26 April 2023
EMA/235043/2023
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bimzelx

International non-proprietary name: bimekizumab

Procedure No. EMEA/H/C/005316/II/0011

Note

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

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List of abbreviations

ACR20/50/70	American College of Rheumatology 20%/50%/70% response criteria
ADAb	antidrug antibody
ADR	adverse drug reaction
AE	adverse event
ALP	alkaline phosphatase
ALT	alanine aminotransferase
AS	ankylosing spondylitis
AST	aspartate aminotransferase
axSpA	axial spondyloarthritis
BA	bioavailability
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
bDMARD	biologic disease-modifying antirheumatic drug
bimekizumab-AI-1mL	1mL bimekizumab auto-injector
bimekizumab-SS-1mL	1mL bimekizumab safety syringe
BMI	body mass index
BSA	body surface area
CASPAR	Classification Criteria for Psoriatic Arthritis
CD	cluster of differentiation
cDMARD	conventional disease-modifying antirheumatic drug
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
COVID-19	coronavirus disease 2019
CSR	clinical study report
CV-CAC	Cardiovascular Event Adjudication Committee
DAPSA	Disease Activity Index for Psoriatic Arthritis
DAS28(CRP)	Disease Activity Score-28 based on C-reactive protein
DDI	drug-drug interaction
DIP	distal interphalangeal
DILI	drug-induced liver injury
DMARD	disease-modifying antirheumatic drug
DMC	Data Monitoring Committee
EAIR	exposure adjusted-incidence rate
ECG	electrocardiogram
eC-SSRS	electronic Columbia Suicide Severity Rating Scale
EMA	European Medicine’s Agency
EOP2	End of Phase 2
EQ-5D-3L	European Qol-5 Dimensions-3 Level
EULAR	European Alliance of Associations for Rheumatology
FACIT	Functional Assessment of Chronic Illness Therapy

FDA	Food and Drug Administration
GRAPPA	Group for Research and Assessment of Psoriasis and Psoriatic Arthritis
HAC	Hepatology Adjudication Committee
HADS	Hospital Anxiety and Depression Scale
HAQ-DI	Health Assessment Questionnaire – Disability Index
HLA-B27	human leukocyte antigen B27
HLT	high-level term
HS	hidradenitis suppurativa
hs-CRP	high sensitivity C-reactive protein
IBD	inflammatory bowel disease
ICH	International Council for Harmonisation
IGA	Investigator's Global Assessment
IgG1	immunoglobulin G
IGRA	interferon gamma release assay
IL	Interleukin
IL-17-RA	IL 17 receptor A
ISAP	Integrated Statistical Analysis Plan
ISE	Integrated Summary of Efficacy
ISS	Integrated Summary of Safety
iR	Inadequate response
LDI	Leeds Dactylitis Index
LEI	Leeds Enthesitis Index
LEF	leflunomide
LFT	liver function test
mAb	monoclonal antibody
MACE	major adverse cardiac event
MDA	Minimal Disease Activity
MedDRA	Medical Dictionary for Regulatory Activities
mNAPSI	modified Nail Psoriasis Severity Index
MTX	methotrexate
NAb	neutralizing antibody
NEC	not elsewhere classified
NSAID	nonsteroidal anti-inflammatory drug
OLE	open-label extension
P1/P2/P3/P4/P5	Process 1/2/3/4/5
PASDAS	Psoriatic Arthritis Disease Activity Score
PASI75/90/100	Psoriasis Area and Severity Index 75%/90%/100%
PCS	Physical Component Summary
PD	pharmacodynamic
PDILI	potential drug-induced liver injury
PFS	prefilled syringe

PHQ-9	Patient Health Questionnaire 9
PK	pharmacokinetic
PRO	patient-reported outcome
PsA	psoriatic arthritis
PsAQol	Psoriatic Arthritis Quality of Life
PsAID-12	Psoriatic Arthritis Impact of Disease-12
PsARC	Psoriatic Arthritis Response Criteria
PSO	psoriasis
PSUR	Periodic Safety Update Report
PT	preferred term
PtAAP	Patient's Assessment of Arthritis Pain
Q2W	every 2 weeks
Q4W	every 4 weeks
Q8W	every 8 weeks
QoL	quality of life
RA	rheumatoid arthritis
SAP	Statistical Analysis Plan
sc	subcutaneously
SF-36	Short Form 36 item Health Survey
SFU	Safety Follow-up
SIB	suicidal ideation and behavior
SJC	swollen joint count
SMQ	standardized MedDRA query
SOC	system organ class
SpA	spondyloarthritis
SPARCC	Spondyloarthritis Research Consortium of Canada
SSZ	sulfasalazine
TB	tuberculosis
TEAE	treatment-emergent adverse event
TEMA	treatment-emergent markedly abnormal
TJC	tender joint count
TN	True North
TNF	tumor necrosis factor
TNFα	tumor necrosis factor alpha
TNFα-IR	tumor necrosis factor α inhibitor inadequate responders/ inadequate responders to TNFα inhibitors
ULN	upper limit of normal
vdHmTSS	van der Heijde modified Total Sharp Score
VLDA	very low disease activity
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 active psoriatic arthritis in adults patients who have had an inadequate response or who have been intolerant to one or more DMARDs for BIMZELX, based on interim results of a Phase III study in biological DMARD naïve study participants (PA0010; BE OPTIMAL) and the final results of the Phase III study in study participants who are inadequate responders (inadequate response or intolerant) to ≤2 prior TNF inhibitors (PA0011; BE COMPLETE). Both Phase III studies are interventional studies aimed to evaluate the efficacy and safety of bimekizumab. For PA0010, the Initial Treatment Period was placebo- and non inferential active reference (adalimumab)-controlled, while PA0011 was placebo-controlled. Further supportive data comprise the results of a Phase 1 study (PA0007), a Phase 2b dose-finding study (PA0008) and a Phase 2 open label extension study (PA0009). A Phase 3 open-label extension study is currently ongoing (PA0012). As a consequence, sections 4.1, 4.2, 4.5, 4.8, 5.1 and 5.2 to the SmPC have been updated. The Package leaflet is updated in accordance. Version 1.1 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.

MAH request for additional market protection

The MAH requested consideration of its application in accordance with Article 14(11) of Regulation (EC) 726/2004 - one year of market protection for a new indication bringing a significant clinical benefit in comparison with existing therapies. During the assessment of the procedure, the MAH withdrew their request for one additional year of market protection.

Scientific advice

The MAH received Scientific Advice from the CHMP on 1 July 2016 (EMEA/H/SA/3306/2/2016/II). The Scientific Advice pertained to clinical aspects of the dossier.

1.2. Steps taken for the assessment of the product

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

Rapporteur: Finbarr Leacy Co-Rapporteur: Christophe Focke

Timetable	Actual dates
Submission date	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

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis, which is classified within the group of the spondyloarthritis. Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases (including psoriatic arthritis [PsA], axial spondyloarthritis [axSpA], reactive arthritis, the arthritis of inflammatory bowel disease [IBD], and undifferentiated spondyloarthritis) that have features in common with each other and distinct from other inflammatory arthritides, particularly rheumatoid arthritis (RA).

Spondyloarthritides generally have distal interphalangeal (DIP) joint involvement, asymmetric distribution, dactylitis (inflammation of the whole digit), enthesitis (inflammation at the site of tendon insertion into bone), spinal involvement, and an association with the Class I human leukocyte antigen B27 (HLA-B27) allele. The assessment of SpondyloArthritis International Society working group established classification criteria to distinguish 2 broad categories of SpA: peripheral SpA and axSpA. This division is based on the body part predominantly involved in the inflammatory process. Therefore, peripheral SpA includes diseases affecting mainly peripheral joints, such as reactive arthritis and PsA, whereas axSpA comprises those diseases with mainly axial involvement (sacroiliac joints and spine), including ankylosing spondylitis diagnosed with definite radiographic changes of the sacroiliac joint and non-radiographic axSpA.

The claimed therapeutic indication

The initially proposed indication for bimekizumab in PsA was as follows:

"Bimekizumab, alone or in combination with conventional disease-modifying antirheumatic drugs (cDMARDs), is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more DMARDs".

Epidemiology

Psoriasis affects 1-3% of the population. Psoriatic arthritis is a chronic inflammatory musculoskeletal disorder, which occurs in approximately 6% to 41% of people affected by psoriasis (PSO). The estimated prevalence of PsA ranges between 0.1% and 1%. Psoriatic arthritis can develop at any time, but for most people it appears between the ages of 30 and 50, and it affects men and women equally.

Biologic features, aetiology and pathogenesis

The etiologic events that underlie the development of psoriasis and PsA are not well understood. Available evidence indicates that these disorders show great complexity and heterogeneity, and that genetic and environmental factors converge to trigger inflammatory events in multiple immune pathways.

It is reasonable to assume, although not proven, that psoriasis skin and joint inflammation share pathogenetic origins. Support for this assumption is based upon overlapping genetic risk alleles, environmental triggers, and cytokine pathways; however, the resident cells that populate the skin and joint are considerably different, and cutaneous and musculoskeletal clinical activity are often divergent in individual patients.

The infiltration of immune cells into the skin and musculoskeletal tissues, coupled with shared disease pathways of innate (TNF) and acquired immunity (interleukin [IL] 23/IL-17 pathway), provides strong support for the concept that the pathogenesis of PsA is directed by a dysregulated immune response (Barnas JL et al, 2015).

Evidence suggests that psoriasis is driven by both adaptive and innate immune responses, although the interplay of innate and adaptive immune mechanisms in PsA is not well understood (McGonagle D, 2011).

Clinical presentation, diagnosis and stage/prognosis

With the exception of the distal interphalangeal joints (hands and feet), there are no predictable joints for involvement in PsA and the signs of inflammation are often non symmetrical and more difficult to detect compared with Rheumatoid Arthritis (RA). Spondyloarthopathy is often present. Some typical features of PsA are dactylitis and nail psoriasis. Extra-cutaneous and extra-articular manifestations are uncommon but may include conjunctivitis, uveitis, aortic insufficiency, and pulmonary fibrosis.

Psoriatic arthritis may start slowly with mild symptoms or develop quickly. Flares and remissions usually characterise the course of PsA. Left untreated, patients with PsA can have persistent inflammation, progressive joint damage, several physical limitations, and disability. For most patients, skin manifestations predate the arthritis. On average PsA is diagnosed 10 years after PSO appears, although in 15% of cases, PsA and PSO occur simultaneously, or PsA precedes the skin disease. Prognosis of PsA may range widely from a mild monoarthritic form with good prognosis to more than 50% progressing to an erosive and destructive polyarticular form, comparable with that in patients with RA. Axial forms may also range from mild to severe and disabling.

Disease specific considerations when evaluating PsA include disease activity (both psoriasis and arthritis), axial and peripheral joint involvement, biologic measures of disease, measure of function, quality of life, measure of structural joint damage, enthesis and dactylitis, safety and global status assessment.

Comorbidities that have an increased prevalence in patients with PsA compared to the general population include an increased prevalence of cardiovascular disease in PsA patients. Autoimmune-related conditions (i.e., coeliac disease, uveitis, and autoimmune bowel disorders), synovitis, acne, pustulosis, hyperstosis, and osteitis (SAPHO) syndrome, depression, and anxiety are also noted to co-occur with PsA.

Management

Psoriatic arthritis is a multidimensional disease requiring a holistic approach to treatment, as patients suffer beyond their joints. While treatment of joints is key, patients also suffer from many other manifestations such as PSO (including nail PSO), enthesitis, and dactylitis, which affect their quality of life and are frequently troublesome to patients with additional burden. Patients often have varying levels of disease activity; therefore, achieving low levels of disease activity is key to improving a patient's quality of life. International guidelines from the European League Against Rheumatism (EULAR) and the Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend that treatment of PsA should be aimed at reaching the target of remission or alternatively low disease activity (EULAR; Gossec et al, 2020) or the lowest possible level of disease activity in all domains of disease (GRAPPA; Coates et al, 2022a).

In the treatment of PsA, there are several options available including conventional disease-modifying antirheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs (Vivekanantham et al, 2021). Conventional DMARDs (eg, hydroxychloroquine, methotrexate [MTX], sulfasalazine [SSZ], and leflunomide [LEF]) are generally the first line of therapy. If the patient does not respond adequately to cDMARDs, a bDMARD or targeted-synthetic DMARD may be considered. Biologic DMARDs include tumor necrosis factor (TNF)α inhibitors (eg, infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol), interleukin (IL)-17A inhibitors (eg, secukinumab and ixekizumab), IL-12/IL-23 inhibitors (eg, ustekinumab), and IL-23 inhibitors (eg, risankizumab and guselkumab). Targeted synthetic DMARDs include as PDE4 inhibitors (eg, apremilast) and JAK inhibitors (eg, tofacitinib, upadacitinib).

Although the availability of treatment options has expanded over the years, there is still an unmet need, in particular in patients who are not responsive to these treatments (defined as achieving American College of Rheumatology 20% [ACR20] response criteria) or who do not maintain a clinical response. Patients with PsA symptoms who are not adequately treated or not well controlled are at risk of irreversible life-long joint damage that impact the patient's quality of life including mobility, ability to work, and control of pain.

The long-term goals of therapy include improvement in symptoms of the disease, psoriatic plaque clearance, inhibition of disease progression, and prevention of bone destruction.

2.1.2. About the product

Bimekizumab is a humanised, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) 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 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

A Phase 1b proof-of-concept study in participants with active PsA (PA0007) demonstrated a strong efficacy signal that warranted further exploration of bimekizumab in this indication, and UCB initiated a full development program in active PsA in adults.

A Phase 2b, dose-ranging study (PA0008) was designed to investigate the efficacy and safety of various bimekizumab dose regimens in study participants with active PsA (doses ranging from bimekizumab 16mg to 320mg every 4 weeks [Q4W]). Data from this Phase 2b study led to dose selection of bimekizumab 160mg Q4W for the Phase 3 studies, and further data from the follow-on open-label extension (OLE) study (PA0009) helped to confirm long term safety of bimekizumab at the 160mg Q4W dose.

Finally, 2 pivotal Phase 3 studies were conducted to investigate the efficacy and safety of bimekizumab for the treatment of active PsA: PA0010 (BE OPTIMAL) and PA0011 (BE COMPLETE). A safety data cut of the ongoing Phase 3 OLE study (PA0012) also contributed to the body of evidence supporting the safety evaluation for bimekizumab in this population.

Prior to initiating the global Phase 2 and Phase 3 studies, EMA Scientific Advice was obtained on the clinical development plan in PsA in July 2016 (EMEA/H/SA/3306/2/2016/II). The overall updated Phase 3

program for PsA was considered acceptable by the CHMP. Subsequently, a number of modifications were incorporated into the program considering the advice provided by EMA, the results from the Phase 2b dose-ranging study (PA0008), and the End of Phase 2 (EOP2) feedback from FDA (Aug 2018).

2.2. Non-clinical aspects

2.2.1. Introduction

The MAH submitted additional pharmacology studies in support of the proposed indication in PsA and an update to the carcinogenicity assessment document with most recent publications.

2.2.2. Pharmacology

Primary pharmacodynamic studies

In vitro pharmacodynamics

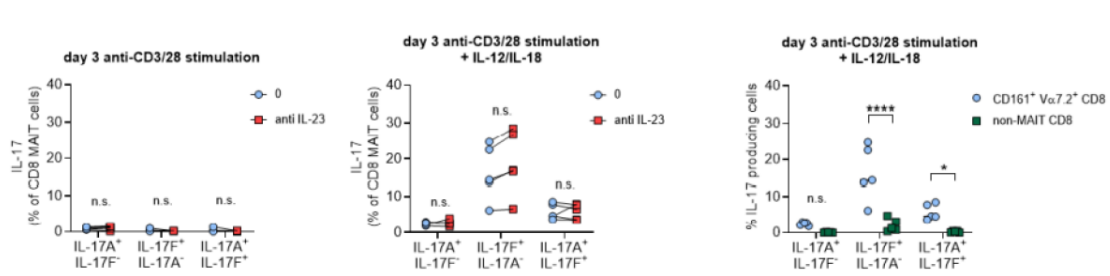
IL-17F is produced in larger amounts than IL-17A by innate immune cells and independently of IL-23

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).

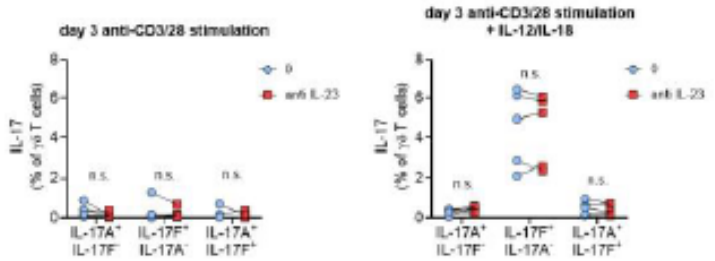
As MAIT cells, γδ T cells produced very little IL-17A or IL-17F upon anti-CD3/CD28 stimulation alone and produced mainly IL-17F upon addition of IL-12 and IL-18 but independently of the presence of IL-23 (Figure 2).

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)

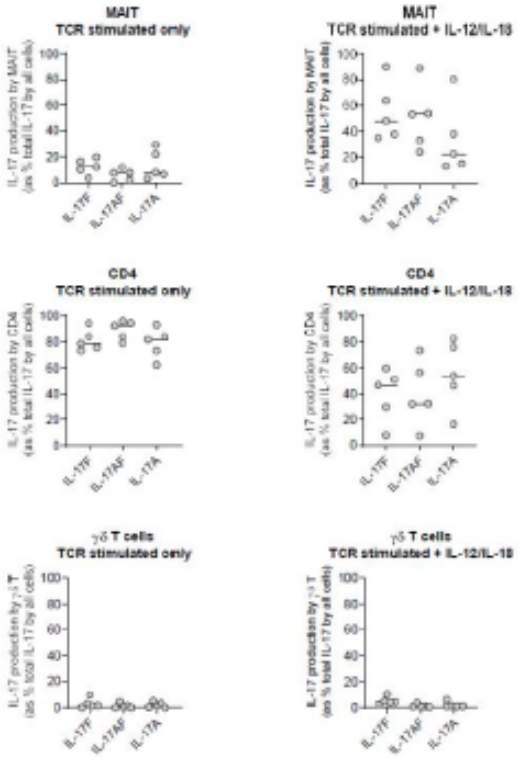
Figure 1: IL-17A and IL-17F production by MAIT cells



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-17 isoforms produced by MAIT, CD4 or γδ T cells as compared to total 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, 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 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 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 initial MA for the PSO indication, the risk of ADCC and CDC was evaluated on IL-17-producing cells. Peripheral blood mononuclear cells were preincubated with anti- CD28 and anti-CD3 antibodies (IL-17-producing cells) 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.

2.2.3. Toxicology

Carcinogenicity

The CAD reviewing the full weight-of-evidence for the role of IL-17A and IL-17F in carcinogenesis and tumor progression, the mode of action of bimekizumab, information from in vitro and in vivo tumor models, published data from patients with tumors, 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 tumor so far for PSO, PsA, or AS (Genovese et al, 2020; Combe et al, 2020; Lebwohl et al, 2021).

2.2.4. 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.

2.2.5. Discussion on non-clinical aspects

The MAH has presented a number of *in vitro* pharmacodynamic studies with relevance to the proposed indication in psoriatic arthritis (as concerns this procedure) and axial spondyloarthritis (parallel procedure, no. EMEA/H/C/005316/II/0010). Some of the data presented is relevant to both indications.

The rationale for IL-17F modification in PsA is supported by the presence of elevated IL-17A and IL-17F in the dermis of psoriatic skin, the synovium of psoriatic arthritic patients and higher levels of circulating cytokines in these patients. Dual IL-17A/IL-17F modulation of inflammatory disease pathology suggests an important role of innate cells, independent of IL-23 signalling. Dual inhibition with bimekizumab is associated with reduced IL-8 and MMP in synoviocytes isolated from PsA patients. IL-17A and IL-17F are pro-osteogenic cytokines and can induce 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). Pre-

incubation of AS serum with bimekizumab reduced RUNX2 expression to a greater extent than antibodies targeting either IL-17A or IL-17F alone. Although these findings were limited to AS patients, enhanced bone formation and bony swelling of the joints is a common and debilitating feature of PsA. Overall, the pharmacodynamic studies discussed provide a solid rationale for the use of bimekizumab in PsA. The proposed updates to section 5.1 of the SmPC (mechanism of action) are considered acceptable.

The MAH also provided an update to the Carcinogenicity Assessment Document. Evidence collected in the post-marketing setting with other IL-17 inhibitors do not indicate an increased risk of malignancies in psoriasis, psoriatic arthritis or ankylosing spondylitis. This is acknowledged.

2.2.6. Conclusion on the non-clinical aspects

The non-clinical package submitted in support of an indication in psoriatic arthritis 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

Introduction

In the context of this new indication for the treatment of adults with PsA, additional PK data were collected and submitted. Bimekizumab doses ranged from 16 mg up to 480 mg.

A total of 4 efficacy safety studies (Phase 2 and 3) provided supportive data including PK, PD, and immunogenicity of bimekizumab in study participants with PsA: a Phase 2b, dose-ranging study (PA0008) and its follow-on Phase 2b open-label extension (OLE) study (PA0009), and 2 pivotal Phase 3 studies (PA0010 and PA0011) to provide evidence of the efficacy and safety of bimekizumab for the treatment of active PsA. A Phase 3 OLE study (PA0012) is ongoing.

One clinical-use device sub-study (DV0004) supporting the self-injection of bimekizumab by participants with PsA was also provided (sub-study of PA0012 study).

Final PK data from the 2 PsA studies (PA0008 and PA0009) were described, as well as a description of the interim PK data up to week 24 of PA0010 and final data from PA0011 and DV0004.

Sparse PK sampling was performed. The majority of the PK samples were collected prior to dosing and reflected plasma trough concentrations. Bimekizumab concentrations in these studies were summarised with descriptive statistics and were also included in an updated integrated population PK analysis of bimekizumab on pooled data from phase 2 and phase 3 studies including participants with PsA, axSpA, or moderate to severe PSO (CL0538 report). The derived PK parameters were subsequently combined with the PD dataset for the population PK/PD modelling of ACR and PASI response following bimekizumab

subcutaneous administration in phase 2 and phase 3 study participants with PsA (CL0540 report). Both the population PK and PK/PD analyses were performed using nonlinear mixed effects modeling.

The table below gives an overview of the studies contributing data to the PsA summary of clinical pharmacology:

Study Number	Study Objectives	Pop-PK	PK/ Efficacy	PK Sampling
Phase 2b efficacy and safety studies in PsA[a]				
PA0008	Dose-ranging study to evaluate efficacy, safety, PK, and PD	X[b]	X[c]	Sparse
PA0009	Long-term safety, efficacy, and PK for participants who complete PA0008			Sparse
Phase 3 pivotal efficacy and safety studies in PsA[a]				
PA0010	Comparison of bimekizumab to placebo in bDMARD-naïve study participants; includes a noninferential active reference (adalimumab)	X[b]	X[c]	Sparse
PA0011	Comparison of bimekizumab to placebo in study participants who are inadequate responders to ≤2 prior TNFα inhibitors	X[b]	X[c]	Sparse
PA0012	Long-term safety, tolerability, efficacy, and PK study participants who complete PA0010 and PA0011	X[b]		Sparse
Additional Phase 3 study in participants with PsA				
DV0004	Clinical-use device presentation substudy of PA0012			Sparse
Additional study in PSO which contributed to summary of clinical pharmacology in PsA				
PS0015	Comparison of bimekizumab to secukinumab in study participants with PSO	X[b]		Sparse

ACR=American College of Rheumatology; axSpA=axial spondyloarthritis; bDMARD=biologic disease-modifying antirheumatic drug; PASI=Psoriasis Area and Severity Index; PD=pharmacodynamics; PK=pharmacokinetics; Pop-PK=population pharmacokinetics; PsA=psoriatic arthritis; PSO=psoriasis; TNFα=tumor necrosis factor α

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

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

[c] CL0540: Population PK-PD modeling of ACR and PASI response following bimekizumab subcutaneous administration in participants with PsA.

The Phase 1 study in participants with active PsA, PA0007, was the first multiple-dose clinical study conducted with bimekizumab. This study utilised intravenous (iv) administration of bimekizumab and evaluated safety, PK, and PD in study participants with PsA who had an inadequate response to at least 1 non-biologic DMARD and/or 1 approved biologic DMARD. Bimekizumab treatment duration was 6 weeks, with study participants receiving a loading dose on Week 1 followed by a maintenance dose at Weeks 4 and 7. The loading/maintenance doses used were 80/40mg (N=6), 160/80mg (N=6), 240/160mg (N=20), and 560/320mg (N=6) and were administered via IV infusion. Results demonstrated that, following multiple iv administrations of bimekizumab, the PK was linear across the tested dose range. Clinically relevant effects were observed on both skin and joints in study participants with PsA.

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 1 (study numbers related to the PsA and axSpA submissions are in bold font).

Table 1: 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 2. 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 2: 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.

	Method validation #1 (PK Method #1)	Method validation #2 (PK Method #2)	Method validation #3 (PK Method #3)	Method validation #4 (PK Method #4)
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.

The characteristics of the different ADAb assays and the contract research organization laboratories responsible for the validations are summarised in Table 3.

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 optimised 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 3, 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 3: 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)

	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)
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 comprises 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.

