and AS0013; Phase 3 studies AS0010 and AS0011; and OLE studies AS0009 and AS0014
Fungal infectious disorder	Events under HLGT Fungal infectious disorder	%, EAIR	Pool SA1: BKZ 6.3% (n=349) Placebo 0% (n=237) Pool SA2: BKZ Total 20.3% (n=928) EAIR 9.9 (95% CI: 8.5, 11.4)	None were systemic. Vast majority were mild-to-moderate and did not lead to treatment discontinuation; responded well to antifungal treatments.	
MACE	Adjudicated MACE	%, EAIR	Pool SA1: BKZ 0.0% (n=349) Placebo 0.0% (n=237) Pool SA2: BKZ Total 0.5% (n=928) EAIR 0.2 (95% CI: 0.1, 0.5)	Incidence low and similar to background	
Cutaneous hyper-sensitivity	As measured by Dermatitis and eczema HLT	%, EAIR	Pool SA1: BKZ 2.0% (n=349) Placebo 0.4% (n=237) Pool SA2: BKZ Total 8.5% (n=928) EAIR 3.7 (95% CI: 3.0, 4.7)	No anaphylactic reactions observed. Potential cutaneous hypersensitivity observed, vast majority mild-moderate and did not lead to treatment discontinuation.	
Adjudicated IBD	TEAEs adjudicated as definite or probable IBD events	%, EAIR	Pool SA1: BKZ 0.6% (n=349) Placebo 0.4% (n=237) Pool SA2: BKZ Total 1.8%	Incidence low and similar to background	

Uveitis	TEAEs of PTs Autoimmune uveitis, Iridocyclitis, Iritis, and Uveitis	%, EAIR	(n=928) EAIR 0.8 (95% CI 0.4, 1.2) Pool SA1: BKZ 0.6% (n=349) Placebo 4.6% (n=237) Pool SA2: BKZ Total 2.9% (n=928) EAIR 1.2 (95% CI: 0.8, 1.8)	Risk of uveitis is considered less with bimekizumab as compared to placebo. Overall, none of uveitis TEAEs seen with bimekizumab were severe and majority resolved	

Abbreviations:

ASAS=Assessment of SpondyloArthritis International Society; ASDAS= Ankylosing Spondylitis Disease Activity Score; AsQoL=Ankylosing Spondylitis Quality of Life; BASDAI=Bath Ankylosing Spondylitis Disease Activity Index; BASFI=Bath Ankylosing Spondylitis Functional Index; BKZ=bimekizumab; EAIR=exposure adjusted incidence rate; HLGT=High Level Group Term; HLT=High level term; IBD=inflammatory bowel disease; MACE=major adverse cardiac events; TEAEs=treatment-emergent adverse events.

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

A clinically relevant and robust effect as measured by ASAS40 has been demonstrated for bimekizumab 160mg Q4W in the target population of subjects with active axial spondyloarthritis. The persistence of this effect was maintained up to week 52. In addition, there are support from key secondary endpoints measuring different aspects of the disease.

The safety findings in the axial spondyloarthritis development programme were generally consistent with the findings in the plaque psoriasis development programme.

The most common TEAEs in participants treated with bimekizumab were in the areas of infection, nasopharyngitis and oral candidiasis. The majority were non serious with only a small subset of events leading to discontinuations.

Use during pregnancy and lactation and long-term safety will be followed-up post approval.

3.7.2. Balance of benefits and risks

Overall, bimekizumab has a positive effect in the treatment of nr-axSpA and AS with benefits that outweigh the risks.

3.8. Conclusions

The overall B/R of Bimzelx in the treatment of AS and nr-AxSpA is positive.

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 adults with active axial spondyloarthritis (axSpA), including non-radiographic axial spondyloarthritis (nr-axSpA) and ankylosing spondylitis (AS, radiographic axial spondyloarthritis), based on results from two interventional and controlled phase III clinical studies: AS0010 (BE MOBILE 1) and AS0011 (BE MOBILE 2), which provide evidence of the efficacy and safety of bimekizumab in axSpA (nr-axSpA and AS), both compared to placebo treatment. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 of the SmPC are updated. The Package leaflet is updated in accordance. The RMP version 1.8 is acceptable. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev.1.

Amendments to the marketing authorisation

In view of the data submitted with the variation, amendments to Annexes I, II 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.0010'

Attachments

1. Product information as adopted by the CHMP 26 April 2023.