Statistical evaluations were performed to determine both validation and study-specific cut points. Statistical reports, including justification of the cut point strategy, are appended to the study specific NAb analytical reports.

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 PsA indication. However, additional considerations for the PsA indications regarding bioavailability are outlined below for study DV0004.

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). 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.

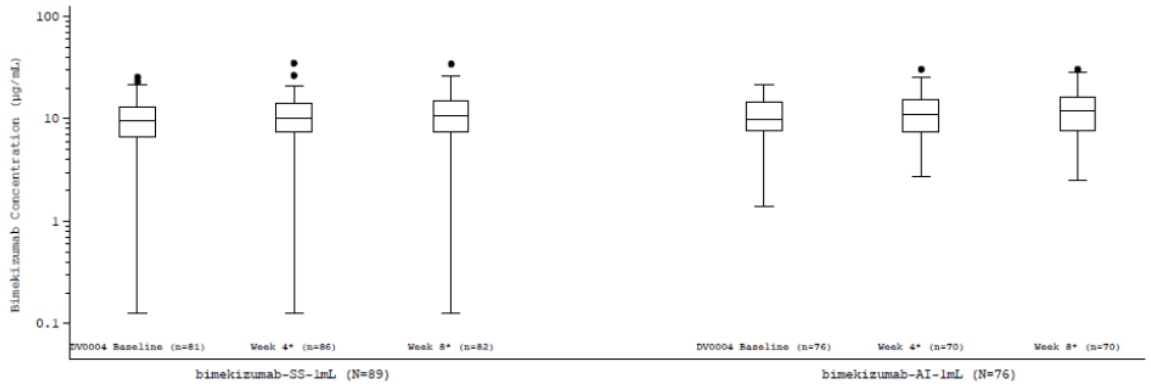
Data supporting self-injection

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 plasma concentration by visit and by device presentation are presented below:

Table 4: 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)

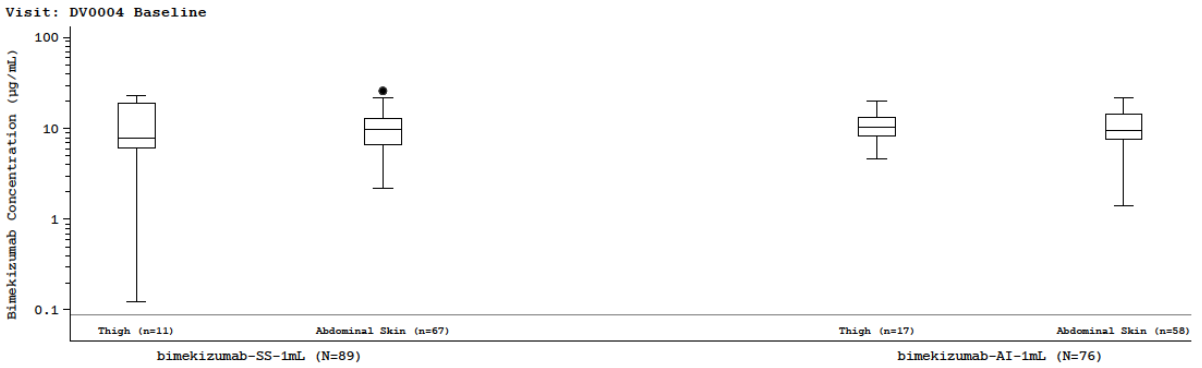
Data supporting sites of injection

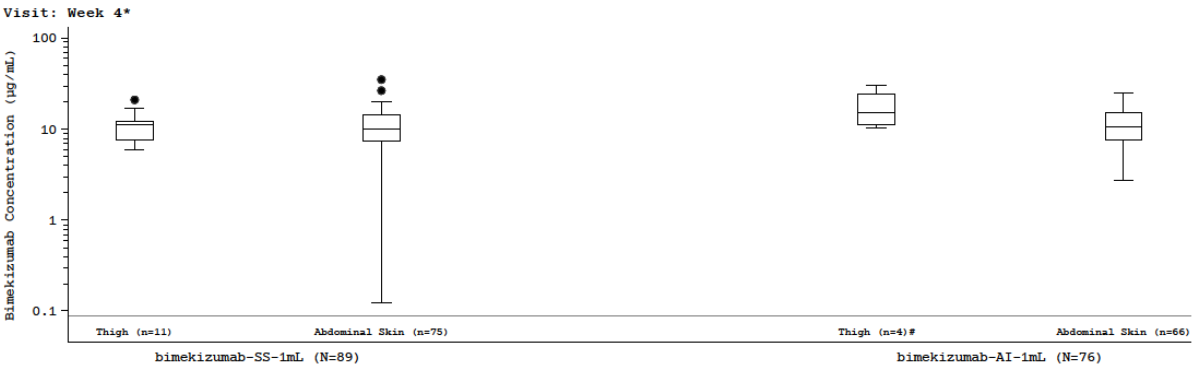
Within both the bimekizumab-SS-1mL and bimekizumab-AI-1mL groups, the trough bimekizumab plasma concentrations between injection sites tended to be similar and the ranges overlapped across all 3 visits, regardless of whether the previous dose had been self-administered or given by study personnel. Summary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

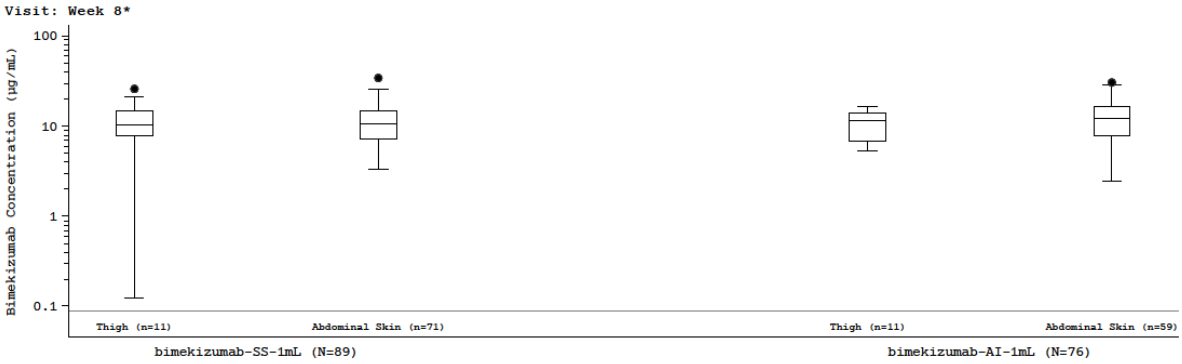
Table 5: Trough bimekizumab plasma concentration (µg/mL) by injection site after self-injection or injection by study personnel (PK-PPS-s and PK-PPS-a)

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 bimekizumab plasma concentration (µg/mL) by visit and injection site (PK-PPS)

Data supporting use across different BMI tertiles

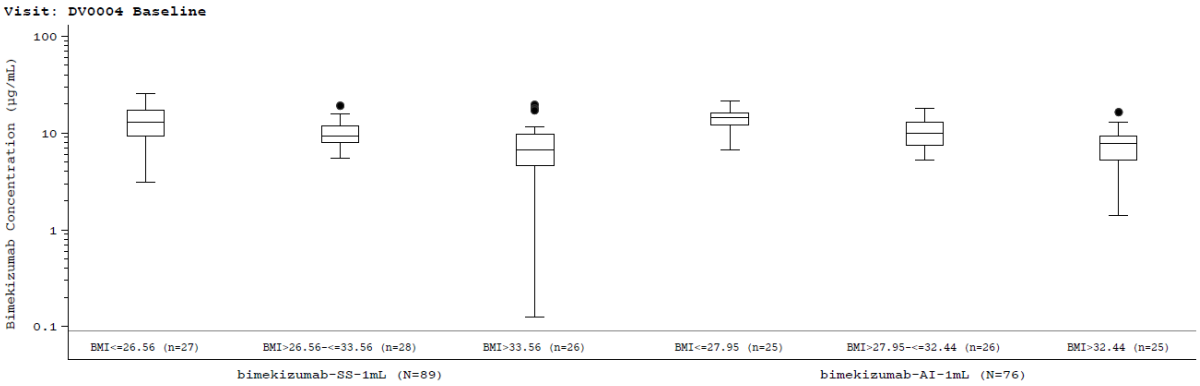
In both the bimekizumab-SS-1mL and bimekizumab-AI-1mL groups, trough concentrations decreased as BMI increased with the lowest geometric mean trough bimekizumab plasma concentrations generally observed for study participants in the highest BMI tertile. Within each tertile, the trough bimekizumab concentrations 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:

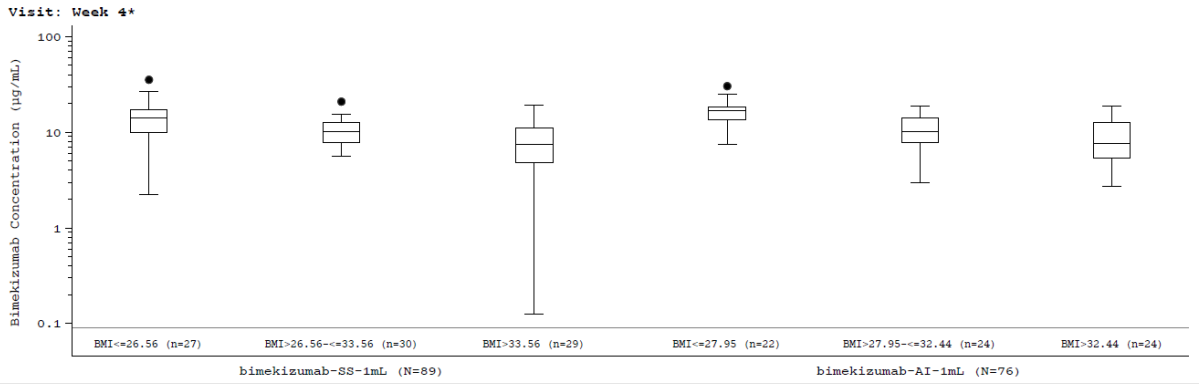
Table 6: Trough bimekizumab plasma concentration (µg/mL) by BMI tertile after self-injection or injection by study personnel (PK-PPS-s and PK-PPS-a)

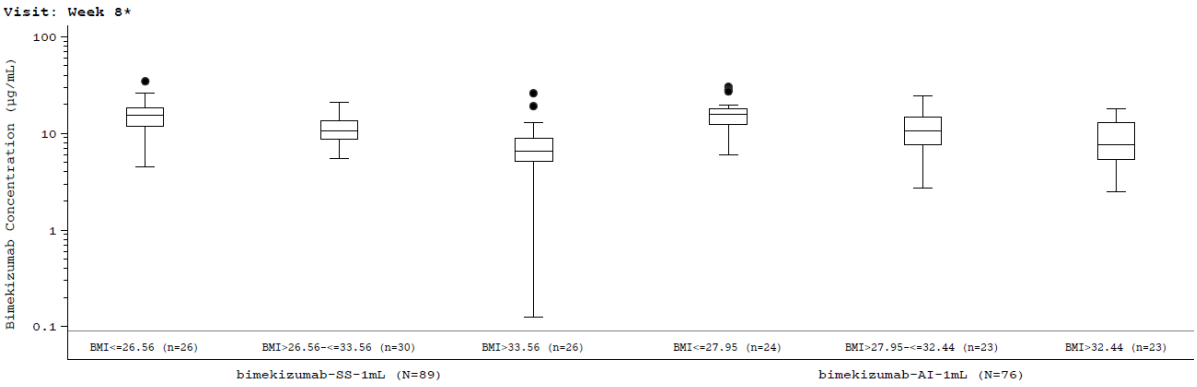
Visit	BMI (kg/m²)	Statistic	BKZ-SS-1mL BKZ 160mg Q4W N=89	BKZ-AI-1mL BKZ 160mg Q4W N=76
Baseline (after injection by study personnel from feeder study)	BMI≤t1	n	27	25
		GeoMean	12.382	13.714
		GeoCV (%)	53.6	29.9
	t1<BMI≤t2	n	28	26
		GeoMean	9.574	9.977
		GeoCV (%)	33.4	33.7
	BMI>t2	n	26	25
		GeoMean	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

Visit	BMI (kg/m^2)	Statistic	BKZ-SS-1mL BKZ 160mg Q4W N=89	BKZ-AI-1mL BKZ 160mg Q4W N=76
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 bimekizumab plasma concentration (µg/mL) by visit and BMI tertile (PK-PPS)

Pharmacokinetics in the target population

Phase 2 studies

Study PA0008

PA0008 was a Phase 2b, multicenter, randomised, double-blind, placebo controlled, parallel-group, dose-ranging study in adult study participants with active PsA. This study included 4 periods: a Screening Period (4 weeks, washout of medications during this period), 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 206 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=42), or to receive bimekizumab subcutaneously every 4 weeks (Q4W) at doses of 16mg (N=41), 160mg (N=41), 320mg (N=41), or with a 320mg loading dose followed by 160mg (from this point on referred to as 160mgLD) (N=41). Blood samples for bimekizumab concentrations during the Double-Blind Period were taken at Baseline, and at Weeks 1, 2, 4, 8, and 12.

After the 12-week Double-blind Period, 199 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 or bimekizumab 16mg Q4W groups were re-randomised in a 1:1 fashion to bimekizumab 160mg or bimekizumab 320mg Q4W; study participants in the bimekizumab 160mg or 160mg LD dose groups continued to receive bimekizumab 160mg Q4W; and study participants in the bimekizumab 320mg dose group continued to receive bimekizumab 320mg Q4W. Blood samples for bimekizumab concentrations during the Dose-Blind Period were taken at Weeks 16, 20, 24, 36 and 48.

Patients may have received 1 prior TNF inhibitor. The following restrictions were applied for bDMARDs:

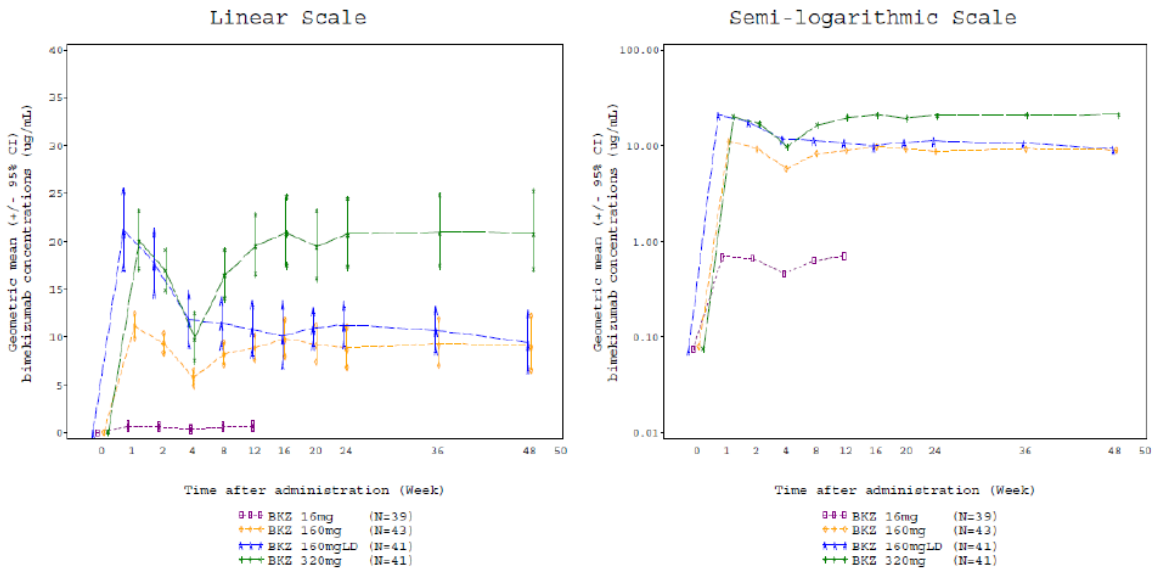
Drug class	Dose	Exclusion criteria
TNF inhibitor[b]: IFX ADA ETN GOL CZP	Any dose	For IFX, ADA, GOL, and CZP any use within the 3 months prior to the Baseline Visit. For ETN, use within the 28 days prior to the Baseline Visit. This applied to biosimilar versions of any TNF inhibitor.
Any non-TNF biologic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

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

[a] Sulfasalazine and apremilast were permitted as per Rescue Therapy (Table 3-3)

[b] Study participants must not have been exposed to more than 1 TNF inhibitor prior to the Baseline Visit.

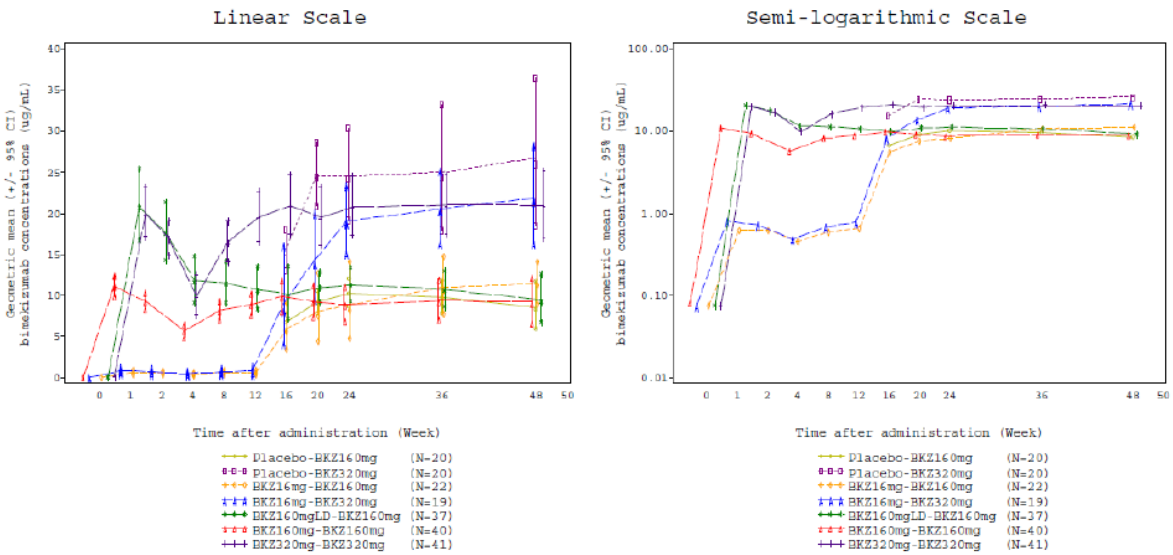
As shown in Figure 7 below, geometric mean plasma bimekizumab concentrations increased in a dose proportional manner during the Double-blind Period for the Pharmacokinetic Per Protocol Set (PK-PPS). Plasma concentrations in the 320mg and 160mg LD groups were similar through Week 4 and afterwards the plasma concentrations of 160mg LD were more similar over time to the 160mg group. For study participants in the 3 highest bimekizumab dose groups (who remained on the same dose after Week 12), steady state in plasma bimekizumab concentrations was achieved between Weeks 16 and 20.



BKZ=bimekizumab; BLQ=below the level of quantification; CI=confidence interval; CoV=coefficient of variation; LD=loading dose; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetic Per-Protocol Set; SD=standard deviation

Figure 7: Bimekizumab concentrations (µg/mL) by week (Overall; PK-PPS)

Figure 8 summarises plasma concentrations of bimekizumab by visit for the overall study and by treatment group for the subset of study participants in the Dose Blind Set who were part of the PK-PPS. For study participants initially randomised to placebo or bimekizumab 16mg, after being re-randomised to bimekizumab 160mg or 320mg at Week 12, geometric mean plasma bimekizumab concentrations quickly increased and were similar to those of study participants initially randomised to bimekizumab 160mg (and 160mg w/LD) or 320mg through Week 48.



BKZ=bimekizumab; BLQ=below the level of quantification; CI=confidence interval; CoV=coefficient of variation; DBS=Dose-blind Set; LD=loading dose; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetics Per-Protocol Set; SD=standard deviation
Note: * indicates that a subset from the DBS was used. The subset contained study participants who were part of the PK-PPS and the DBS.

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

Study PA0009

PA0009 was a Phase 2b multicenter, open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult study participants with psoriatic arthritis who completed the Phase 2b study PA0008.

Bimekizumab was administered at a dose of 160mg Q4W upon entry into PA0009, regardless of the dose received in PA0008. The study duration for each participant was estimated to be up to a maximum of 120 weeks and consisted of an open label treatment period of up to 100 weeks (~2 years). 183 participants received at least one dose of bimekizumab and 161 participants completed PA0009. Blood samples for bimekizumab concentrations were taken at the Entry Visit, and at Weeks 12, 24, 36, 48, 72, 96, and 104.

The following restrictions were applied for bDMARDs:

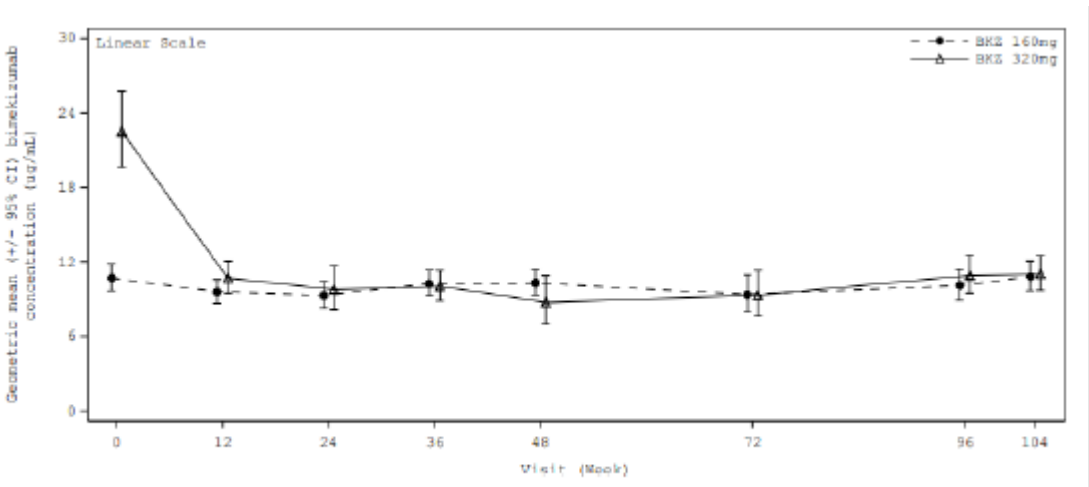
Drug class	Dose	Comments
TNF inhibitor: -infliximab -adalimumab -etanercept -golimumab -certolizumab pegol	Any dose	This applies to biosimilar versions of any TNF inhibitors.
Any non-TNF biologic medications	Any dose	Any exposure history is prohibited.

A summary of plasma bimekizumab concentrations by visit is presented in Table 7 and Figure 9. Study participants who had received bimekizumab 160mg Q4W during PA0008 maintained relatively constant bimekizumab concentrations during the subsequent PA0009, indicating steady state had been achieved. Study participants who received bimekizumab 320mg Q4W during PA0008 had bimekizumab concentrations approximately 2 times higher than the bimekizumab 160mg group at Visit 1 (EV), then decreased to similar levels as the PA0008 160mg group at Week 12, which were steady state levels.

Table 7: Plasma concentrations of bimekizumab in PA0009 (SS)

PA0009 Week Statistic	BKZ dose at PA0008 completion→BKZ dose in PA0009		All PA0009 participants (BKZ 160mg a) N=181
	BKZ 160mg→160mg a N=108	BKZ 320mg→160mg a N=73	
Visit 1 (EV)			
GeoMean (geoCV%)	10.67 (55.5)	22.50 (62.9)	14.53 (73.2)
Visit 4 (Week 12)			
GeoMean (geoCV%)	9.568 (53.2)	10.66 (55.5)	9.998 (54.3)
Visit 5 (Week 24)			
GeoMean (geoCV%)	9.267 (64.0)	9.742 (84.6)	9.455 (72.3)
Visit 6 (Week 36)			
GeoMean (geoCV%)	10.21 (53.6)	9.999 (54.7)	10.12 (53.9)
Visit 7 (Week 48)			
GeoMean (geoCV%)	10.27 (55.4)	8.731 (112.7)	9.615 (79.9)
Visit 9 (Week 72)			
GeoMean (geoCV%)	9.345 (91.2)	9.286 (94.8)	9.321 (92.3)
Visit 11 (Week 96)			
GeoMean (geoCV%)	10.06 (68.4)	10.88 (61.1)	10.38 (65.5)
Visit 13 (Week 104)			
GeoMean (geoCV%)	10.78 (55.3)	10.99 (52.2)	10.87 (53.8)
SFU			
GeoMean (geoCV%)	-	0.4822 (152.9)	0.4296 (141.2)

BKZ=bimekizumab; BLQ=below limit of quantification; CI=confidence interval; CV=coefficient of variation; Geo=geometric; LLOQ=lower limit of quantification; Max=maximum; Min=minimum; SD=standard deviation; SFU=Safety Follow-up.



BKZ=bimekizumab; BLQ=below limit of quantification; CI=confidence interval; LLOQ=lower limit of quantification; Q4W=every 4 weeks

Figure 9: Bimekizumab plasma concentration in PA0009 by treatment at completion of PA0008 (SS)

Phase 3 studies

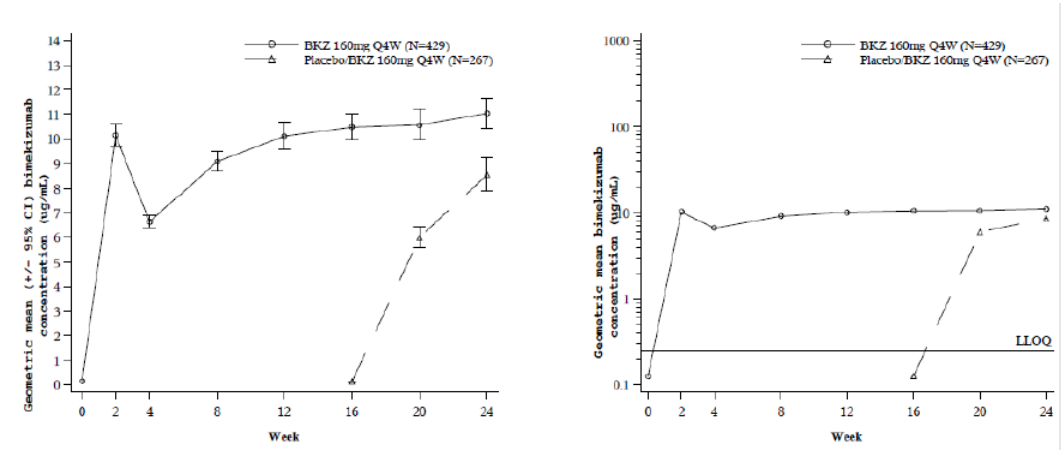
Study PA0010

PA0010 is a Phase 3 multicenter study consisting of a 16-week, randomised, double-blind, placebo-controlled, active-reference Treatment Period followed by a 36-week Active Treatment-Blind Period to evaluate the efficacy and safety of bimekizumab in adult study participants with active PsA. The data for this assessment is from an interim report up to Week 24.

During the Double-Blind Treatment Period, participants were randomised to 160mg bimekizumab SC Q4W (n=431), adalimumab SC Q2W (n=140), and placebo (n=281). After the 16-week Double-Blind period into the 36-week Active Treatment-Blind Period, participants continued 160mg bimekizumab (n=414) or adalimumab (n=136), and participants in the placebo group received bimekizumab Q4W starting at week 16 (n=271). Blood samples for bimekizumab concentrations during the study were taken at Baseline, and Weeks 2, 4, 8, 12, 16, 20, 24, 36, and 52.

Subjects with current or prior exposure to any biologics for the treatment of PsA or PSO were excluded.

Figure 10 shows that geometric mean bimekizumab concentrations increased over time and steady state was achieved by Week 16 of dosing with 160mg Q4W. A 1.58-fold accumulation in geometric mean bimekizumab trough concentration was observed between Week 4 and Week 16, consistent with the expected accumulation of bimekizumab concentrations with repeat dosing. In the placebo/bimekizumab 160mg Q4W group, once study participants switched to bimekizumab treatment, the concentrations 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 10: Geometric mean of bimekizumab plasma concentration over time (PK-PPS)

Table 8 below summarises the bimekizumab plasma concentrations for the Japanese study participants. Overall the plasma concentrations in Japanese study participants were comparable with those observed in the overall study population.

Table 8: Bimekizumab plasma concentrations by visit for the BKZ 160mg Q4W group (PK-PPS)

Visit	Overall population N=430	Japan N=14
Week 16, n	404	13
GeoMean (GeoCV)	10.472 (56.1)	9.020 (50.9)
Geometric 95% CI	9.950, 11.022	6.749, 12.057
Week 24, n	369	13
Geomean (GeoCV)	11.031 (58.1)	8.306 (81.1)
Geometric 95% CI	10.438, 11.657	5.406, 12.761

BKZ=bimekizumab; BLQ=below the limit of quantification; CI=confidence interval; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; LLOQ=lower limit of quantification

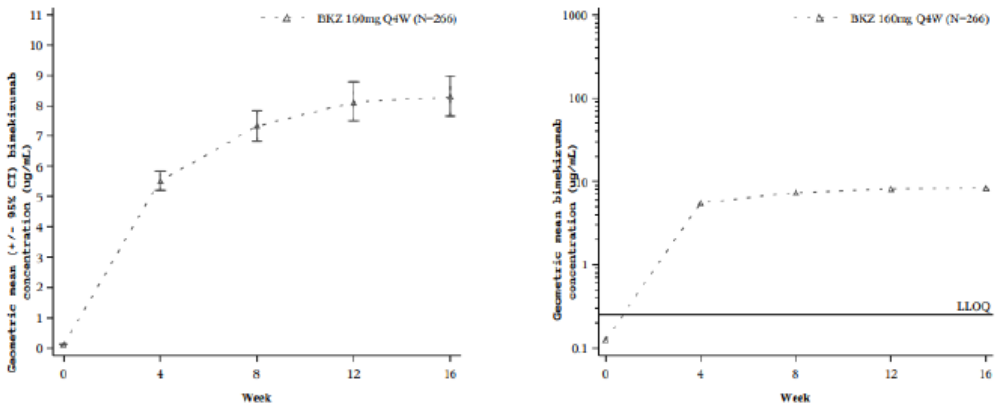
Study PA0011

PA0011 was a Phase 3 multicenter study consisting of a 16-week randomised, double-blind, placebo-controlled treatment period to evaluate the efficacy and safety of bimekizumab in study participants with active PsA.

A total of 400 study participants were randomised and started the Double-Blind Treatment Period as follows: 267 study participants in the bimekizumab 160mg Q4W group and 133 study participants in the placebo group. Study participants who completed Week 16 and were eligible for enrollment in the open-label extension (OLE) study, PA0012, continued to receive bimekizumab 160mg SC Q4W; a total of 388 participants completed the Double-blind Period, and 378 participants entered the OLE study. Blood samples for bimekizumab concentrations during the study were taken at baseline, and Weeks 4, 8, 12, and 16.

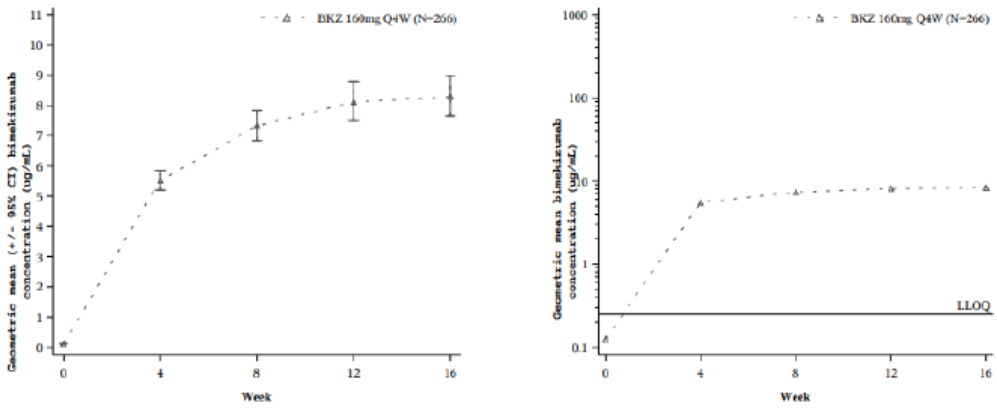
Study participants had a history of inadequate response or intolerance to treatment with 1 or 2 TNFα inhibitors for either PsA or PSO. Study participants with current or prior exposure to any biologics except tumor necrosis factor (TNF) inhibitors for the treatment of PsA or PSO were excluded. The following wash-out periods were applied:

Drug class	Dose	Exclusion/Washout
TNF inhibitor [a] -infliximab -adalimumab -etanercept -golimumab -certolizumab pegol	Any dose	For ADA, IFX, 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



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

Figure 11 below summarises the geometric mean plasma bimekizumab concentrations up to Week 16 on linear and semi-logarithmic scales. The geometric mean plasma bimekizumab concentrations increased over time and a steady state was achieved by Week 16 of dosing with bimekizumab 160mg Q4W. Concentrations were within the expected ranges at each visit, and the approach to steady state was consistent with the expectations for bimekizumab as a drug with linear PK. A 1.50-fold accumulation in geometric mean trough plasma bimekizumab concentration was observed between Week 4 and Week 16, consistent with the expected accumulation of bimekizumab concentrations with repeat dosing.



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

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

Table 9 below summarises the bimekizumab plasma concentrations for the Japanese study participants. Overall the plasma concentrations in Japanese study participants were comparable with those observed in the overall study population.

Table 9: Bimekizumab plasma concentrations by visit for the BKZ 160mg Q4W group (PK-PPS)

Visit	Overall population N=266	Japan N=8
Week 12, n	251	8
GeoMean (GeoCV)	8.114 (72.2)	7.729 (60.9)
Geometric 95% CI	7.486, 8.794	4.834, 12.357
Week 16, n	247	8
Geomean (GeoCV)	8.284 (70.8)	8.223 (62.8)
Geometric 95% CI	7.648, 8.972	5.077, 13.319

BKZ=bimekizumab; BLQ=below the limit of quantification; CI=confidence interval; GeoCV=geometric coefficient of variation; GeoMean=geometric mean; LLOQ=lower limit of quantification; PK-PPS=Pharmacokinetics 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 neutralising 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 are presented by disease indication for: baseline continuous covariates (Table 10), baseline categorical covariates (Table 11), and combined ADAb and neutralising antibodies (NAb) status (Table 12).

Table 10: Baseline characteristics for the participants in the PK analysis data set: continuous 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 11: Baseline characteristics for the participants in the PK analysis data set: categorical 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 12: Combined ADAb/Nab status categorical covariate 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 13. GOF plots are presented in Figure 12 (observed versus predicted concentrations) and Figure 13 (CWRES versus predicted concentrations and time). The GOF plots do not show any unacceptable trends overall. Figure 14 and Figure 15 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 13: 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 $\mathrm{CL/F} = 0.343 \cdot (\frac{\mathrm{WT}}{84})^{0.996}$; $\mathrm{V/F} = 11.2 \cdot (\frac{\mathrm{WT}}{84})^{0.733}$
The effect of race on CL/F is calculated as a proportional change (1+ final model value), compared to Caucasian, Black or others. The equations of the covariate effects are described in detail in Appendix 4.3.4.
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

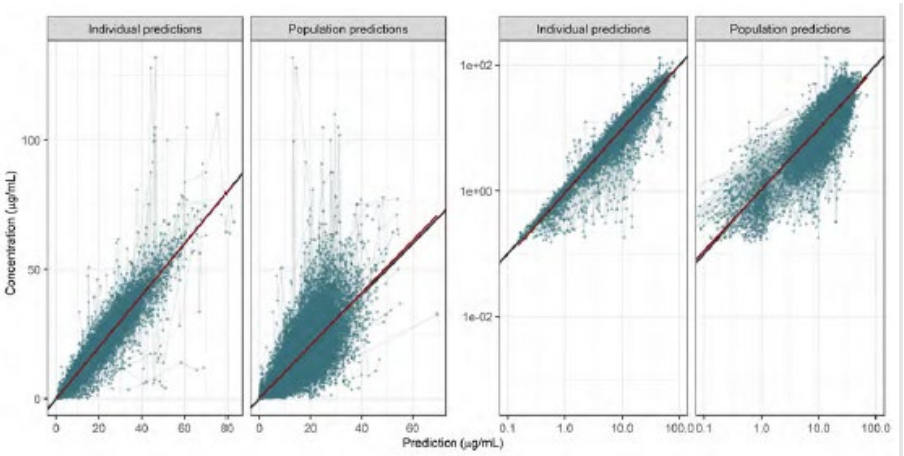


Figure 12: Observed concentrations versus PRED and IPRED for the final population PK model for bimekizumab concentrations. The left panel shows the data on a linear scale and the right panel shows the same plot with logarithmic scales. Individual data points are indicated by dots and the points for each individual visits are connected with a line. The diagonal black line is the line of identity and the red line is a smooth (span 0.75).

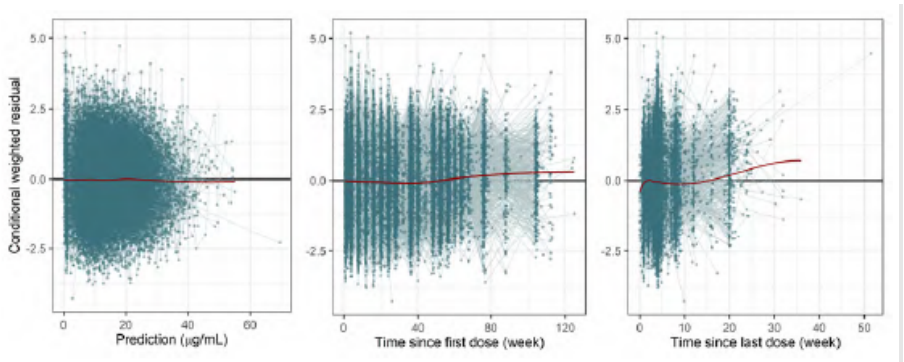


Figure 13: CWRES versus PRED (ledt panel), time since first dose (middle panel) and time since last dose (right panel) of bimekizumab concentrations for the final population PK model. Individual data points are indicated by dots and the points for each individual and visit are connected with a line. The horizontal black line is the zero line and the red line is a smooth. Observations associated with population predictions greater than 60 or time since last dose greater than 50 are excluded from the smooths (span 0.75).

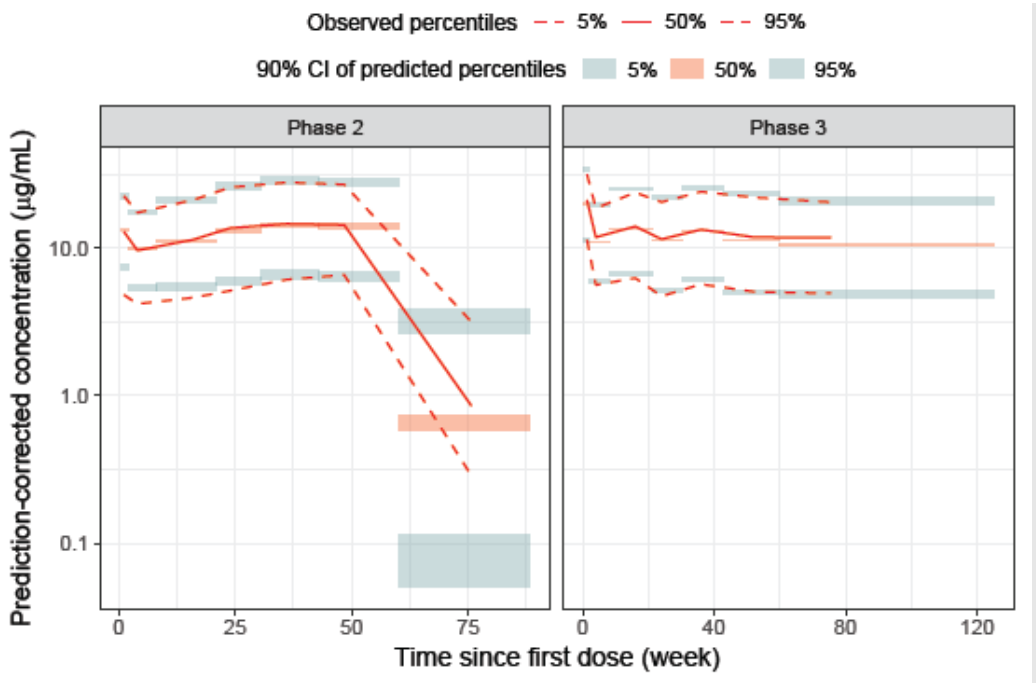


Figure 14: Prediction corrected visual predictive check of bimekizumab concentrations for the final bimekizumab population PK model. Bimekizumab concentrations are displayed versus time after first dose on a semi-logarithmic scale. The solid and dashed red lines represent the median, 5th and 95th percentiles 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.

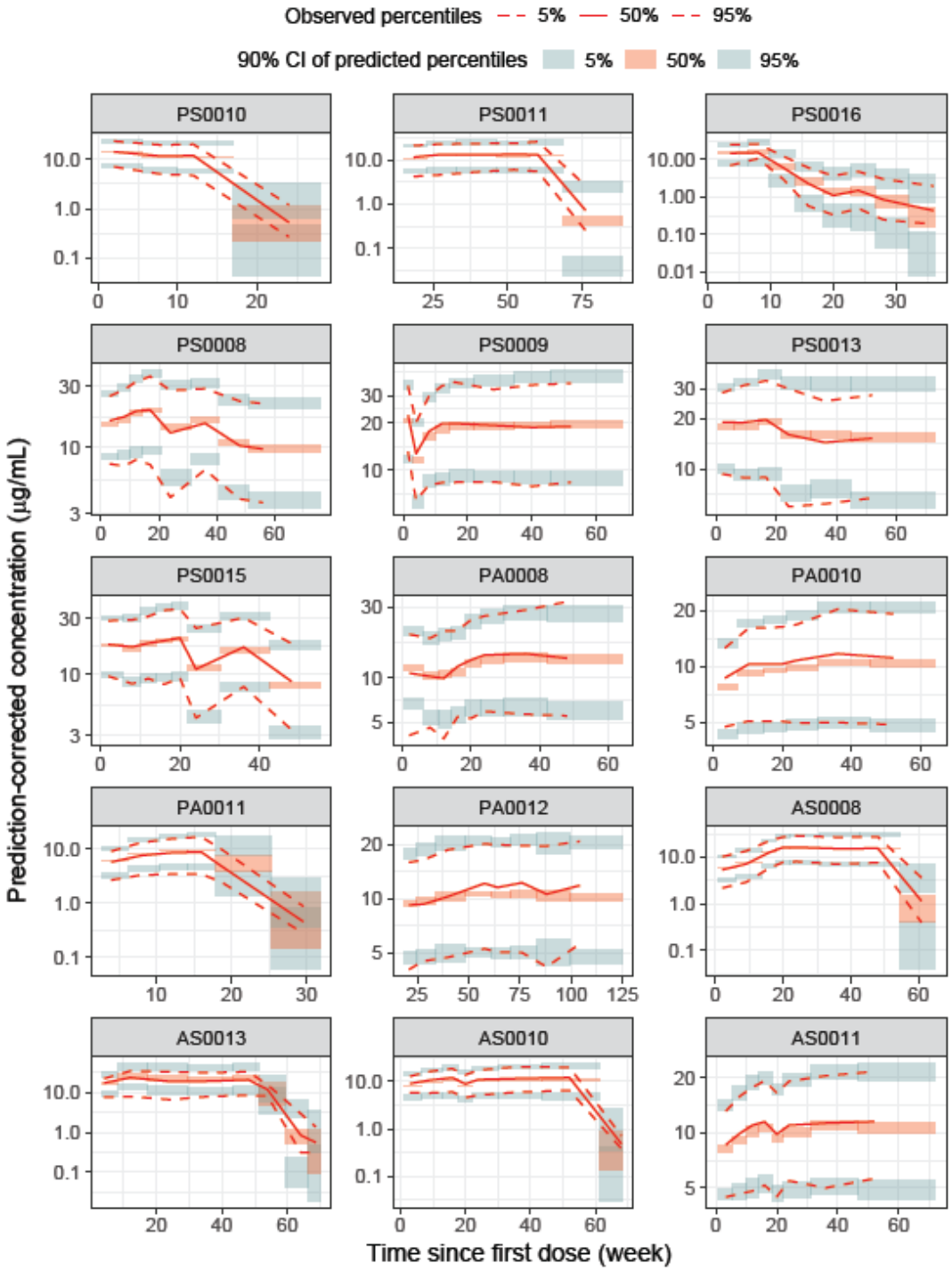


Figure 15: Prediction corrected visual predictive check of bimekizumab concentrations, stratified by study, for the final bimekizumab population PK model. Bimekizumab concentrations are displayed versus time after first dose on a semi-logarithmic scale. The solid and dashed red lines represent the median, 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 90% confidence 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 16 and Figure 17, 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.

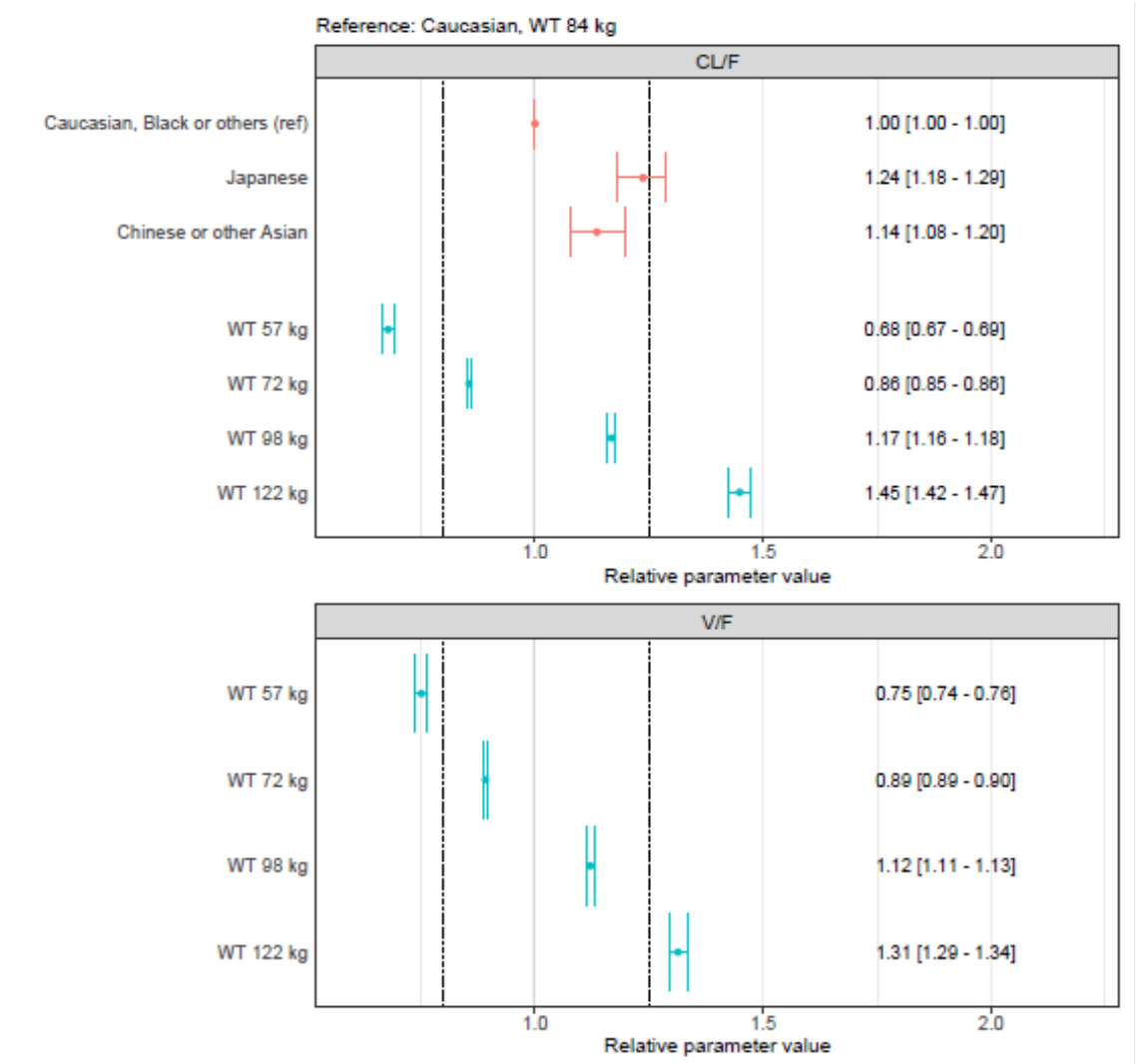


Figure 16: Forest plots illustrating the effects of covariates on bimekizumab PK parameters CL/F and V/F, conditioned on a typical study participant, based on the final bimekizumab model. Closed dots and errors bars, together with their specific values, represent the median of the predictive relative change from the reference participant and its associated 95% Cis; these values are calculated based on 250 samples 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.

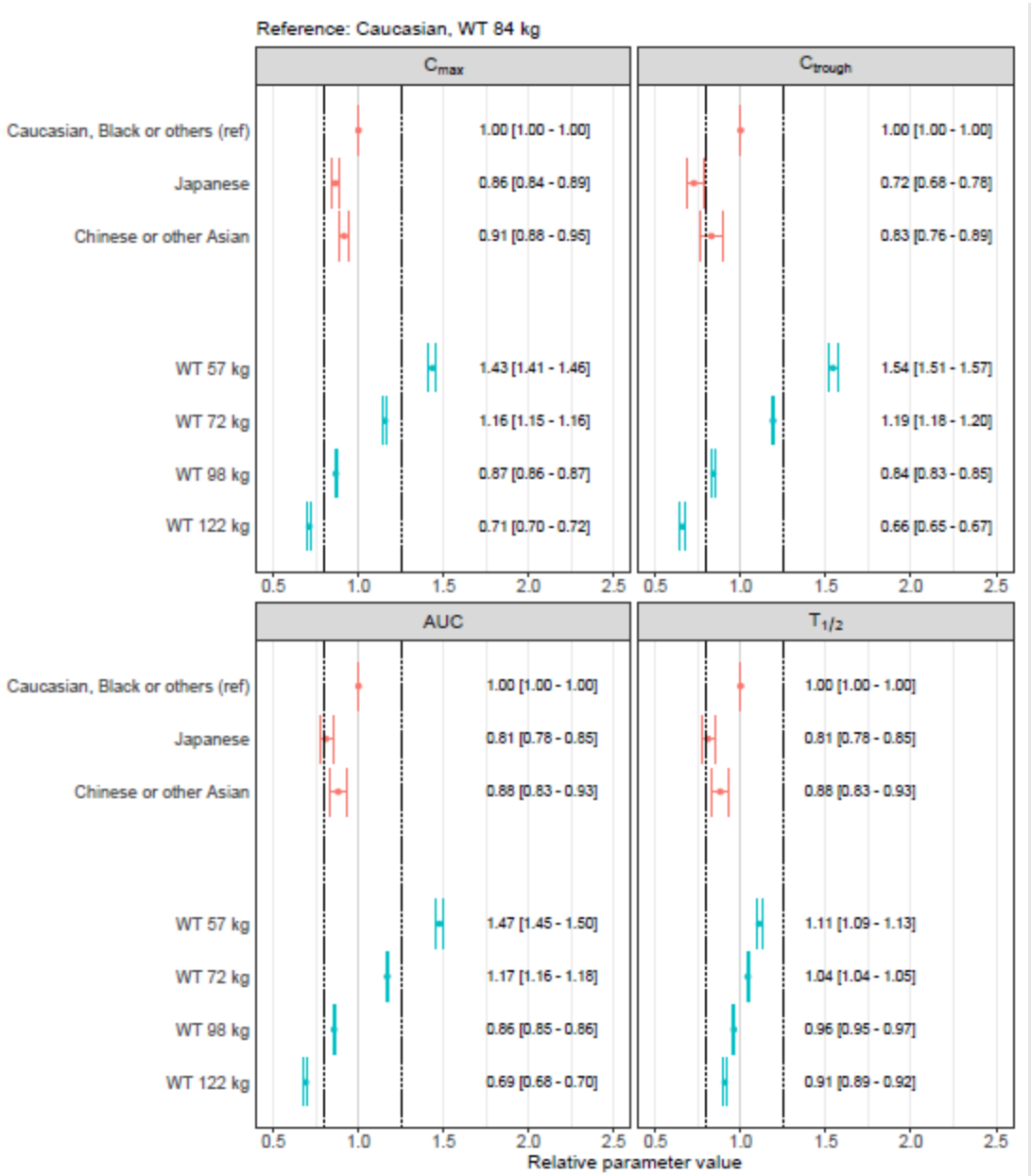


Figure 17: Forest plots illustrating the effects of covariates on bimekizumab PK parameters Cmax, Ctrough, AUC, and t1/2, conditioned on a typical study participant, for a 160 mg Q4W dosing regimen, bse don the final bimekizumab model. Closed dots and errors bars, together with their specific values, represent the median of the predicted relative change from the reference participant and its assiocated 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 13.

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 2

Study PA0008

PA0008 was a Phase 2b, multicenter, randomised, double-blind, placebo controlled, parallel-group, dose-ranging study in adult study participants with active PsA. This study included 4 periods: a Screening Period (4 weeks, washout of medications during this period), 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 blood samples for Bimekizumab antibody detection were taken at Baseline, and Weeks 4, 8, and 12. During the Dose-Blind Period, blood samples for Bimekizumab antibody detection were taken at Weeks 16, 20, 24, 36 and 48.

A summary of ADAb status by visit for the PK-PPS is presented in Table 14. Overall, the highest percentage of ADAb positive study participants occurred in the lowest dose group, bimekizumab 16mg (11 study participants; 26.8%); study participants only remained on this dose for 12 weeks before being re-randomised to a higher dose. The incidence of ADAb positivity consistently increased through Week 12 in the bimekizumab 16mg group. For the 3 highest bimekizumab dose groups, ADAb status was determined through Week 48. The overall percentage of study participants who were ADAb positive at some point up to Week 48 in these dose groups was 25.6% (11 study participants) in the bimekizumab 160mg group and 9.8% (4 study participants) each in the bimekizumab 160mg w/LD and bimekizumab 320mg groups. The incidence of ADAb positivity was low across all visits in the bimekizumab 160mg w/LD and bimekizumab 320mg groups with no apparent temporal relationship.

Table 14: ADAb status by visit (PK-PPS)

Visit	ADAb status	Placebo N=42 n (%)	BKZ 16mg N=39 n (%)	BKZ 160mg N=43 n (%)	BKZ 160mg w/LD N=41 n (%)	BKZ 320mg N=41 n (%)
Overall [a]	ADAb+	1 (2.4)	11 (28.2)	11 (25.6)	4 (9.8)	4 (9.8)
	ADAb-	41 (97.6)	28 (71.8)	32 (74.4)	37 (90.2)	37 (90.2)
	Total	42 (100)	39 (100)	43 (100)	41 (100)	41 (100)
Day 1, Baseline [b]	ADAb+	0	0	3 (7.0)	1 (2.4)	4 (9.8)
	ADAb-	42 (100)	39 (100)	40 (93.0)	40 (97.6)	37 (90.2)
	Total	42 (100)	39 (100)	43 (100)	41 (100)	41 (100)
Week 4 [b]	ADAb+	0	4 (10.3)	1 (2.3)	1 (2.4)	2 (4.9)
	ADAb-	41 (97.6)	35 (89.7)	41 (95.3)	40 (97.6)	39 (95.1)
	Total	41 (97.6)	39 (100)	42 (97.7)	41 (100)	41 (100)
Week 8 [b]	ADAb+	1 (2.4)	5 (12.8)	3 (7.0)	0	3 (7.3)
	ADAb-	40 (95.2)	34 (87.2)	40 (93.0)	39 (95.1)	38 (92.7)
	Total	41 (97.6)	39 (100)	43 (100)	39 (95.1)	41 (100)
Week 12 [b]	ADAb+	0	8 (20.5)	1 (2.3)	1 (2.4)	2 (4.9)
	ADAb-	42 (100)	31 (79.5)	42 (97.7)	38 (92.7)	39 (95.1)
	Total	42 (100)	39 (100)	43 (100)	39 (95.1)	41 (100)
Week 16 [b]	ADAb+	-	-	0	1 (2.4)	0
	ADAb-	-	-	42 (97.7)	37 (90.2)	41 (100)
	Total	-	-	42 (97.7)	38 (92.7)	41 (100)
Week 20 [b]	ADAb+	-	-	1 (2.3)	0	1 (2.4)
	ADAb-	-	-	41 (95.3)	37 (90.2)	39 (95.1)
	Total	-	-	42 (97.7)	37 (90.2)	40 (97.6)
Week 24 [b]	ADAb+	-	-	3 (7.0)	0	0
	ADAb-	-	-	38 (88.4)	36 (87.8)	40 (97.6)
	Total	-	-	41 (95.3)	36 (87.8)	40 (97.6)
Week 36 [b]	ADAb+	-	-	0	0	0
	ADAb-	-	-	41 (95.3)	34 (82.9)	39 (95.1)
	Total	-	-	41 (95.3)	34 (82.9)	39 (95.1)
Week 48 [b]	ADAb+	-	-	6 (14.0)	2 (4.9)	1 (2.4)
	ADAb-	-	-	35 (81.4)	32 (78.0)	39 (95.1)
	Total	-	-	41 (95.3)	34 (82.9)	40 (97.6)

ADAb=anti-drug antibody; BKZ=bimekizumab; LD=loading dose; PK-PPS=Pharmacokinetic Per-Protocol Set

The impact of ADAb on the PK of bimekizumab was determined, which was defined as a reduction in bimekizumab plasma concentrations by one-half in the presence of ADAb. Based on the above criteria, in 3 of the 11 study participants in the bimekizumab 16mg group and 1 of the 4 study participants in the bimekizumab 160mg w/LD group who were ADAb positive, the presence of ADAb had an impact on bimekizumab plasma concentrations during the Double-blind Period. During the Dose-blind Period, the impact on plasma concentrations continued for only 1 study participant (from the 16mg group). At all other bimekizumab doses, the presence of ADAb did not have an impact on bimekizumab plasma concentrations.

Study PA0009

PA0009 was a Phase 2b multicenter open-label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult study participants with PsA who completed the Phase 2b study PA0008. During the study blood samples for Bimekizumab antibody detection were taken at the Entry Visit, and at Weeks 12, 24, 36, 48, 72, 96, and 104.

A summary of ADAb status in PA0009 is presented for the Safety Set in Table 15. The overall incidences of ADAb positivity in PA0009 alone were 18 study participants (16.5%) and 14 study participants (18.9%) for the PA0009 study participants who had received bimekizumab 160mg Q4W and bimekizumab 320mg Q4W at the completion of PA0008, respectively.

Table 15: Anti-bimekizumab antibody status in PA0009 by treatment at completion of PA0008 (SS)

Visit (Week)	Incidence of ADAb Positivity	BKZ 160mg N=109 n (%)	BKZ 320mg N=74 n (%)
Overall [a]	ADAb+	18 (16.5)	14 (18.9)
	ADAb-	88 (80.7)	56 (75.7)
	Total	106 (97.2)	70 (94.6)
Overall including SFU [b]	ADAb+	22 (20.2)	23 (31.1)
	ADAb-	81 (74.3)	47 (63.5)
	Total	103 (94.5)	70 (94.6)

ADAb=anti-bimekizumab antibody, BKZ=bimekizumab, SFU=Safety Follow-up.
[a] Overall ADAb+ is defined as having a result above the cut point and confirmed positive at any time in the PA0009 treatment period. Overall ADAb- is defined as all results either below the cut point or above the cut point and not confirmed positive during the PA0009 treatment period. The treatment period does not include PA0008 Baseline/pre-treatment samples.
[b] Definition as in [a], with the inclusion of the SFU visit.

A summary of ADAb status in PA0008 and PA0009 overall is presented for the SS in Table 16. The overall incidences of ADAb positivity (study participant was considered ADAb positive if at least 1 assessment was confirmed positive at any time in the PA0008 and PA0009 Treatment Periods) were 25 study participants (22.9%) and 24 study participants (32.4%) for the PA0009 study participants who had received bimekizumab 160mg Q4W and bimekizumab 320mg Q4W at the completion of PA0008, respectively. Overall, ADAb status did not have an impact on the number of ACR50 responders.

Table 16: Anti-bimekizumab status in PA0008 and PA009 by treatment completion of PA0008 (SS)

Visit (Week)	ADAb status	BKZ dose at PA0008 completion→BKZ dose in PA0009	
		BKZ 160mg→160mg [a] N=109 n (%)	BKZ 320mg→160mg [a] N=74 n (%)
Overall [b]	ADAb+	25 (22.9)	24 (32.4)
	ADAb-	81 (74.3)	46 (62.2)
	Total	106 (97.2)	70 (94.6)
Overall including SFU [c]	ADAb+	28 (25.7)	30 (40.5)
	ADAb-	75 (68.8)	40 (54.1)
	Total	103 (94.5)	70 (94.6)

ADAb=antidrug antibody; BKZ=bimekizumab; SFU=Safety Follow-up; SS=Safety Set

Phase 3

Study PA0010

PA0010 is a Phase 3 multicenter study consisting of a 16-week, randomised, double-blind, placebo-controlled, active-reference Treatment Period followed by a 36-week Active Treatment-Blind Period to evaluate the efficacy and safety of bimekizumab in adult study participants with active PsA. The data for this assessment are from an interim report up to Week 24.

During the study, blood samples for Bimekizumab antibody detection were taken at the Baseline, and at Weeks 4, 8, 12, 16, 20, 24, 36, and 52.

Summaries of the overall ADAb incidences up to Week 16 and Week 24 and the number and percentage of study participants for each ADAb sub-category up to Week 24 are presented for the SS in Table 17. By Week 24, 36.4% of study participants in the bimekizumab 160mg Q4W group had anti-drug antibodies, with low ADAb positive rates at Baseline and the majority of the ADAb positivity developed after bimekizumab treatment initiation (32.7% of study participants had treatment-emergent ADAb positive result in the bimekizumab 160mg Q4W group by Week 24). The plasma concentration levels of bimekizumab were slightly reduced in study participants who were ADAb positive compared with those who were ADAb negative. Anti-drug antibodies had no clear impact on clinical efficacy (ACR50 and PASI90) up to Week 24 or safety (TEAE incidence) of study participants treated with bimekizumab during the study.

Table 17: Anti-drug antibody status overall and in each ADAb subcategory by treatment group (SS)

Study period	ADAb category	Placebo/BKZ 160mg Q4W N=271 n (%)	BKZ 160mg Q4W N=431 n (%)
Overall up to Week 16[a]	Positive	-	118 (27.4)
	Negative	-	302 (70.1)
	Total	-	420 (97.4)
	Missing	-	11 (2.6)
Overall up to Week 16 for efficacy subgroup analysis[b]	Positive	-	55 (12.8)
	Negative	-	365 (84.7)
	Total	-	420 (97.4)
	Missing	-	11 (2.6)
Overall up to Week 24[a]	Positive	38 (14.0)	157 (36.4)
	Negative	226 (83.4)	248 (57.5)
	Total	264 (97.4)	405 (94.0)
	Missing	7 (2.6)	26 (6.0)
Overall up to Week 24 for efficacy subgroup analysis[b]	Positive	8 (3.0)	96 (22.3)
	Negative	256 (94.5)	309 (71.7)
	Total	264 (97.4)	405 (94.0)
	Missing	7 (2.6)	26 (6.0)
Incidence by ADAb subcategory [c]			
1. Pre ADAb negative – treatment emergent ADAb negative		226 (83.4)	248 (57.5)
2. Pre ADAb negative – treatment emergent ADAb positive		30 (11.1)	141 (32.7)
3. Pre ADAb positive – treatment emergent reduced ADAb		4 (1.5)	2 (0.5)
4. Pre ADAb positive – treatment emergent unaffected ADAb positive		2 (0.7)	13 (3.0)
5. Pre ADAb positive – treatment boosted ADAb positive		2 (0.7)	0
6. Inconclusive		0	1 (0.2)
7. Total treatment emergent (categories 2 and 5)		32 (11.8)	141 (32.7)
8. Total prevalence of pre-ADAb positivity (categories 3-6)		8 (3.0)	16 (3.7)
9. Missing		7 (2.6)	26 (6.0)

ADAb=anti-BKZ antibody; BKZ=bimekizumab; NI=negative immunodepletion; NS=negative screen; PI=positive immunodepletion; PS=positive screen; Q4W=every 4 weeks

Study PA0011

PA0011 was a Phase 3 multicenter study consisting of a 16-week randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in study participants with active PsA. During the study, blood samples for bimekizumab antibody detection were taken at Baseline, and at Weeks 4, 8, 12, and 16.

Summaries of the overall ADAb incidences up to Week 16 and the number and percentage of study participants for each ADAb sub-category up to Week 24 are presented for the SS in Table 18. By Week 16, 37.5% of study participants in the bimekizumab 160mg Q4W group were ADAb positive, with low ADAb positive rates at Baseline and the majority of ADAb positivity developing after bimekizumab treatment initiation (33.3% of study participants who were pre-treatment ADAb negative became treatment emergent ADAb positive by SFU). The plasma concentrations of bimekizumab after 160mg Q4W dosing were lower in study participants who were NAb positive compared with those who were ADAb negative. However, anti-drug antibodies had no clear impact on clinical efficacy (ACR50 and PASI90) up to Week 16 or safety (TEAE incidence) of study participants treated with bimekizumab during the study.

Table 18: Anti-drug antibody status by visit and category (SS)

Study period	ADAb category	BKZ 160mg Q4W N=267 n (%)
Overall up to Week 16[a]	Positive	100 (37.5)
	Negative	162 (60.7)
	Total	262 (98.1)
Overall up to Week 16 for efficacy subgroup analysis[b]	Positive	52 (19.5)
	Negative	210 (78.7)
	Total	262 (98.1)
Overall including SFU[c]	Positive	101 (37.8)
	Negative	161 (60.3)
	Total	262 (98.1)
Overall including SFU for efficacy subgroup analysis[c]	Positive	52 (19.5)
	Negative	210 (78.7)
	Total	262 (98.1)

ADAb=anti-BKZ antibody; BKZ=bimekizumab; NI = negative immunodepletion; NS=negative screen; PI=positive immunodepletion; PS=positive screen; Q4W=every 4 weeks; SFU=Safety Follow-Up; SS=Safety Set

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.

In the population PK/PD analyses, there was no evidence of a statistically significant impact for anti-drug-antibodies (ADAb)/neutralising antibodies (NAb) status on PASI or ACR response rates.

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 metabolised in the liver. Thus, no dose adjustment is proposed in these patient populations by the MAH.

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 19.

Table 19: Simulated AUCss, Cmaxss, Ctroughss, Tmaxss 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 ACR response, age was a statistically significant covariate on Emax; ACR response increased with decreasing age. The predicted Week 16 ACR50 response probability was 0.56 and 0.37 in study participants <45 and ≥45 years, respectively, following bimekizumab 160mg Q4W. The predicted Week 16 ACR50 response probability was 0.46 and 0.26 in study participants <65 and ≥65 years, respectively, following bimekizumab 160mg Q4W.

Since age had no clinically relevant impact on bimekizumab PK, with the 95% CI of the PK parameters and exposure ratios falling completely within 0.8 to 1.25 compared to a typical participant, age-related changes in PK would not drive the predicted change in ACR50 response with age. Thus, according to the MAH, no dose adjustment for age is required.

Gender

In the PK/PD model of ACR response, sex was a statistically significant covariate on the probability of achieving an ACR response. The predicted Week 16 ACR50 response probability was 0.51 and 0.38 in males and females, respectively, following bimekizumab 160mg Q4W. This appears to be a PD-related sex effect rather than an effect driven by differences in PK.

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. Therefore, sex-related changes in PK would not drive the predicted change in ACR50 response. Thus, 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 summarised for the reference race group (Caucasian, Black, American Indian or Alska Native, Hawaiian or other Pacific islander, missing and others, referred to as Caucasian), Chinese and other Asian (referred to as Chinese), and Japanese study participants in Table 20.

Table 20: Median and 2.5th-97.5th AUCss, Cmaxss and Ctroughss 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 [2.5th-97.5th percentiles]
[e]: The dosing regimen was Q4W, thus the AUC_{ss} was multiplied by 2 to obtain AUC_{ss} over 8 weeks.

Keeping all PD covariates in the PK/PD model at the reference level (female, age of 49 years, baseline hs-CRP of 4.5 mg/L), the predicted ACR50 probability at Week 16 was 0.35 for Japanese study participants weighing 103 kg, compared to 0.38 in study participants with typical PK parameters (WT=84 kg and Caucasian race). This 3% difference in response rates may be considered not clinically relevant. Thus, based on the overall data, no dose adjustment for race or ethnicity is required, according to the MAH.

Bodyweight

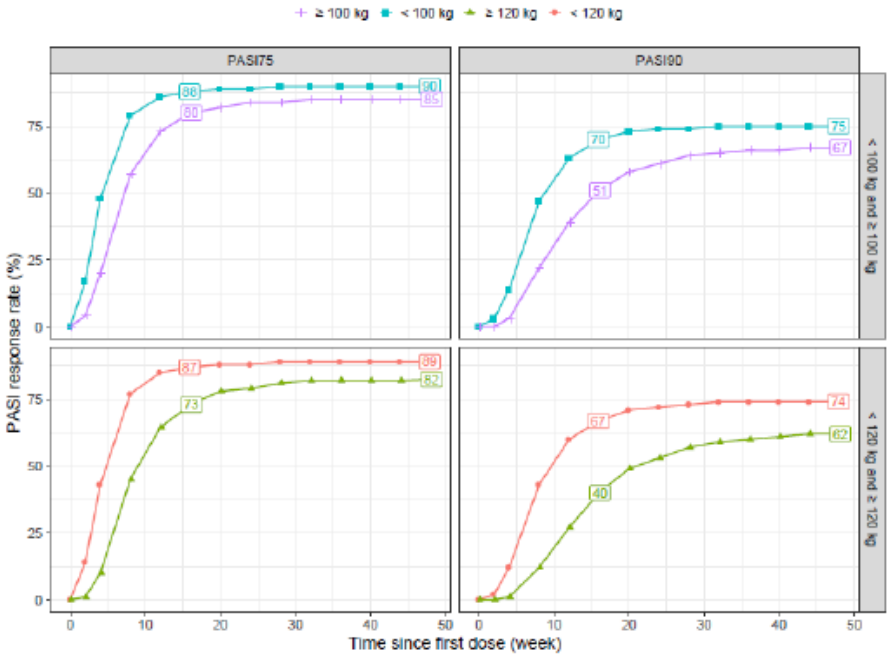
In the integrated popPK model, WT had the largest impact on CL/F and impacted V/F to a lesser extent. Compared to the reference WT of 84 kg, the steady-state AUC was predicted to be approximately 30% lower for a subject weighing 122 kg and 50% higher for a subject weighing 57 kg. According to the MAH, the predicted magnitude of drop in exposure for a patient weighing 122 kg is less likely to be seen in patients with PsA (or axSpA) compared to patients with PSO, since more than 95% of patients with PsA and axSpA 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 21.

Table 21: Median and 2.5th-97.5th AUCss, Cmaxss and Ctroughss 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.

Baseline body weight was the covariate that had the largest impact on PK and PASI responses, respectively. Bimekizumab exposure decreased with increasing body weight, and higher body weight was predictive of longer PASI t1/2. Figure 18 shows the simulated median PASI75 and PASI90 profiles following 160mg Q4W dosing for subpopulations by 100kg and 120kg cut-offs. The PASI90 response rate appears to be more sensitive than PASI75 to the body weight effect. The simulations showed a ~12% difference in Week 48 PASI90 response rate for study participants weighing ≥120kg compared with <120kg, while a smaller difference (~8%) was predicted between study participants weighing ≥100kg compared with <100kg. The results suggest that patients with PsA and concomitant moderate to severe PSO weighing ≥120kg may benefit from an increased dose or dosing frequency to maintain maximal PASI90 responses.



PASI=Psoriasis Area and Severity Index; PASI75/90=75%/90% improvement in PASI; Q4W=every 4 weeks
Note: The labels indicate the median response rates at Week 16 and Week 48 for the weight subgroup. These simulation results represent the median predictions in the study population which is defined by ≥3% body surface area of psoriasis at Baseline, a median body weight of 85.5kg (CL0540 Table 4), and no prior biologics use for 61.6% of study participants (CL0540 Table 5).

Figure 18: Simulated median PASI75 and PASI90 response rates following 160mg Q4W dosing over time, stratified by body weight subgroups and response category (CL0540)

Simulations based on the PK/PD model for ACR response were conducted with 160mg Q4W to evaluate the impact of decreasing exposure with increasing body weight. For patients with PsA overall, the Week 16 ACR50 response probability ranged from 0.36 for a patient weighing 120kg (95th percentile for body weight) to 0.40 for a patient weighing 57kg (5th percentile for body weight) (Table 22). According to the MAH, these differences are not considered to be clinically meaningful and would not warrant dose adjustment by body weight in patients with PsA.

Table 22: Predicted probabilities of ACR response at week 16, stratified by body weight percentiles, assuming a 160mg Q4W dosing regimen (CL0540)

Body weight percentile	Body weight (kg)	ACR20 response[a]	ACR50 response[a]	ACR70 response[a]
5th	57	0.67 [0.65 - 0.69]	0.40 [0.38 - 0.43]	0.21 [0.19 - 0.23]
25th	72	0.66 [0.64 - 0.68]	0.39 [0.37 - 0.42]	0.20 [0.18 - 0.22]
50th	84	0.66 [0.64 - 0.68]	0.38 [0.36 - 0.41]	0.20 [0.18 - 0.21]
75th	97	0.65 [0.63 - 0.67]	0.37 [0.35 - 0.40]	0.19 [0.17 - 0.21]
95th	120	0.64 [0.61 - 0.66]	0.36 [0.34 - 0.38]	0.17 [0.16 - 0.19]

ACR20/50/70=American College of Rheumatology 20%, 50%, and 70% response criteria; Q4W=every 4 weeks
[a] Probability at Week 16: median [2.5th - 97.5th percentile].

Drug 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 metabolised by the cytochrome P450 (CYP450) system.

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 of use of these concomitant medications on either probability of achieving ACR response or Emax in the PK/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 humanized, 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

Study PA0008

PA0008 was a Phase 2b, multicenter, randomised, double-blind, placebo controlled, parallel-group, dose-ranging study in adult study participants with active psoriatic arthritis (PsA). This study included 4 periods: a Screening Period (4 weeks, washout of medications during this period), 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).

The PD variables were concentrations of cytokines of relevance to interleukin (IL)-17A/F signalling pathway and PsA biology, and included but were not limited to IL-17A, IL-23, IL-6, and tumor necrosis factor-alpha (TNFα). During the Double-Blind Period blood samples for cytokines, complement, and biomarker analysis were taken at Baseline, and Weeks 1, 4, and 12. During the Dose-Blind Period blood samples for cytokines, complement, and biomarker analysis were taken at Weeks 24 and 48.

None of the cytokines or chemokines that were measured showed clinically relevant changes (where an appropriate number of data points were available) during the Double-blind Treatment Period, either with dose or with duration. No other PD analyses, outside of the efficacy analyses, were conducted in PA0008.

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. As described in the initial 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 PsA clinical studies, and the incidence of major adverse cardiac events was low.

2.3.4. PK/PD modelling

Population PK/PD modelling of ACR and PASI response from Phase 2 studies

Using data from the 12-week placebo-controlled period in PA0008, population PK and PK/PD models were developed to establish the dose-exposure-response relationship between bimekizumab and both ACR20/50/70 and PASI scores as well as the time courses of these endpoints (CL0464 and CL0463). These analyses were conducted to support the dose regimen selection for the pivotal Phase 3 studies in the PsA program.

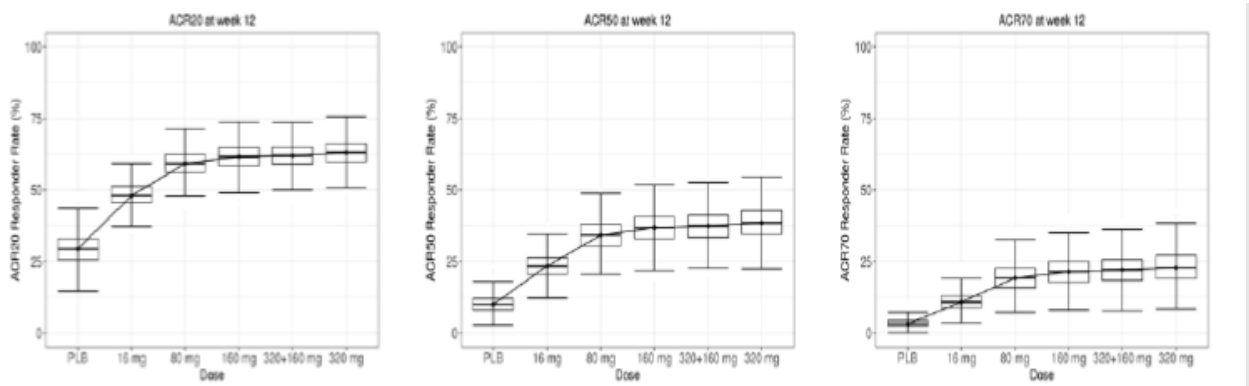
ACR response model

For the popPK model, a total of 771 plasma bimekizumab concentration records from 159 study participants were available, while 986 ACR observations from 199 study participants were available for the ACR PK/PD model. The dependent variable (ACR 20/50/70) was a categorical variable, based on 20% improvement in ACR response (ACR20), 50% improvement in ACR response (ACR50) and 70% improvement in ACR response (ACR70).

Bimekizumab PK was described by a one-compartment model with linear absorption and elimination. Body weight was a significant covariate on both CL/F and V/F, indicating plasma concentration decreased with increasing body weight. A mixed-effects logistic regression model was used to describe placebo and bimekizumab effects on ACR20/50/70 responses simultaneously. A latent variable captured the time delay between PK and bimekizumab effect while a serial correlation term with ACR kept the memory of the previous state.

While body weight was found to be a covariate on both CL/F and V/F, the exposure-response analysis revealed that body weight did not impact ACR response rate. Baseline tender joint count (TJC) was found to be a significant covariate on the probability of achieving ACR50 response; study participants with higher Baseline TJC had lower ACR response. The higher Baseline TJC for the bimekizumab 320mg Q4W arm (median TJC of 19.00) partly explained the reduced Week 12 ACR50 response with this dose level compared with the bimekizumab 160mg dose groups (median TJCs of 14.00 and 16.00). None of the other covariates tested, including body mass index (BMI), Baseline swollen joint count, disease duration, sex, previous cDMARDs, prior biologics, number of cDMARDs, or study center, had a significant impact on ACR response.

Simulations were performed using the PK/PD model to predict the dose response of Week 12 ACR20, ACR50, and ACR70 response rates. Based on the simulations, the maximum ACR response rate was predicted to be achieved with the 160mg Q4W dose (Figure 19). Higher doses, such as 320mg, were unlikely to provide additional benefit.



ACR20/50/70=American College of Rheumatology 20%/50%/70% improvement criteria; BKZ=bimekizumab; PLB=placebo (0mg Q4W); Q4W=every 4 weeks
Note: 16mg=16mg BKZ Q4W; 80mg=80mg BKZ Q4W; 160mg=160mg BKZ Q4W; 320mg=320mg BKZ Q4W, 320+160=320mg loading dose +160mg BKZ Q4W.

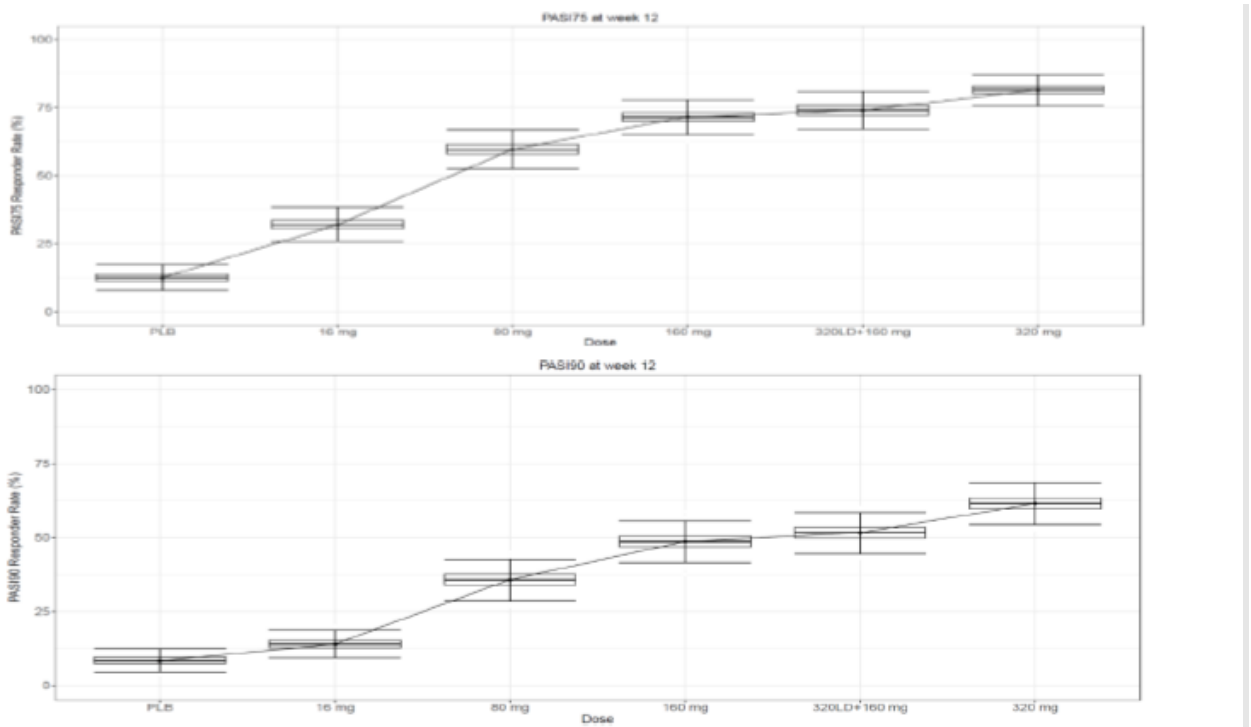
Figure 19: Week 12 simulated ACR20/50/70 response rate (CL0464)

PASI response model

For the population PK/PD model to describe the exposure-response relationship between plasma bimekizumab concentration and PASI score as well as the time course of PASI (CL0463), a total of 649 PASI scores from 131 study participants were included in the analysis dataset.

The PK/PD rate model was an indirect response model with a zero order production (Kin) and a first order elimination rate from the indirect response compartment (Kout, parameterized as PASI turnout t1/2). Bimekizumab changed the PASI score through inhibiting Kin. In this model, body weight was found to be a covariate on the turnout half-life, suggesting a longer time to achieve maximum PASI response in patients with higher body weight. Notably, simulations revealed only marginal differences in the time of maximum effect between participants with higher and lower body weight. None of the other covariates tested (including BMI, age, BSA, Baseline PASI, sex, race, or ADAb presence) had a significant impact on PASI.

Simulations from the model indicated that PASI75 and PASI90 response rates were near maximal at 160mg Q4W for the overall PsA population (with mostly mild to moderate skin disease). The simulations also indicated that doses lower than 160mg may provide reduced PASI75 and PASI90 responses (Figure 20). While some improvement in Week 12 PASI90 was predicted with the 320mg Q4W regimen, the limited number of participants with PsA and concomitant moderate to severe PSO in study PA0008 precluded robust assessment of PASI responses for this subgroup. Thus, the Phase 3 PsA program utilised bimekizumab 160mg Q4W with no recommendation of other regimens for participants with concomitant moderate to severe PSO.



PASI75/90=Psoriasis Area and Severity Index 75%/90%; BKZ=bimekizumab; PLB=placebo (0mg Q4W); Q4W=every 4 weeks
Note: 16mg=16mg BKZ Q4W; 80mg=80mg BKZ Q4W; 160mg=160mg BKZ Q4W; 320mg=320mg BKZ Q4W, 320LD+160=320mg loading dose +160mg BKZ Q4W.

Figure 20: Week 12 simulated PASI75 and PASI90 response rates (CL0463)

The modelling results of CL0464 and CL0463 indicated that prior biologic use had no impact on PK/PD parameters; thus, in Phase 3 studies, bimekizumab 160mg Q4W was tested in both bDMARD-naïve participants (PA0010) and participants who were inadequate responders to ≤2 prior anti-TNFα treatments (PA0011).

Population PK-PD modelling of PASI and ACR response following bimekizumab subcutaneous administration in patients with psoriatic arthritis

The aims of these analyses were to characterise the exposure-response relationships between bimekizumab plasma concentrations and the two efficacy endpoints, Psoriasis Area and Severity Index (PASI) and American College of Rheumatology (ACR) response, in patients with PsA, using a population PK-PD modelling approach. The data originated from one completed studies PA0008, PA0010 and PA0011.

The impact of the exploratory covariates was investigated using the SCM procedure with adaptive scope reduction. Covariates evaluated in the PK-PD models are presented in Table 23.

Table 23: Covariates included (mechanistic) or tested (structural/exploratory) in the PK-PD models

Model[a]	Type	Covariate[b]
PASI model: Baseline	Exploratory	sex, body weight, prior use of biologics, MTX use at baseline, disease duration, baseline hs-CRP
PASI model: Placebo effect	Exploratory	age, sex, body weight, race[c], region, prior use of biologics, prior anti-TNF therapy[d], MTX use at baseline, corticosteroids use at baseline, disease duration, baseline PASI, baseline percentage of BSA affected by PSO[e], presence of nail PSO at baseline, baseline hs-CRP
PASI model: EC50	Exploratory	age, sex, body weight, race[c], region, ADAb and NAb status[f], prior use of biologics, prior anti-TNF therapy[d], MTX use at baseline, corticosteroids use at baseline, disease duration, baseline PASI, baseline percentage of BSA affected by PSO[e], presence of nail PSO at baseline, baseline hs-CRP
PASI model: PASI $t_{1/2}$	Exploratory	sex, body weight, prior use of biologics, MTX use at baseline, disease duration, baseline PASI, baseline percentage of BSA affected by PSO[e], baseline hs-CRP, age
ACR response model: probability of response	Exploratory	age, sex, body weight, race[c], region, ADAb and NAb status[d], prior use of biologics, prior anti-TNF therapy, conventional synthetic DMARDs use at baseline, MTX use at baseline, corticosteroids use at baseline, disease duration, baseline SJC, baseline TJC, presence of enthesitis at baseline, presence of dactylitis at baseline, baseline hs-CRP
ACR response model: E_{max}	Exploratory	age, sex, body weight, race[c], region, ADAb and NAb status[d], prior use of biologics, prior anti-TNF therapy, conventional synthetic DMARDs use at baseline, MTX use at baseline, corticosteroids use at baseline, disease duration, baseline SJC, baseline TJC, presence of enthesitis at baseline, presence of dactylitis at baseline, baseline hs-CRP

[a] The covariates were only considered for parameters that were associated with IIV.
[b] In this analysis no time-varying covariates were considered, the value at baseline was used, except for ADAb and NAb status which were defined on patient level.
[c] Specifically in this analysis, it was planned to look at race, with the following additional stratification for Asian study participants: Japanese (Asian study participants living in Japan) and other Asian (other Asian study participants, excluding Japanese). The latter was lumped with the race group defined as *others* at the modeling stage.
[d] Was not actually tested as it was perfectly correlated with prior use of biologics, and would have resulted in the same drop in OFV.
[e] Was tested as a continuous covariate, and as a categorical covariate [≥3 to <10% and ≥10%].
[f] 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 48/24/16 week follow-up (PASI model) or 12/16/16 week follow-up (ACR response model) for PA0008, PA0010 and PA0011 respectively.

ACR response model

ACR 20/50/70 response was the primary efficacy endpoint in study participants with PsA. In total, 7124 ACR response observations from 1314 patients with PsA were included in this analysis.

The final ACR response model was a proportional odds model with a treatment effect (placebo and drug effects). The probabilities of ACR20, ACR50 and ACR70 response were a function of the baseline probabilities, the placebo effect, which increased with increasing time (log-linear relationship), and the drug effect, which increased with increasing bimekizumab plasma concentration and increasing time. The active drug model was constituted of an Emax function of the individual bimekizumab plasma

concentration, and an exponential decay function of time. The EC90 was 14.6 µg/mL in the final model. The median Ctrough,ss for a 160 mg Q4W dosing regimen is 10.7 µg/mL, which corresponds to EC87 (i.e., concentration at 87% maximum effect). The model predicted the largest increase in drug effect, independent of concentration, to be achieved by approximately Week 6, which supports fast onset of bimekizumab effect on ACR response in patients with PsA.

The final model included the effect of age and baseline high sensitivity C-reactive protein (hs-CRP) on Emax, as well as the effect of sex on the probability of response. Under active treatment, the probability of ACR response increased with decreasing age and with increasing baseline hs-CRP. Males had higher probability of ACR response than females. There was no evidence of a statistically significant impact for ADAb/NAb status, use of concomitant medications at baseline (MTX, csDMARDs or corticosteroids) or disease duration on either probability of ACR response or Emax.

The parameter estimates of the final ACR response model, compared to the base model, are presented in Table 24. VPC plots for the final model are presented in Figure 21 and Figure 22. These figures demonstrate that the final ACR response model provides a good description of the observed data overall.

Table 24: Parameter estimates of the final ACR response model, compared to the base model.

		Final model		Base model	
Run		36		32	
OFV		9645.46		9716.46	
Condition number		16.62		13.04	
		Final model		**Base model**	
	Unit	**Value**	**RSE (%)**	**Value**	**RSE (%)**
BL_{20}: Baseline ACR20 probability		-30.0	(FIX)	-30.0	(FIX)
$DiffBL_{50}$: Baseline difference for ACR50 probability		-2.18	2.96	-2.19	2.96
$DiffBL_{70}$: Baseline difference for ACR70 probability		-3.97	2.52	-3.98	2.52
Placebo slope	/day	902	(FIX)	902	(FIX)
Placebo intercept		16.4	(FIX)	16.4	(FIX)
E_{max}		3.73	6.10	4.16	5.29
EC_{50}	µg/mL	1.62	28.8	1.37	29.7
k_{time}	/day	0.0624	8.03	0.0650	7.67
Sex effect on the probability of response		0.535	27.0		
Age effect on E_{max}		-0.0167	15.8		
Baseline hs-CRP effect on E_{max}		0.00603	25.4		
IIV response	(CV)	2.12	4.74	2.22	4.55
IIV E_{max}	(CV)	2.35	11.0	2.45	10.4

BL_{20}, $DiffBL_{50}$ and $DiffBL_{70}$ probabilities are reported on the logit scale.
The detailed equations for the covariate effects are presented in Appendix 4.3.4.
The RSE for IIV parameters are reported on the approximate SD scale.

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

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

$$LP_{70} = BL_{20} + DiffBL_{70} + \log(1 + Slope_{pbo} \cdot time) + Int_{pbo} + (1 - e^{-k_{time} \cdot time}) \cdot \frac{E_{max} \cdot concentration}{concentration + EC_{50}} + IIV_{response}$$

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

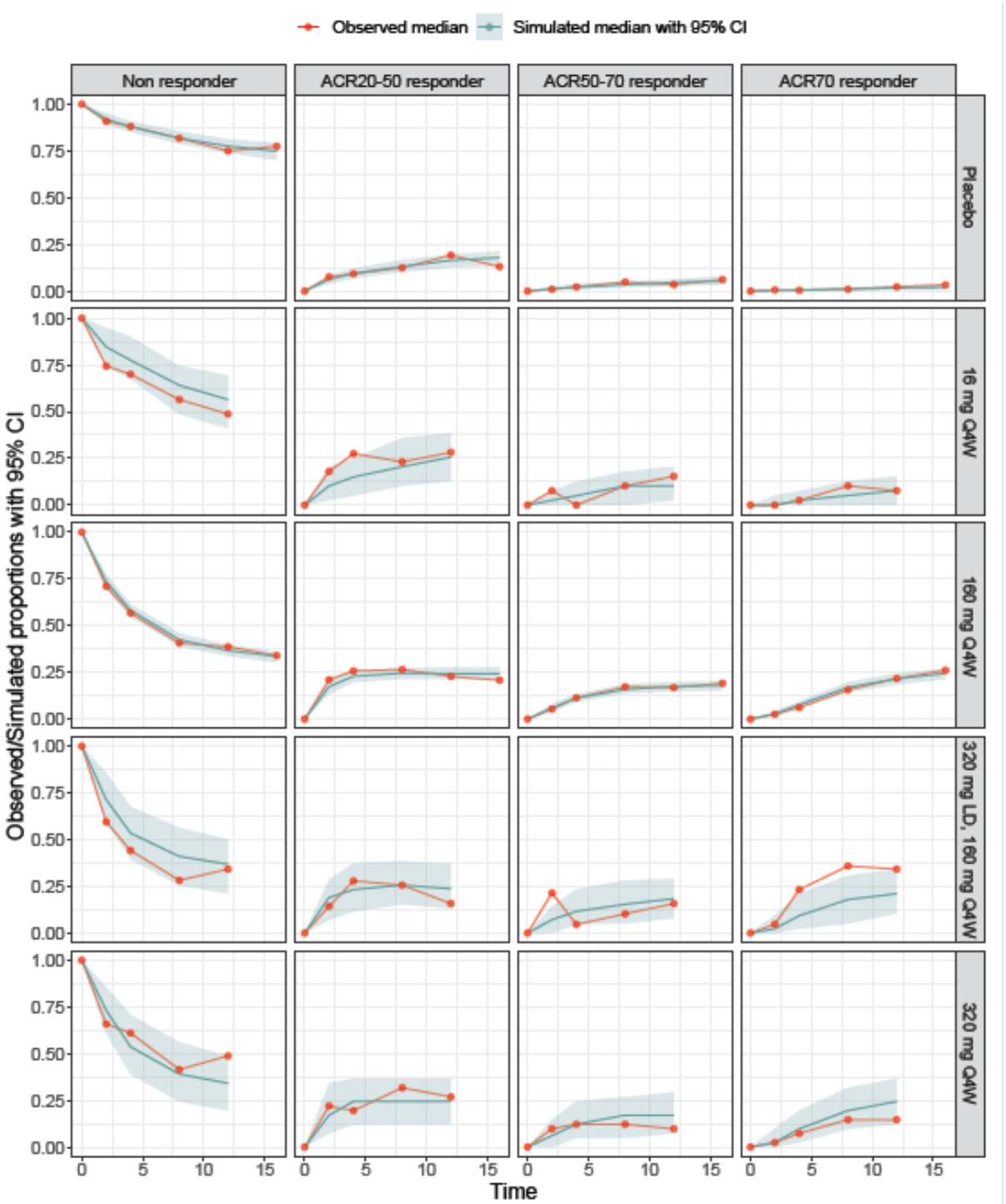

Observed median
Simulated median with 95% CI
Non responder
ACR20-50 responder
ACR50-70 responder
ACR70 responder
Placebo
16 mg Q4W
160 mg Q4W
320 mg LD, 160 mg Q4W
320 mg Q4W
Observed/Simulated proportions with 95% CI
Time

Figure 21: Visual predictive check of the proportion of ACR non-responders, ACR20-50, ACR50-70 and ACR70 responders versus nominal time since first dose, stratified by dose group, for the final ACR response model. 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 ACR analysis data set, and the red line is the observed median. Note that, in this figure, ACR70 and ACR50 responders were not counted as ACR20 responders, and ACR70 responders were not counted as ACR50 responders.

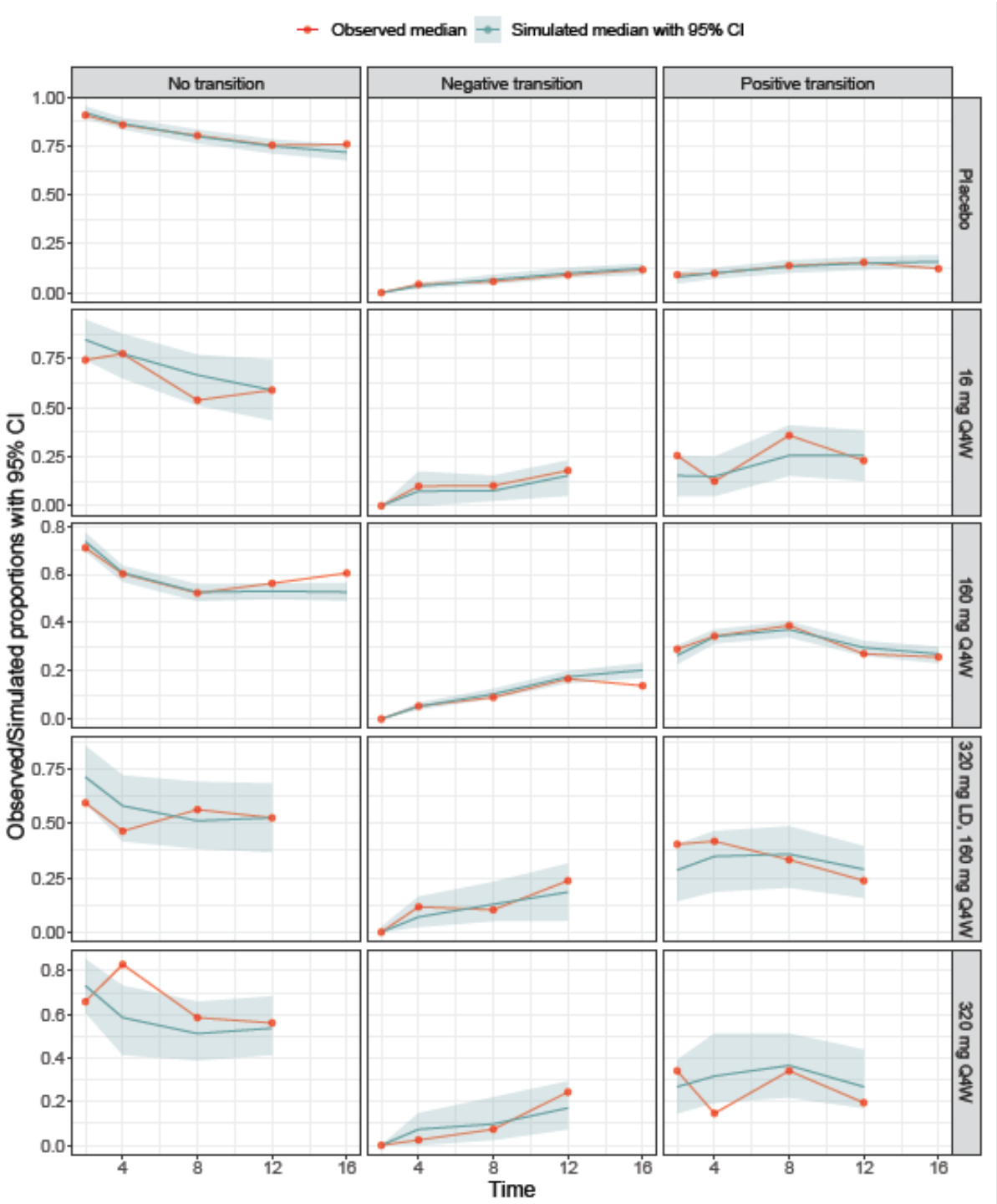


Figure 22: Visual predictive check of the proportion of study participants with no ACR transition, negative ACR transition, and positive ACR transition from the previous visit, versus nominal time since first dose, stratified by dose group, for the final ACR response model. The blue line and the blue 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 ACR analysis data set, and the red line is the observed median. Note that, in this figure, ACR70 and ACR50 responders were not counted as ACR20 responders, and ACR70 responders were not counted as ACR50 responders.

Forest plots based on the final model for the predicted probabilities of ACR response at Week 16 are presented in Figure 23.

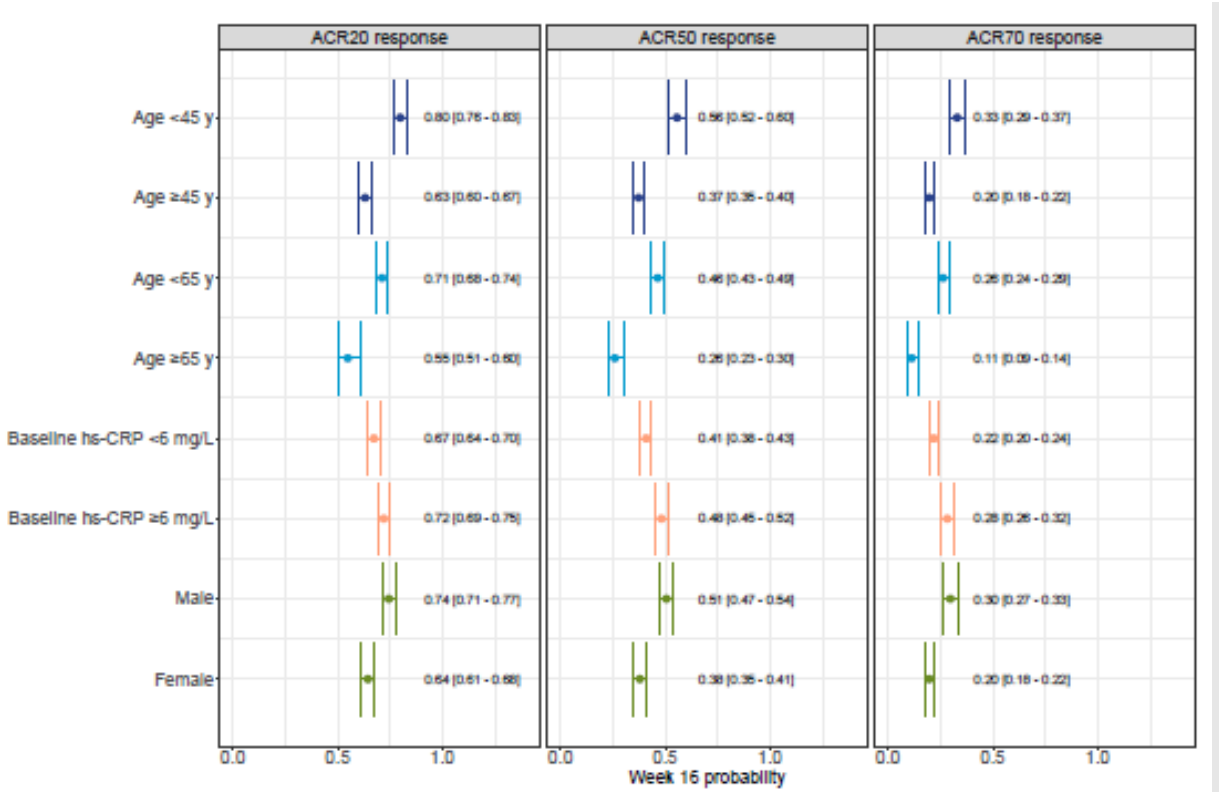


Figure 23: Forest plots based on the final ACR response model. The impact of identified covariates on the week 16 ACR response probabilities was evaluated at the values shown on the y-axis, bimekizumab 160mg Q4W. The points and the horizontal error bars represent the median and 95% CI of the mean probabilities for the different covariate subgroups. The plot is based on 250 parameter samples obtained from the NONMEM variance-covariance matrix.

Simulations were performed to assess the impact of change in PK parameters on the predicted probabilities of ACR response, following 160 mg Q4W. The results are presented in Figure 24, which shows minor changes in ACR response probabilities with changing CL/F. This indicates a shallow ER relationship around 160 mg Q4W. An increase of 20% in bimekizumab CL/F led to a decrease of 1.4% in the median predicted probability of ACR50 at Week 16. A decrease of 20% in bimekizumab CL/F led to an increase of 1.6% in the median predicted probability of ACR50 at Week 16.

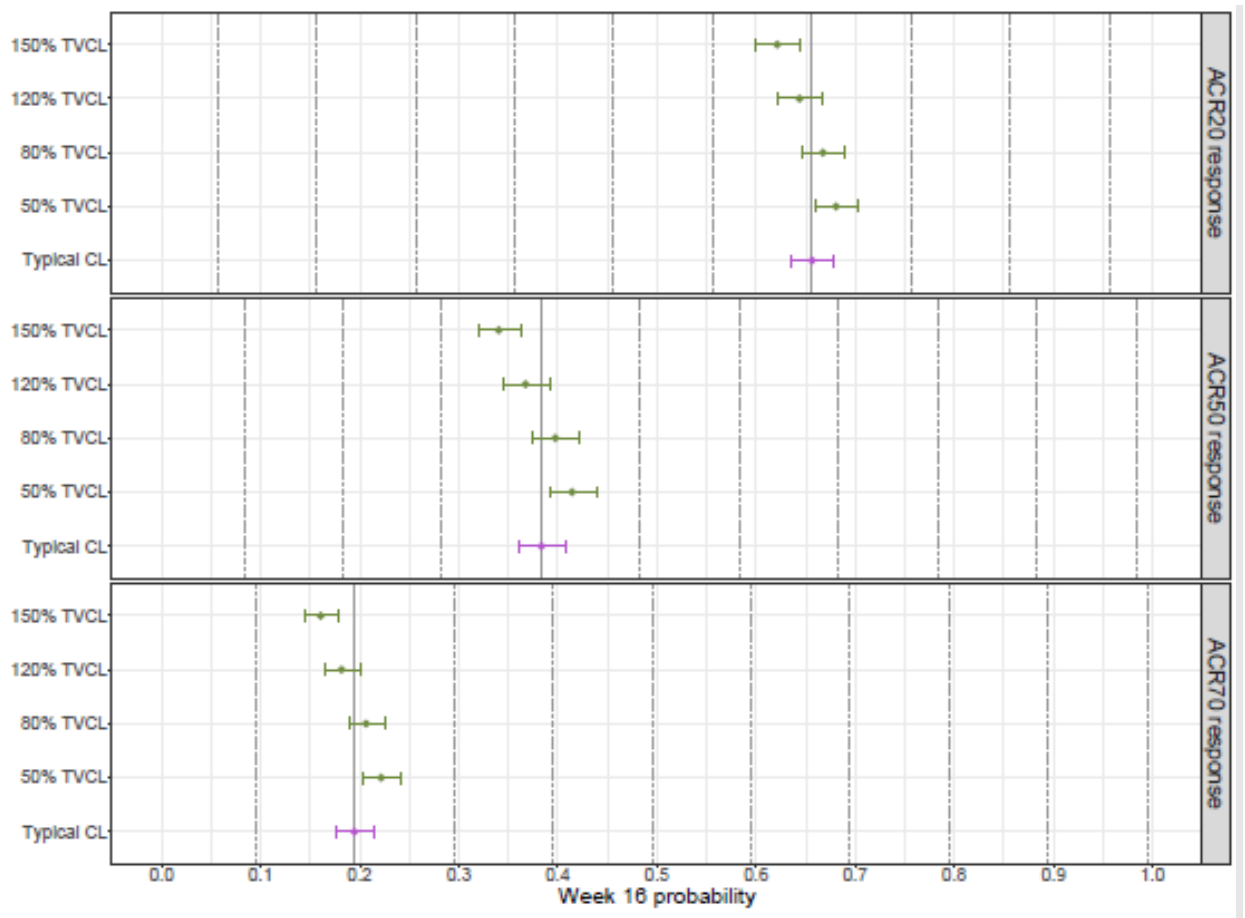


Figure 24: Impact of change in CL/F on week 16 predicated probabilities of ACR response. The points and the horizontal errors bars represent the median and 95% PI of the mean probabilities for the different PK parameter values. The vertical grey line indicates the median probability for typical CL/F, and the vertical dashed lines represent 10% difference intervals, compared to the median probability for typical PK parameters. The plot is based on 862 bootstrap samples of 862 simulated study participants, with a dosing regimen of bimekizumab 160 mg Q4W.

The simulated probabilities of ACR response at Week 16 for different dose levels are presented in Figure 25. The dose-response relationship was steep with the ACR response reaching a plateau by 160 mg Q4W. The predicted probability of ACR50 response at Week 16 were 0.04, 0.15, 0.33, 0.38, 0.39, and 0.41 for placebo, 16 mg Q4W, 80 mg Q4W, 160 mg Q4W, 320 mg loading dose, followed by 160 mg Q4W and 320 mg Q4W dosing regimens, respectively. Further, the ACR response was predicted to be relatively similar between the 10th and the 90th bimekizumab concentration percentiles (ACR50 response rate ranged from 0.32 to 0.41).

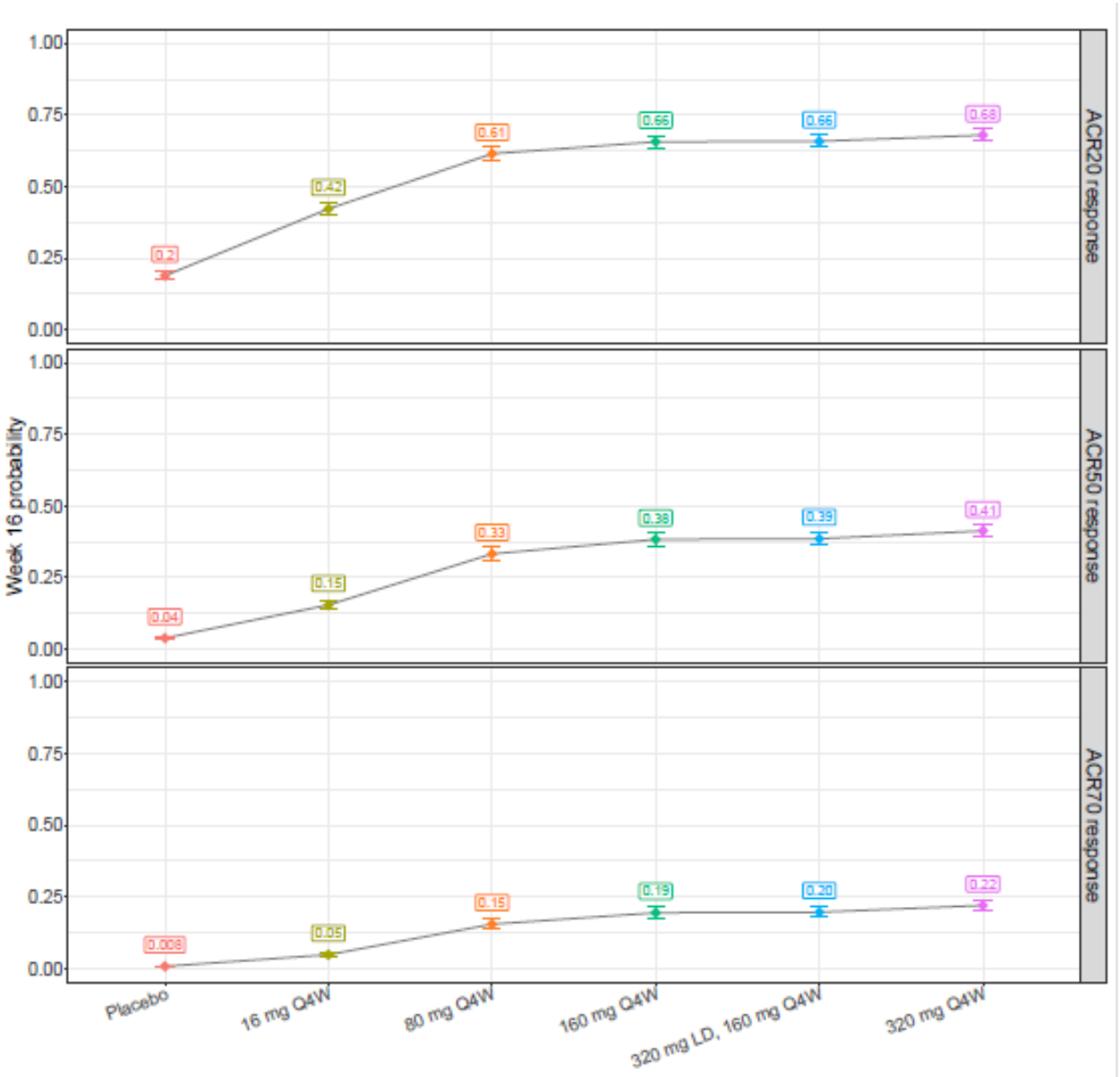


Figure 25: Predicted probabilities of ACR response at week 16 versus dose. The points and the vertical errors bars represent the median and 95% PI of the mean probabilities for each dose group. The labels indicate the median response rates for each dose. The plot is baed on 862 samples of 862 simulated study participants, with dose administered Q4W.

PASI response model

In total, 5079 PASI response observations from 757 patients with PsA were included in this analysis. The dependent variable (DV) was the PASI score. The starting model, an indirect response model describing the time course of PASI score, was based on the legacy model developed with phase 2 data to inform phase 3 dose selection.

The final PASI model was an indirect response model with a treatment effect (placebo and active drug effects) affecting the production rate (kin). The elimination rate constant kout was expressed in the model as the t1/2 of PASI response (kout = ln(2)/PASI t1/2). The model supported a PASI t1/2 of 10.7 days for a typical subject weighing 85.5 kg in the PASI analysis data set. Thus, the time to reach half-maximal PASI reduction with steady-state concentration is estimated to be approximately 1.5 weeks. The PASI t1/2 value was fixed in the final model with an IIV reflecting variation between individuals in the

rate of PASI change and time to achieve maximum PASI reduction. Exploratory and modelling analysis supported that the placebo effect was constant during the 16-week initial period of the study. Thus, placebo effect (Eplac) was estimated by a single maximum placebo effect parameter, with IIV, inhibiting kin after placebo dose. The drug effect (Edrug) was an Emax function of the individual predicted bimekizumab plasma concentrations.

The final PASI model included the following covariates: prior use of biologics and study (PA0008) on baseline PASI and body weight on PASI half-life (t1/2). There was no evidence of a statistically significant impact for anti-drug-antibodies (ADAb)/neutralizing antibodies (NAb) status, use of concomitant medications at baseline (MTX, csDMARDs or corticosteroids), markers of baseline disease severity (baseline PASI score, baseline percentage of BSA affected by PSO or baseline hs-CRP) or disease duration on parameters of placebo or drug effects in the model.

Although prior biologics use was identified as a statistically significant covariate, patients with prior biologics use had an estimated 16% higher baseline PASI score compared with biologic naive patients, and there did not appear to be a large difference in either the PASI75 or PASI90 response rates at Week 48, between the two sub-populations. Study PA0008 was estimated to have a slightly lower baseline PASI score (~20% lower) compared with studies PA0010 and PA0011.

The developed population PK-PD model provided a good description of the ER relationship between bimekizumab concentrations and PASI score. The parameter estimates of the final PASI model are presented in Table 25. Figure 26 presents pcVPC plots for the PASI score, stratified by study. The pcVPC plots show that the final PASI model provides an adequate description of both the general trend and the variability in all studies. A VPC of the response rate is presented in Figure 27. The VPC illustrates that PASI75 and PASI90 response rates are adequately captured by the model. However, the model predicts no response for subjects on placebo, while a slight response was observed.

Table 25: Parameter estimates of the final PASI model

		final model for PASI		
OFV		5963.62		
Condition number		28.86		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
Baseline PASI score		5.93	3.51	
PASI $t_{1/2}$[a]	(day)	10.7	(FIX)	
EC_{50}	(µg/mL)	0.624	9.74	
Maximum placebo effect		0.845	0.742	
Prior biologics use on baseline PASI		0.164	38.8	
Weight on PASI $t_{1/2}$		1.26	17.3	
Study PA0008 on baseline PASI		-0.211	32.4	
IIV baseline PASI	(CV)	0.691	3.49	7.58
IIV PASI $t_{1/2}$	(CV)	0.818	6.33	21.8
Corr. baseline PASI - PASI $t_{1/2}$		0.294	8.16	
IIV placebo effect	(CV)	0.396	37.9	20.4
Corr. baseline PASI - placebo effect		-0.599	12.4	
Corr. PASI $t_{1/2}$ - placebo effect		-0.672	13.7	
IIV EC_{50}	(CV)	1.82	3.77	11.2
Corr. baseline PASI -EC_{50}		-0.498	5.45	
Corr. placebo effect - EC_{50}		0.221	43.3	
Additive RUV		0.478		11.9

[a]The parameter was fixed to its estimated value to increase model stability.
The detailed equations for the covariate effects are presented in Appendix 4.3.3.
The RSE for IIV and RUV parameters are reported on the approximate SD scale.

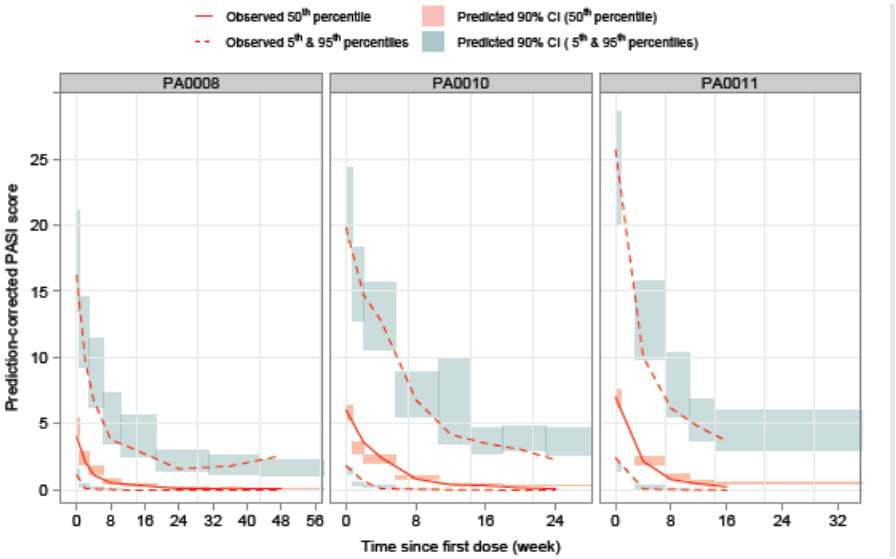


Figure 26: Predicted corrected visual predictive check of the PASI score, for the final population PK-PD model for PASI, stratified by study. The observations are displayed versus time since first dose. The solid and dashed red lines represent the median, 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 90% CI of the median, 5th and 95th percentiles predicted by the model. The pcVPCs are based on 200 simulations.

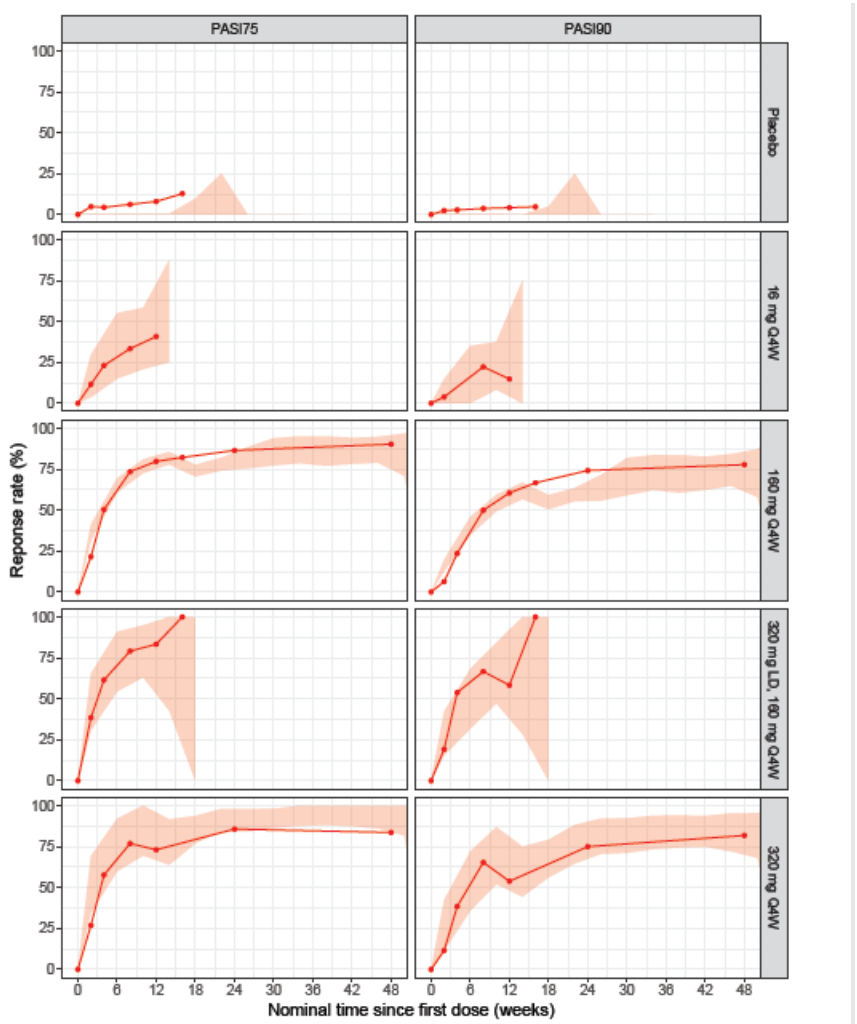


Figure 27: Visual predictive check of the PASI response rates, for the final population PK-PD model for PASI, stratified by PASI response category and dose. The observations are displayed versus nominal time since first dose. The solid red lines represents the observed response rate; the shaded red areas represent the 95% prediction interval of the response rate predicted by the model. The VPCs are based on 200 simulations.

Simulations were performed to assess the dose-response for PASI75 and PASI90 response rates and predict responses with various dose regimens given in the initial 16-week treatment phase (placebo, 16, 80, 160 and 320 mg Q4W), Figure 28. Covariate distributions (including baseline PASI), as well as individual PK parameters were kept but all subjects were assumed to have no prior biologics therapy. The Week 16 PASI75 and PASI90 response rates increased with increasing dose (Table 26). Compared to 160 mg Q4W, the simulations showed more prominent effect for the higher dose regimen of 320 mg Q4W on week 16 PASI90 than PASI75 response rates. The time course of PASI90 response rate also demonstrated faster onset of response after treatment initiation with 320 mg Q4W compared with 160 mg Q4W.

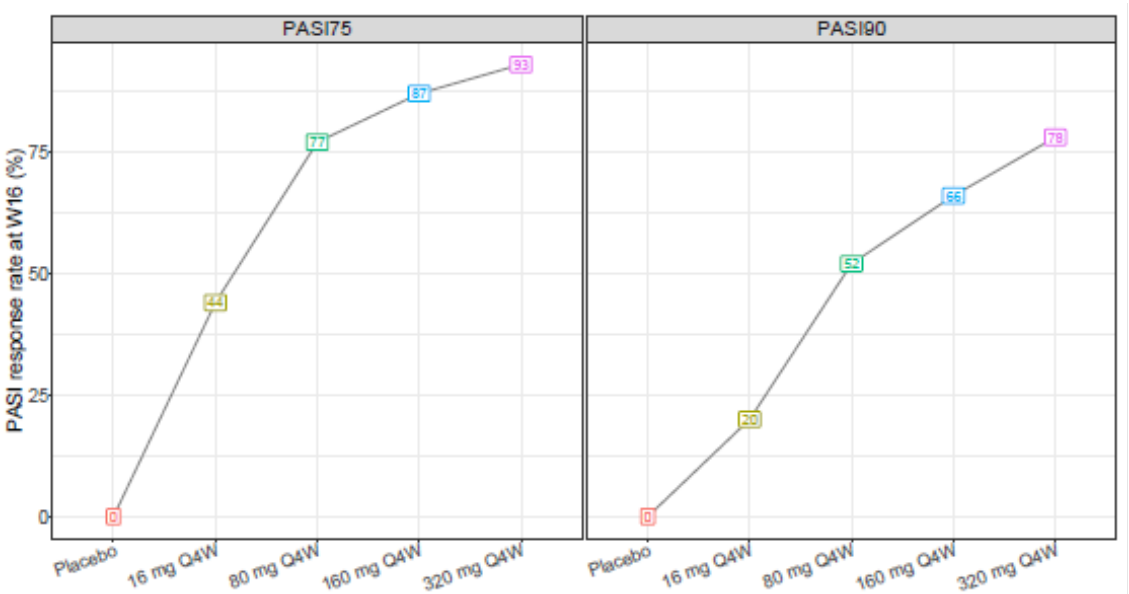


Figure 21: Predicted median Week 16 PASI75 and PASI90 response rates versus dose colored by dose. The labels indicate the median response rates for each dose.

Figure 28: Predicted median week 16 PASI75 and PASI90 response rates versus dose colored by dose. The labels indicate the median response rates for each dose.

Table 26: Simulated median and 95% PI of PASI75 and PASI90 response rates at week 16 following placebo or 16, 80, 160 or 320 mg Q4W bimekizumab administration.

Dosing regimen	Response rate[a]
PASI75	
Placebo	0 [0-3]
16 mg Q4W	44 [19-72]
80 mg Q4W	77 [53-93]
160 mg Q4W	87 [66-97]
320 mg Q4W	93 [78-99]
PASI90	
Placebo	0 [0-0]
16 mg Q4W	20 [3-56]
80 mg Q4W	52 [21-85]
160 mg Q4W	66 [33-92]
320 mg Q4W	78 [47-96]

*: Median [2.5th - 97.5th prediction interval].

The impact of identified covariates on the PASI75 and PASI90 response rates was assessed by simulations. Patients with prior use of biologics had slightly higher baseline PASI. There was no relevant difference in either PASI75 or PASI90 response rates between these sub-populations (Figure 29).

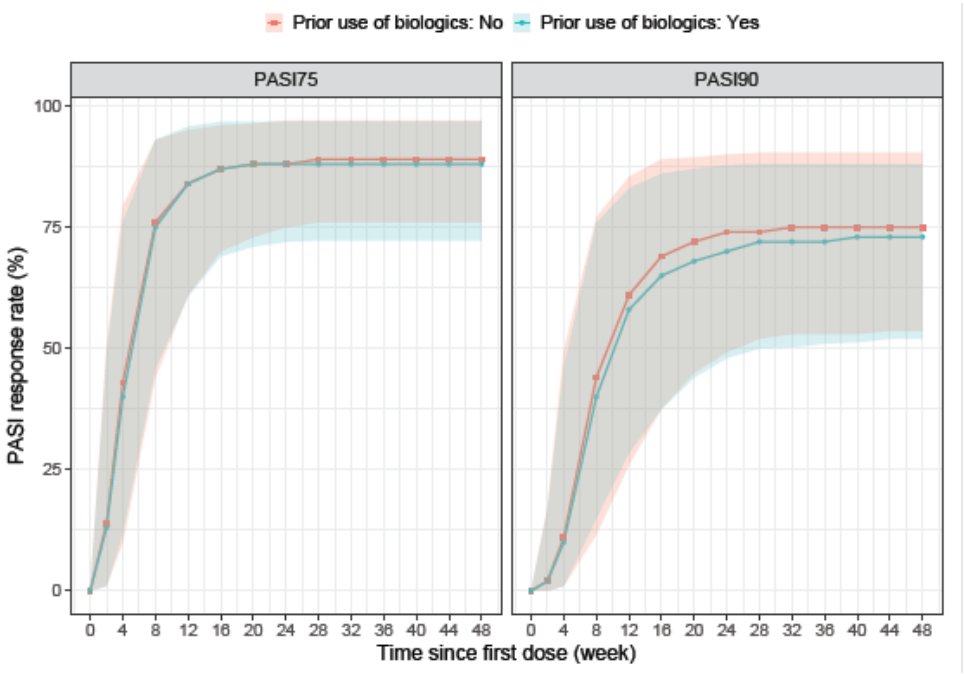


Figure 29: Simulated PASI75 and PASI90 response rates versus time since first dose, stratified by the prior use of biologics. The plot was based on 100 simulations performed with the PASI analysis dataset population. Subjects were treated with bimekizumab160mg Q4W during 48 weeks. The solid lines and the shaded areas represent the median and the 95% PI of the PASI response rates, respectively.

PASI t1/2 increased with increasing WT. The PASI t1/2 was predicted to increase by 22% and 53% for a patient weighing 100 and 120 kg, respectively, compared to a typical patient (85.5 kg). Thus, the time to achieve half-maximal PASI reduction with steady-state concentrations is estimated to be approximately 13 and 16 days in subjects weighing 100 kg and 120 kg, respectively. WT also impacted bimekizumab exposure and PASI90 response rate appeared to be more sensitive to body weight changes compared with PASI75. Simulations based on the final PASI model in study participants with PsA showed that participants weighing ≥120kg had a ~12% lower PASI90 response rate at Week 48 compared with participants weighing <120kg following bimekizumab 160mg Q4W continuous dosing (Figure 30).

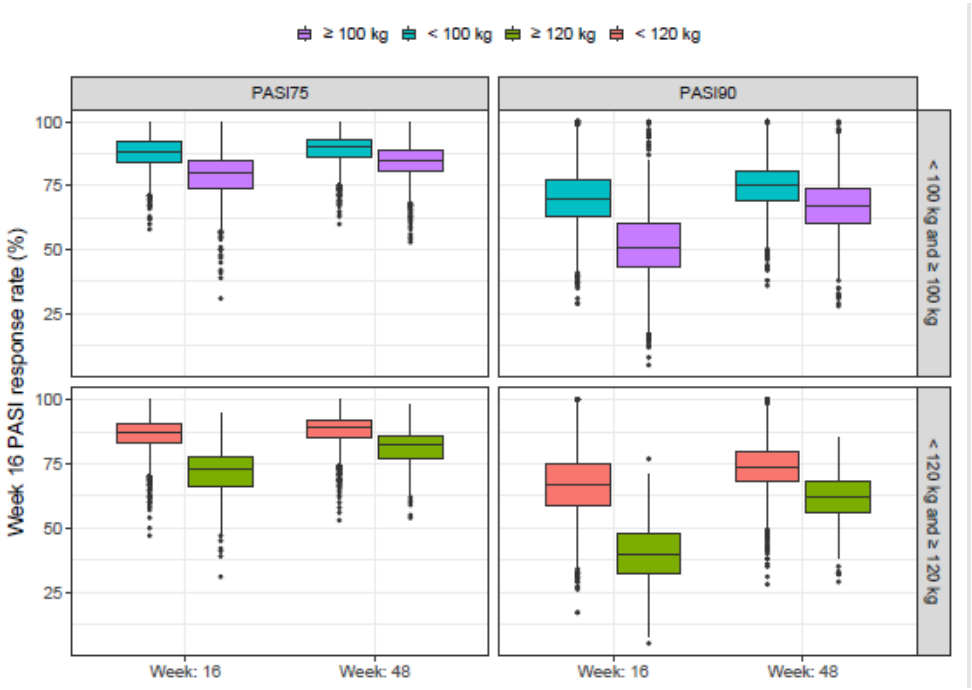


Figure 30: Simulated PASI75 and PASI90 response rates at week 16 and 48 stratified by the evaluated weight subgroups following 160mg Q4W dosing.

Exposure-safety analysis of bimekizumab

The exposure-response relationships for safety include data from only Phase 3 studies, PA0010, PA0011, and PA0012. 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 incidences of infection TEAEs. The incidences of TEAEs in the first, second, third, and fourth concentration quartiles were 77.1%, 72.3%, 79.7%, and 81.0%, respectively, and the incidences of infection TEAEs were 50.3%, 42.6%, 54.4%, and 56.9%, respectively (Table 27). 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 (8.3%, 12.9%, 19.0%, and 11.8%, respectively) or the high level term of Candida infection (4.5%, 6.5%, 12.0%, and 7.8%, respectively).

Thus, no clear trend was observed between bimekizumab exposure following 160mg Q4W in study participants with PsA 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 27).

Table 27: Incidence of TEAEs and infection TEAEs per 100 participant-years reported by ≥5% of study participants at the PT level during the combined initial, maintenance, and OLE treatment period by week 24 bimekizumab trough plasma concentration quartile (study participants initially randomised to bimekizumab; pool SP2)

	Phase 3 BKZ 160mg Q4W Trough Plasma Concentration Quartile			
MedDRA v19.0 PT	≤7.51µg/mL N=157 100 participant-yrs=2.31 n (%) [#] Incidence (95% CI)	>7.51 to ≤10.7µg/mL N=155 100 participant-yrs=2.42 n (%) [#] Incidence (95% CI)	>10.7 to ≤14.7µg/mL N=158 100 participant-yrs=2.32 n (%) [#] Incidence (95% CI)	>14.7ug/mL N=153 100 participant-yrs=2.60 n (%) [#] Incidence (95% CI)
Any TEAE	121 (77.1) [494] 146.2 (121.3, 174.7)	112 (72.3) [485] 116.2 (95.7, 139.8)	126 (79.7) [581] 163.5 (136.2, 194.7)	124 (81.0) [623] 160.3 (133.4, 191.2)
Any Infections TEAE [a]	79 (50.3) [163] 56.4 (44.7, 70.3)	66 (42.6) [152] 41.2 (31.9, 52.4)	86 (54.4) [196] 65.3 (52.2, 80.6)	87 (56.9) [204] 60.4 (48.4, 74.5)
Oral candidiasis	3 (1.9) [4] 1.3 (0.3, 3.8)	8 (5.2) [11] 3.4 (1.5, 6.7)	16 (10.1) [29] 7.4 (4.2, 12.0)	10 (6.5) [21] 4.0 (1.9, 7.4)
Nasopharyngitis	11 (7.0) [15] 5.1 (2.5, 9.1)	10 (6.5) [12] 4.3 (2.1, 7.9)	23 (14.6) [29] 11.7 (7.4, 17.5)	28 (18.3) [37] 12.8 (8.5, 18.4)
Upper respiratory tract infection	9 (5.7) [11] 4.1 (1.9, 7.8)	17 (11.0) [21] 7.8 (4.5, 12.4)	15 (9.5) [19] 6.8 (3.8, 11.2)	9 (5.9) [12] 3.6 (1.7, 6.9)
Sinusitis	6 (3.8) [7] 2.7 (1.0, 5.8)	8 (5.2) [8] 3.4 (1.5, 6.7)	3 (1.9) [6] 1.3 (0.3, 3.8)	1 (0.7) [1] 0.4 (0.0, 2.1)
Urinary tract infection	15 (9.6) [23] 7.0 (3.9, 11.5)	9 (5.8) [10] 3.9 (1.8, 7.3)	9 (5.7) [12] 4.1 (1.9, 7.7)	12 (7.8) [17] 4.8 (2.5, 8.5)
Corona virus infection	13 (8.3) [14] 5.8 (3.1, 10.0)	9 (5.8) [11] 3.9 (1.8, 7.3)	12 (7.6) [12] 5.4 (2.8, 9.4)	13 (8.5) [13] 5.2 (2.8, 8.9)

BKZ=bimekizumab; CI=confidence interval; MedDRA=Medical Dictionary for Regulatory Activities; OLE=Open-label Extension; 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.

[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. The new PK method (PK Method #4), which was not included in the initial MAA, has been appropriately validated in accordance with ICH M10. Method performance data from the clinical studies were provided in the bioanalytical reports, 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 trials have been provided and showed 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 PsAwere appropriately described.

Device use study

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 considered that self-administration into the upper arm was not convenient (especially for patients with limited hand dexterity) and thus was 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 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.

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 PA0008 indicated dose-proportional PK of bimekizumab between the dose ranges studied (16mg, 160mg and 320mg), which is consistent with other PK studies of bimekizumab in different populations. Steady state was reached between weeks 16-20, which is consistent with bimekizumab half-life of 23 days.

The results of PA0009 showed that participants who had received 160mg Q4W in PA0008 remained at steady state throughout the study. As expected, participants who received 320mg Q4W in PA0008 showed almost double plasma concentrations compared with the 160mg Q4W group at PA0009 EV. Plasma bimekizumab concentrations for study participants who received bimekizumab 320mg Q4W in PA0008 decreased at Week 12 of PA0009, and reached similar levels to the bimekizumab 160mg group from PA0008 from Week 24 onwards, indicating that steady state levels had been achieved.

Phase 3

The study designs and methodologies of PA0010 and PA0011 studies in adults with active PsA were appropriate. The pharmacokinetic sampling schemes in these studies were adequate; PK samples were collected prior to dosing. PK samples were also collected at safety follow-up visits.

The PK results of PA0010 and PA0011 indicated that mean plasma bimekizumab concentrations increased with repeat dosing, reaching steady state concentrations by Week 16, which is in-line with the other studies in this application.

Bimekizumab plasma concentrations observed in Japanese study participants were generally comparable with those observed in the overall study population following bimekizumab 160 mg Q4W. However, the small number of Japanese study participants included limits conclusions.

Overall, final PK data from the phase 2 PsA studies, PA0008 and PA0009, and from the phase 3 PsA study PA0011 were provided and summarised with descriptive statistics. Summarised PK data up to Week 24 were also provided by the MAH for the study PA0010 in this submission.

For study PA0012, no individual CSR presenting the PK data was provided. The POPPK report CL0538 is describing that blood PK samples are collected at entry visit (i.e. Week 52 of PA0010 or Week 16 of PA0011), at weeks 4, 12, 24, 52, 72, 96, 120, 140, and at the end of the SFU period. All samples are pre-dose trough samples. Available data from study PA0012 at the time of the PA0011 data cut are included in the integrated popPK analysis. The interim bioanalytical reports for the study PA0012 were provided.

Upon CHMP's request, final PK data have been submitted for study PA0010. The study PA0012 is still ongoing. The MAH has committed to submit the final data and CSR in September 2026. It is expected that the consistency with the current PK conclusions will be verified at that time.

In study PA0010, the results by week 52 confirmed that steady state was reached by week 16 and maintained up to Week 52. The BKZ plasma concentrations by week 52 were consistent to those observed by week 16 and week 24 (see initial assessment before) in Japanese patients (from final CSR PA0010).

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.

Dosing simulations based on the final popPK model predicted a lower median Ctrough,ss (6.34 µg/mL) with a dose regimen of 320 mg Q8W compared with a median Ctrough,ss (10.7 µg/mL) with a dose regimen of 160 mg Q4W. Given that the proposed maintenance dose of bimekizumab in patients with PsA and concomitant moderate to severe PSO is 320 mg Q8W, as opposed to 160 mg Q4W in patients with PsA, the MAH has revised the recommended posology of bimekizumab in such patients. An option for

dosing patients with PsA and concomitant moderate to severe plaque psoriasis at 160 mg Q4W after Week 16, based on clinical response in the joints, has now been included in Section 4.2 of the SmPC. This is agreed.

Immunogenicity

Bimekizumab plasma concentrations were lower in ADAb-positive and NAb-positive study participants in the pooled Phase 3 PsA studies at Week 16. The impact of ADAb and NAb positivity on bimekizumab plasma concentrations beyond Week 24 based on available data from PA0010 was consistent with the impact observed in the pooled data up to Week 16. However, ADAb status, ADAb titers, and NAb status were not identified as clinically relevant covariates in the population PK analysis. Based on the final popPK model, steady-state bimekizumab exposures were predicted to be similar in ADAb+/NAb+ patients compared to ADAb- and ADAb+/NAb-patients.

Key efficacy endpoints (ACR20 and ACR50) showed numerically lower response rates in ADAb-positive and NAb-positive study participants compared with ADAb-negative participants in the pooled Phase 3 PsA studies at Week 16. However, no clinically meaningful impact of ADAb or NAb status on efficacy was observed at Week 24 based on the available data from PA0010. Further, ADAb and NAb status were not identified as statistically significant covariates in the population exposure-response (ACR) PK/PD analysis. In addition, ADAb or NAb positivity had no clinically meaningful impact on the safety profile of bimekizumab, including no increase in hypersensitivity TEAEs. Overall, the impact of ADAb and NAb positivity on efficacy and safety of bimekizumab in patients with PsA does is not considered to be clinically meaningful by the CHMP.

Upon CHMP's request, individual study and pooled data up to week 52 were provided for further analysis of immunogenicity data. The results indicated that the plasma concentration levels of bimekizumab were reduced in study participants who were ADAb positive and NAb positive compared with those who were ADAb negative. However, ADAb and NAb had no impact on the clinical efficacy (ACR20 and ACR50 response rates) up to Week 52 or the safety (TEAE incidence including injection site reactions or hypersensitivity reactions) of study participants treated with bimekizumab. No events were reported for anaphylactic reactions in the Phase 3 studies in PsA. Further, results from the population PK analyses using data to approximately 1 year across indications confirmed no clinically meaningful impact for ADAb or NAb positivity on bimekizumab PK. Finally, based on the population PK/PD modeling of ACR response in patients with PsA, ADAb and NAb status were not identified as statistically significant covariates on either the probability of ACR response or maximum effect for dose/bimekizumab concentration effect.

Data on ADA and Nab status by week 52 from study PA0010 as well as pooled data on ADA- and NAb status by Week 16 were reflected in the section 5.2 of the SmPC.

Special populations

A dose adjustment in terms of renal/hepatic impairment, age and sex is not considered warranted.

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.

The section 5.2 of the SmPC was 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 ACR response (the primary efficacy endpoint in study participants with PsA), an increase of 20% in bimekizumab CL/F led to a decrease of only 1.4% in the median predicted probability of achieving ACR50 at Week 16 following 160mg Q4W. Simulations from the ACR PK/PD model showed that drops larger than 20% in exposure with increasing body weight were predicted to have minimal impact on ACR20, ACR50, or ACR70 response rates. Additionally, bimekizumab exposure following 160mg Q4W at the higher end of the exposure range in study participants with PsA did not appear to be associated with increased incidences of overall TEAEs and infection TEAEs. Therefore, a dose adjustment of bimekizumab in patients with PsA, without concomitant moderate to severe PSO, is not considered warranted in terms of body weight including overweight patients (≥120 kg).

In contrast, the PK/PD model of PASI response indicated that body weight had the largest impact on PASI response rates. This can be explained by body weight impact on both PK (bimekizumab exposure) and PD (PASI t1/2). Simulations based on the PK/PD model showed a ~12% difference in Week 48 PASI90 response rate for study participants weighing ≥120kg compared with <120kg, while a smaller difference (~8%) was predicted between study participants weighing ≥100kg compared with <100kg. As such, the MAH considers that an increased dose or dosing frequency may be of benefit in patients with PsA and concomitant moderate to severe PSO weighing ≥120kg. This is agreed and is consistent with the approved dosing recommendation for patients with PSO. The section 4.2 of the SmPC has been updated accordingly.

Pharmacodynamics

Primary pharmacology

The PD biomarkers evaluated in PA0008 were appropriate given the mechanism of action of bimekizumab. However, the results did not show any clinically relevant impact of bimekizumab on these biomarkers.

No biomarker assessments were conducted in studies PA0009, PA0010, or PA0011. However, clinical response in terms of PASI and ACR was evaluated. See PK/PD modelling for further details.

PK/PD modelling

Phase 2

The Phase 2 PK/PD analyses were conducted to select the dose regimen/s to be tested in the pivotal Phase 3 studies. Whilst it could be argued that the 320 mg Q4W regimen may have been appropriate to test in patients with PsA and concomitant moderate to severe PSO, in addition to the selected 160 mg Q4W, this was not the case. The MAH's justification for the selected dose regimen for the pivotal Phase 3 studies can be followed.

Phase 2 and Phase 3

The developed population PK-PD models described the ER relationships between bimekizumab concentrations and the two efficacy endpoints (PASI and ACR). Covariates were identified and their impact on the PASI or ACR response was evaluated. The results were used to inform the rationale for the proposed dose regimens in patients with PsA, and patients with PsA and concomitant moderate to severe PSO.

ACR model

The final PK/PD model provided an adequate description of the ER relationship between bimekizumab concentrations and ACR response. VPCs showed that the predictive performance of the model was reasonable overall.

The following covariates were included in the final model: age and baseline hs-CRP on Emax, as well as sex on the probability of response. Under active treatment, the probability of ACR response increased with decreasing age, and with increasing baseline hs-CRP. Males had higher probability of ACR response than females. However, the impact of these covariates on ACR response were not considered to be driven by PK changes. There was no evidence of a statistically significant impact for ADAb/NAb status, use of concomitant medications at baseline or disease duration on either probability of ACR response or Emax.

The dose-response relationship was shown to be steep with the ACR response but appeared to plateau by 160 mg Q4W. This supports the proposed bimekizumab dose of 160 mg Q4W for PsA patients without concomitant moderate to severe PSO.

PASI model

The final PK/PD model for PASI provided an adequate description of the data. VPCs showed that the model predicted the median and the variability in PASI75 and PASI90 response rates reasonably well.

The following covariates were included in the final model: prior biologics use and study (PA0008) on baseline PASI and body weight on PASI t1/2. Patients with prior biologics use had an estimated 16% higher baseline PASI score compared with biologic naive patients, and there did not appear to be a large difference in either the PASI75 or PASI90 response rates at Week 48, between the two sub-populations.

Higher body weight was predictive of longer PASI t1/2. Compared with a typical subject with PsA (median WT is 85.5 kg), the PASI t1/2 was predicted to increase by 22% and 53% for a patient weighing 100 kg and 120 kg, respectively. Body weight also impacted bimekizumab exposure, and exposure was found to decrease with increasing body weight. See Special Populations for further discussion of the impact of body weight on bimekizumab PK and PASI response.

Additional simulations evaluated the Week 16 PASI75 and PASI90 response rates with placebo, 16, 80, 160 and 320 mg Q4W dose regimens. The PASI90 response rates were predicted to increase with increasing doses to 320 mg Q4W. Doses lower than 160 mg Q4W were predicted to result in lower PASI75 and PASI90 response rates. Compared to 160 mg Q4W, the simulations showed more prominent effect for the higher dose regimen of 320 mg Q4W on Week 16 PASI90 than PASI75 response rates. The predicted Week 16 median PASI90 response rates were 66% and 78% with 160 and 320 mg Q4W, respectively. The time course of PASI90 response rate also demonstrated faster onset of response after treatment initiation with 320 mg Q4W compared with 160 mg Q4W. These results provide support for the proposed dose of 320 mg Q4W for treatment initiation in patients with PsA and concomitant moderate to severe PSO (see section 4.2 of the SmPC).

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.

2.3.6. Conclusions on clinical pharmacology

The bimekizumab pharmacokinetics in adult patients with PsA has been adequately characterised and the PK properties were similar in patients with plaque psoriasis and axSpA. Section 5.2 of the SmPC was updated accordingly. The selected dose regimen of 160 mg Q4W for patients with PsA in the Phase 3

studies is considered appropriate. The proposed dose adjustment in patients with PsA and concomitant moderate to severe plaque psoriasis is also supported. 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

In support of this extension to the indication, the following data has been submitted:

- ***PA0010:*** Placebo-controlled study with adalimumab reference arm BE OPTIMAL. (DMARD naïve)
    - Week 24 data cut. Approximately 75% of study participants in this study reached Week 52 at the time of the 24-week data cut-off.
    - Upon CHMP's request: complete efficacy 52-week study data was provided.
- ***PA0011:*** Completed Phase 3 placebo-controlled study. BE COMPLETE. (DMARD iR and intolerant)
    - Week 16 data cut
- ***PA0007:*** Completed Phase 1 study
- ***PA0008:*** Completed Phase 2 study and ***PA0009***, its OLE study
- ***PA0012:*** Open-label extension study for eligible PA0010 and PA0011 completers, ongoing, proposed as part of pharmacovigilance plan for PsA program (see RMP section below)
- ***DV0004:*** Completed Phase 3 device sub-study within the OLE study PA0012

2.4.1. Dose response study

The recommended dose and dosing regimen tested in the Phase 3 studies of bimekizumab was selected based on safety, efficacy, and PK data from the Phase 2b dose response study PA0008 in adult patients with PsA, as well as PK/PD modelling in that study (CL0464) and was as follows:

- For adult patients with PsA, the recommended dose of bimekizumab is *160mg Q4W.*

While a loading dose was initially considered for faster onset of action, it was determined that higher exposures associated with the initial loading dose could result in treatment effects at an early timepoint that were not reflective of long-term efficacy of a chronic therapy. The loading dose could artificially inflate the response seen at Week 16 or at Week 24, which would not be reflective of maintenance response in a chronic disease.

PA0008 Phase 2b

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 PsA. PA0008 study results were used to guide the selection of doses and clinical indices in the Phase 3 development.

Adult patients with a documented diagnosis of adult onset PsA with active psoriatic lesions and/or a documented history of psoriasis, negative for RF and for anti-CPP antibodies, were recruited. Patients were anti-TNF naïve or have received 1 prior TNF inhibitor (max 30% of patients). Stable and defined doses of NSAIDs or COX-2 inhibitors, corticosteroids, MTX or LEF were allowed.

In the 12-week DB treatment period, 5 dosing regimens were investigated. After week 12, patients in the 16 mg Q4W arm were re-randomised to 160 mg or 320 mg Q4W. Patients in the other treatment arms remained on their assigned treatment for the 36-week dose blind period.

Eligible study participants were randomised in a 1:1:1:1:1 ratio to receive placebo, bimekizumab 16mg Q4W, bimekizumab 160mg Q4W, bimekizumab 160mg Q4W with a 320mg loading dose at Baseline, and bimekizumab 320mg Q4W.

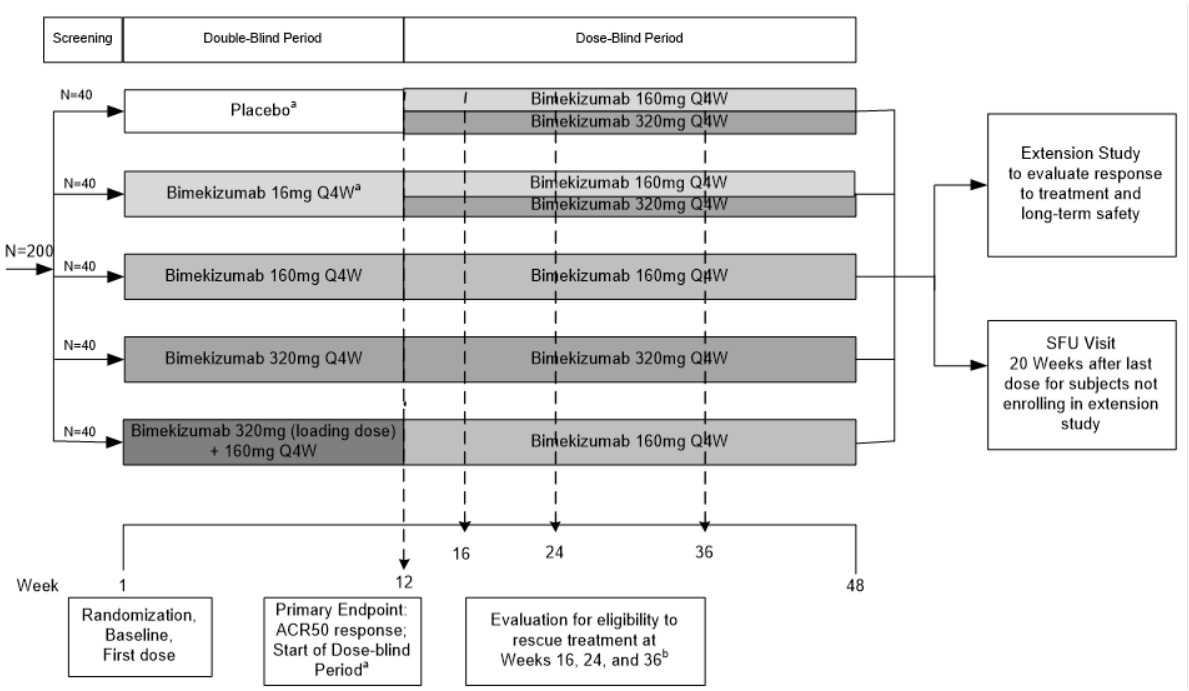


Figure 31: Schematic diagram for PA0008

Study participants in any treatment group who completed the 12-week Double-Blind Period entered the 36- week Dose Blind Period.

At the Week 12 Visit, study participants were allocated to the bimekizumab treatment regimens as follows:

- study participants in the placebo group and the bimekizumab 16mg group were re-randomised 1:1 to bimekizumab 160mg or bimekizumab 320mg Q4W;
- study participants in the bimekizumab 160mg and bimekizumab 160mg w/LD groups continued to receive bimekizumab 160mg Q4W;
- and study participants in the bimekizumab 320mg group continued to receive bimekizumab 320mg Q4W.

After the completion of the Dose-Blind Period, all study participants not continuing in the extension study (PA0009), or those withdrawn from IMP, were to have an SFU Visit 20 weeks after their last dose of IMP.

The main efficacy analyses were performed at week 12 through ACR and PASI scoring. PK, PD, immunological and safety assessments were performed as specified. Subgroup analysis included a.o. BASDAI score, prior anti-TNF exposure, anti-drug Ab development and extent of psoriasis.

Baseline data

Demographic characteristics were generally well balanced across treatment groups. Treatment groups were generally well balanced with respect to PsA-related and other Baseline disease characteristics.

Prior anti-TNF therapy had been used by 18.9% of all study participants. At Baseline, the majority of study participants were using 1 NSAID therapy (62.1%) and/or sDMARDs (67.0%, primarily MTX (63.6%). Mean and median TJC scores were higher in the bimekizumab 320mg group compared with the other treatment groups. The majority of study participants had ≥3% PSO BSA at Baseline (66.5%). A substantial proportion of study participants at Baseline also had nail PSO (75.2%), dactylitis (28.6%), and/or enthesitis (51.9%), with some variability across groups; in particular, a lower proportion of study participants had dactylitis at Baseline in the bimekizumab 16mg group (12.2%) compared with the other treatment groups (range: 26.8% to 39.0%).

Overall, 5 study participants in each of the FAS and DBS (2.4% and 2.5%, respectively) used a rescue medication during the study; the incidence of rescue medication was similar across treatment groups. The reported rescue medications were sulfasalazine (3 study participants), apremilast (1 study participant), and MTX and celecoxib (both used by the same 1 study participant at different times).

PA0008 Results

In PA0008, both ACR50 and Reduction of 90% from Baseline in Psoriasis Area and Severity Index (PASI90) responder rates saturated at bimekizumab 160mg Q4W, and a further increase in dose did not provide a significant benefit on either ACR50 or PASI90 responder rates. An exposure-response analysis performed on both endpoints also indicated that bimekizumab 160mg Q4W was the optimal dose for these study participants.

Double-blind period

A total of 206 study participants were randomised and started the study as follows: 42 study participants in the placebo group and 41 study participants each in the bimekizumab 16mg, 160mg, 160mg w/LD, and 320mg groups. Overall, 203 of 206 study participants (98.5%) completed the Double-Blind Period. The primary reason for study discontinuation given by the 3 study participants (1.5%) who discontinued the study during the Double-blind Period was AE by 2 study participants (1.0%) and "other" by 1 study participant (0.5%).

Overall, 189 of 206 study participants (91.7%) completed the study; the percentages of study participants who completed the study were high and similar across all bimekizumab groups and the placebo group (range across groups: 82.9% to 97.6%).

Dose-blind period

A total of 199 study participants started the Dose-Blind Period. Of the 199 study participants (100%) who started the Dose-blind Period, 186 study participants (93.5%) completed IMP treatment and 9 study participants (4.5%) discontinued IMP treatment; no study participants discontinued IMP treatment for reasons of intolerance or lack of efficacy; 4 study participants had their Visit 15 injections interrupted due to AEs, therefore these study participants were not presented as having completed nor as having discontinued IMP; all 4 study participants completed the study.

There were 184 study participants who completed the study and enrolled into the extension study, PA0009.

Primary analysis of the primary efficacy variable- Across the bimekizumab doses included in the Cochran-Mantel-Haenszel test, a statistically significant dose response was observed in ACR50 responder rates at Week 12 (p=0.031; Table 28). This dose response was linear at bimekizumab doses up to 160mg, with ACR50 responder rates at Week 12 ranging from 26.8% (bimekizumab 16mg) to 41.5% (bimekizumab 160mg). The ACR50 responder rate at Week 12 in the placebo group was 7.1%.

Table 28: Dose response of ACR50 response at week 12 with Cochran-Mantel-Haenszel test (FAS[NRI]) (PA0008)

Variable	Placebo N=42	BKZ 16mg N=41	BKZ 160mg N=41	BKZ 320mg N=41	Correlation statistic [a]	p-value [a]
Responders, n (%)	3 (7.1)	11 (26.8)	17 (41.5)	10 (24.4)	4.6	0.031

ACR50=American College of Rheumatology 50% improvement criteria; 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

Secondary, supportive, and sensitivity analyses of the primary efficacy variable - demonstrated significantly better ACR50 responder rates at Week 12 for the bimekizumab 16mg, 160mg, and 160mg w/LD doses vs placebo; the comparison for the bimekizumab 320mg dose vs placebo was not statistically significant, although the difference was clinically relevant. All supportive and sensitivity analyses were consistent with the primary and secondary efficacy analyses. Improvement in the individual components of the ACR was consistent with the secondary analysis of the primary efficacy variable.

Secondary efficacy variables- The results of all 4 secondary endpoints are consistent and support the findings of the primary endpoint.

- ACR20 response at Week 12- Clinically relevant differences were observed in the pairwise comparison of ACR20 response at Week 12 for the bimekizumab 16mg (53.7%), 160mg (73.2%), 160mg w/LD (61.0%), and 320mg (51.2%) groups compared with the placebo group (19.0%; p≤0.004 for each comparison).
- ACR70 response at Week 12- A greater percentage of ACR70 responders at Week 12 was observed in the bimekizumab 16mg (12.2%), 160mg (19.5%), 160mg w/LD (31.7%), and 320mg (14.6%) groups compared with the placebo group (4.8%); the comparison to placebo was significant for the bimekizumab 160mg w/LD group only (p=0.006).
- PASI75 response at Week 12- Clinically relevant differences were observed in the pairwise comparison of PASI75 response at Week 12 for the bimekizumab 16mg (44.8%), 160mg (64.3%), 160mg w/LD (76.9%), and 320mg (73.1%) groups compared with the placebo group (7.1%; p≤0.005 for each comparison) (Table 29).
- PASI90 response at Week 12- A greater percentage of PASI90 responders at Week 12 was observed in the bimekizumab 16mg (20.7%), 160mg (46.4%), 160mg w/LD (53.8%), and 320mg (53.8%) groups compared with the placebo group (7.1%); the comparison to the placebo group was significant for the 3 highest bimekizumab dose groups (p≤0.002; Table 29).

Table 29: Pairwise comparisons of PASI75 and PASI90 response at week 12 with logistic regression analysis (FAS [NRI]) (PA0008)

Variable Statistic	Placebo N=28	BKZ 16mg N=29	BKZ 160mg N=28	BKZ 160mg w/LD N=26	BKZ 320mg N=26
PASI75 Responders, n (%)	2 (7.1)	13 (44.8)	18 (64.3)	20 (76.9)	19 (73.1)
Odds ratio vs placebo[a]	-	8.8	21.6	34.7	27.1
95% CI for responder rate	-	1.94, 39.77	4.59, 101.62	6.95, 173.28	5.61, 131.13
p-value	-	0.005	<0.001	<0.001	<0.001
PASI90 Responders, n (%)	2 (7.1)	6 (20.7)	13 (46.4)	14 (53.8)	14 (53.8)
Odds ratio vs placebo [a]	-	2.9	11.2	12.9	12.1
95% CI for responder rate	-	0.59, 14.27	2.41, 52.26	2.77, 60.45	2.61, 56.16
p-value	-	0.187	0.002	0.001	0.001

Other efficacy endpoints:

In general, improvements were observed in all bimekizumab treatment groups for all other efficacy variables (except for SF-36 Mental Component Summary (MCS) and Hospital Anxiety and Depression Scale (HADS) scores), which were maintained through Week 48, and these results support the conclusions of the primary analysis.

Simulations were performed using the PK/PD model to predict the dose response of Week 12 ACR20, ACR50, and ACR70 response rates. Based on the simulations, the maximum ACR response rate was predicted to be achieved with the 160mg Q4W dose. Higher doses, such as 320mg, were unlikely to provide additional benefit. Simulations from the model indicated that PASI75 and PASI90 response rates were near maximal at 160mg Q4W for the overall PsA population (with mostly mild to moderate skin disease). The simulations also indicated that doses lower than 160mg may provide reduced PASI75 and PASI90 responses. While some improvement in Week 12 PASI90 was predicted with the 320mg Q4W regimen, the limited number of participants with PsA and concomitant moderate to severe PSO in study PA0008 precluded robust assessment of PASI responses for this subgroup. Thus, the Phase 3 PsA programme utilized bimekizumab 160mg Q4W for all participants, including participants with concomitant moderate to severe PSO.

2.4.2. Main studies

Title of Studies PA0010 and PA0011

The bimekizumab PsA clinical development program consisted of 2 pivotal Phase 3 studies. PA0010 and PA0011 are randomised, multicenter, double-blind, parallel-group, placebo-controlled studies to evaluate the efficacy and safety of bimekizumab in adult study participants with active PsA through 52 weeks and 16 weeks, respectively. PA0010 also included an active reference arm (adalimumab).

Study number/clinical development phase/study design	Study Period	Number of study participants randomized			Maximum duration of treatment
		BKZ	PBO	Active reference arm	
Primary efficacy studies					
PA0010/ Phase 3/ multicenter, randomized, double-blind, parallel-group, placebo-controlled and active reference study	Double-blind Treatment Period	160mg Q4W: 431	281	ADA: 140	16 weeks
	Active Treatment-blind Period [a]	160mg Q4W: 414 PBO/BKZ 160mg Q4W: 211 [b]	NA [b]	ADA: 136 [c]	36 weeks
PA0011/ Phase 3/ multicenter, randomized, double-blind, placebo-controlled study	Double-blind Treatment Period	160mg Q4W: 267	133	NA	16 weeks
Total exposed during primary efficacy studies		**160mg Q4W: 969**	**414**	**ADA: 140**	

[a] The PA0010 Maintenance Treatment Period remains blinded.
[b] PBO-treated study participants in PA0010 who completed Week 16 received BKZ 160mg Q4W in the Active Treatment-blind Period.
[c] Four ADA-treated study participants in PA0010 discontinued during the Double-blind Treatment Period.

PA0010 (BE OPTIMAL)

A Phase 3, multicenter, randomised, double-blind, placebo-controlled, non-inferential active reference (adalimumab) study to evaluate the efficacy and safety of bimekizumab in study participants with active PsA who are **bDMARD-naïve**.

PA0011 (BE COMPLETE),

A Phase 3, multicenter, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab in study participants with active PsA with **inadequate response** (lack of efficacy after at least 3 months of therapy at an approved dose) **or intolerance** to treatment with 1 or 2 TNFα inhibitors for either PsA or PSO (TNFα-IR).

Methods

A randomised, double-blind, placebo-controlled study design was selected to demonstrate efficacy and safety of bimekizumab in both studies PA0010 and PA0011.

Both studies were placebo-controlled during the 16-week double-blind periods (Initial Treatment Period). PA0010 also included an active reference arm (adalimumab), and the study duration extended beyond the Initial Treatment Period to allow for collection of long-term safety and efficacy data through 52 weeks of treatment. An interim analysis was performed for PA0010 at Week 24 and for PA0011 at Week 16, which included the Week 16 primary analysis time point in each study.

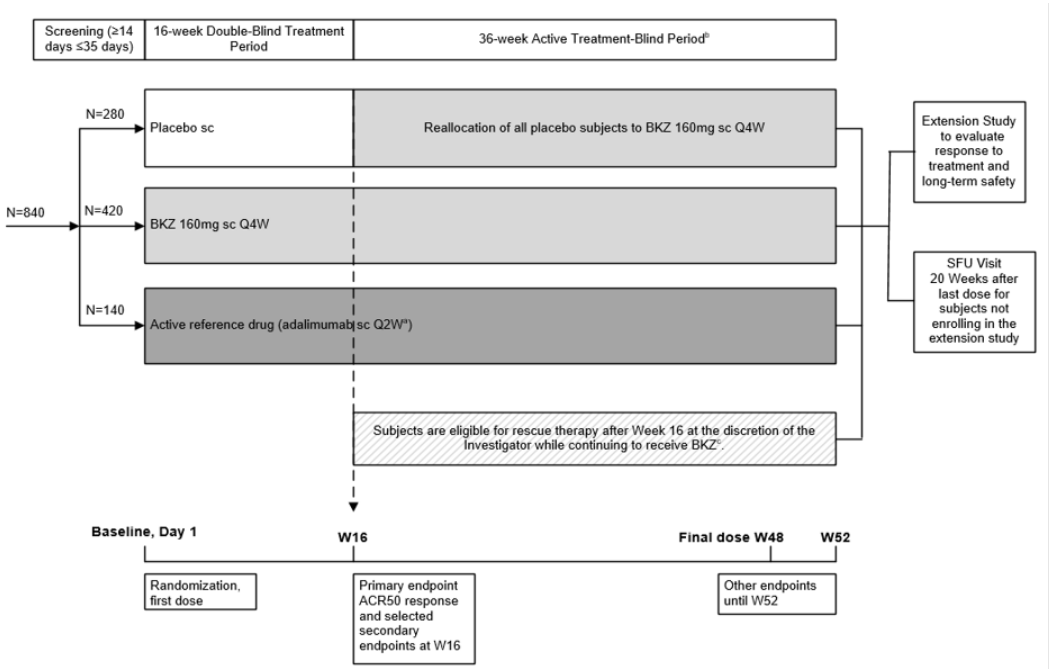
At the time of the Week 24 data cut-off in PA0010, the 36-week Active Treatment Blind Period was ongoing; however, 75% of study participants in PA0010 had reached Week 52.

After completion of the treatment period of PA0010 or PA0011, eligible study participants were allowed to enrol in an OLE study, PA0012, where ongoing data on the long-term safety, tolerability, and efficacy of bimekizumab in this population will be collected for up to 160 weeks. Study participants who did not enrol into PA0012 entered a 20-week Safety Follow-Up (SFU) Period in PA0010 or PA0011.

PA0010

The overall study design consists of a Screening Period (≥14 days to ≤35 days), a 16-week placebo controlled Double Blind Treatment Period, a 36-week Active Treatment-Blind Period (through Week 52 and including the adalimumab treatment arm), and a SFU Visit 20 weeks after the final dose of investigational medicinal product (IMP) (for participants not entering the OLE study or who discontinue early, including those withdrawn from IMP). Efficacy data from the completed PA0010 study (up to Week 52) was provided upon CHMP's request.

Study participants were randomised 3:2:1 (stratified by region and bone erosion [0, ≥1]) to receive 1 of 3 blinded treatments (bimekizumab 160mg subcutaneous [sc] Q4W, placebo, or active-reference [adalimumab 40mg sc every 2 weeks]) and remained on their allowable background medication.



Note: This schematic reflects the number of study participants planned to be randomized to study treatment.

Figure 32: Schematic diagram for PA0010

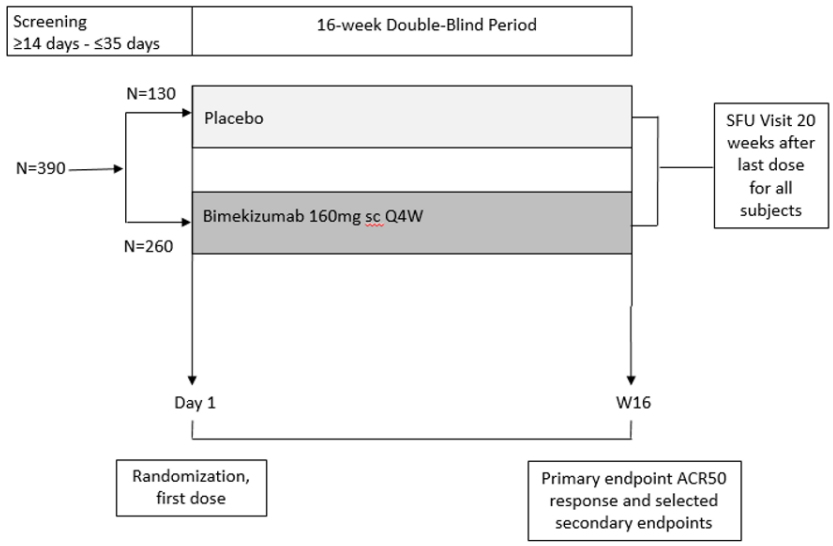
After 16 weeks of double-blind treatment (Double Blind Treatment Period), study participants entered the Active Treatment-Blind Period. All study participants randomised to placebo were reallocated to receive bimekizumab 160mg Q4W. Study participants randomised to bimekizumab 160mg Q4W continued to receive their originally randomised dose. Study participants randomised to active-reference (adalimumab) continued with their active treatment. After Week 16, if the study participants were not responding adequately as per Investigators' judgement, rescue therapy was allowed.

PA0011

The overall study design consisted of a Screening Period (≥14 days to ≤35 days), a 16-week placebo controlled Double Blind Treatment Period, and a SFU Visit, 20 weeks after the final dose of IMP (for participants not entering the OLE study or who discontinued early, including those withdrawn from IMP). Participants completing Week 16 were eligible for enrollment in an OLE study to continue to receive bimekizumab. The PA0011 study is complete**.**

Study participants who completed Week 16 and were eligible for enrollment in the open-label extension (OLE) study, PA0012, continued to receive bimekizumab 160mg sc Q4W. Study participants who did not enter PA0012 after completing the IMP treatment period entered a 20-week SFU Period.

The maximum study duration per study participant was up to 37 weeks.



Note: This schematic reflects the number of study participants planned to be randomized to study treatment.

Figure 33: Schematic diagram for PA0011

Number of Patients Planned for Each Dose Group

PA0010

Approximately 840 study participants were planned to be randomly assigned in a 3:2:1 ratio (stratified by region and bone erosion [0, ≥1]) to the following treatment groups:

- bimekizumab 160mg sc Q4W (420 study participants),
- placebo (280 study participants), and
- adalimumab sc 40mg every 2 weeks (140 study participants).

A total of 852 study participants were randomised and started the Double-Blind Treatment Period.

PA0011

Approximately 390 study participants were planned to be randomly assigned in a 2:1 ratio to the following treatment groups:

- 260 study participants bimekizumab 160mg sc Q4W and
- 130 study participants placebo

A total of 400 study participants were randomised and started the Double-Blind Treatment Period.

Interim analysis

PA0010

The interim analysis initially submitted by the MAH was done following the last scheduled Week 24 visit; this Week 24 interim analysis forms the basis of the Week 24 clinical study report (CSR). It included all efficacy data up to Week 24 and all available safety data up to the data cut of the Week 24 interim analysis (25 October 2021), which included additional safety data for any study participant who was ongoing in this 52 week study or in the SFU Period at the time of the Week 24 data cut. At the time of the

Week 24 data cut-off in PA0010, the 36-week Active Treatment Blind Period was ongoing; however, 75% of study participants in PA0010 had reached Week 52. Upon CHMP's request, the final CSR (with data up to week 52) was also submitted by the MAH.

PA0011

The Week 16 interim analysis was done following the last scheduled Week 16 visit. It included all efficacy data up to the Week 16 primary analysis time point and all available safety data up to Week 16, which included additional safety data for any study participants who were in or who completed the SFU Period at the time of the data cut of the Week 16 interim analysis (22 December 2021). Only 3 study participants were in the SFU Period at the time of the Week 16 interim analysis database lock; all other study participants had completed the study or the SFU Period. All data, including the SFU data, were included in the final PA0011 CSR. The PA0011 final CSR database lock (04 March 2022) was performed after the SFU Period was complete.

Study participants

To be eligible to participate in these studies, adult study participants were to have a diagnosis of active PsA based on the Classification Criteria for Psoriatic Arthritis (CASPAR) criteria and have active disease with tender joint count (TJC) ≥3 and swollen joint count (SJC) ≥3. The eligibility criteria of PA0010 and PA0011 are identical with 2 exceptions:

1) PA0011 study participants must have a history of **inadequate response or intolerance** to 1 or 2 TNFα inhibitors for either PsA or PSO and

2) PA0010 study participants must have been **bDMARD naïve and able to receive adalimumab**.

In addition, both studies used the same dose, dosage form, and dosing schedule from Week 0 to Week 16.

Key Inclusion criteria:

PA0010

Adults with a diagnosis of active PsA based on the CASPAR criteria and have active disease with TJC ≥3 and SJC ≥3 who were naïve to bDMARDs.

It was planned to enroll a minimum of 45% of study participants who had elevated high sensitivity- C-reactive protein (hs-CRP ≥6mg/L) and/or who had at least 1 bone erosion at Screening.

PA0011

Adults with a diagnosis of active PsA based on the CASPAR criteria and have active disease with TJC ≥3 and SJC ≥3 who had

- Inadequate response: lack of efficacy after at least 3 months of therapy at an approved dose or
- Intolerance to treatment: with 1 or 2 tumor necrosis factor alpha (TNFα) inhibitors for either PsA or PSO.

PA0010 and PA0011 common inclusion criteria

- male or female at least 18 years of age.
- a documented diagnosis of adult-onset PsA classified and meeting the CASPAR classification criteria for at least 6 months prior to Screening with active PsA and must have had at Baseline TJC ≥3 out of 68 and SJC ≥3 out of 66 (dactylitis of a digit counts as 1 joint each).

- must have been negative for rheumatoid factor and anti-cyclic citrullinated peptide (CCP) antibodies.
- must have had at least 1 active psoriatic lesion(s) and/or a documented history of PSO.
- Study participants who were regularly taking NSAIDs/cyclooxygenase-2 (COX-2) inhibitors or analgesics (including mild opioids) as part of their PsA therapy were required to be on a stable dose/dose regimen for at least 14 days before Baseline and should have remained on a stable dose until Week 16.
- Study participants taking oral corticosteroids must have been on an average daily dose of ≤ 10mg/day prednisone or equivalent for at least 14 days before Baseline and should have remained on a stable dose until Week 16.
- Study participants taking methotrexate (MTX) (≤25mg/week) were allowed to continue their medication if started at least 12 weeks prior to Baseline, with a stable dose for at least 8 weeks before randomisation. Dose, dosing schedule and route of administration (oral or sc) were to remain stable until Week 16. It was strongly recommended that study participants taking MTX were also taking folic acid supplementation.
- Study participants taking leflunomide (LEF) (≤20mg/day or an average of 20mg/day if not dosed daily) were allowed to continue their medication if started at least 12 weeks prior to Baseline, with a stable dose for at least 8 weeks before randomisation. Dose and dosing schedule were to remain stable until Week 16.
- Study participants taking sulfasalazine (SSZ) (up to 3g/day, for arthritis or 4g/day if in accordance with local standard of care, HCQ (up to 400mg/day), or apremilast (up to 60mg/day and dosed as per local label) were allowed to continue their medication if started 8 weeks prior Baseline, with a stable dose for at least 4 weeks before randomisation. Dose and dosing schedule were to remain stable until Week 16.

PA0010 and PA0011 common exclusion criteria

- Female study participants who are breastfeeding, pregnant, or planned to become pregnant during the study or within 20 weeks following last dose of IMP.
- current or prior exposure to any biologics for the treatment of PsA or PSO, including participation in a bimekizumab clinical study who received at least 1 dose of IMP (including placebo).
- an active infection or history of infections
- concurrent acute or chronic viral hepatitis B or C or HIV infection. Study participants who had evidence of or tested positive for hepatitis B or hepatitis C were excluded.
- received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline
- received Bacillus Calmette-Guerin vaccinations within 1 year prior to the Baseline Visit.
- known TB infection, was at high risk of acquiring TB infection, or had current or history of nontuberculous mycobacterium (NTMB) infection.
- a history of a lymphoproliferative disorder including lymphoma and/or current signs and symptoms suggestive of lymphoproliferative disease.
- a diagnosis of inflammatory conditions other than PSO or PsA including, but not limited to RA, sarcoidosis, systemic lupus erythematosus, and reactive arthritis. Study participants with a

diagnosis of Crohn's disease, UC, or other IBD were allowed as long as they had no active symptomatic disease at Screening or Baseline.

- acute anterior uveitis within 6 weeks of Baseline.
- fibromyalgia or osteoarthritis symptoms that in the Investigator's opinion would have had potential to interfere with efficacy assessments.
- any active malignancy or history of malignancy within 5 years prior to the Screening Visit EXCEPT treated and considered cured cutaneous squamous or basal cell carcinoma, or in situ cervical cancer.
- Study participant had a form of PSO other than chronic plaque-type (eg, pustular, erythrodermic and guttate PSO, or drug-induced PSO).

Treatments

The PsA Phase 3 clinical studies evaluated a dose regimen of bimekizumab **160mg Q4W.**

In these studies, bimekizumab was supplied in a 1mL prefilled syringe (PFS) at a nominal formulation of 160mg/mL (55mM sodium acetate, 220mM glycine, 0.04% polysorbate 80 at pH 5.0) for subcutaneous (sc) injection. All Phase 3 studies used the bimekizumab-True North (TN) device presentation.

PA0010

Adalimumab: commercially available and was supplied as a PFS for sc injection (at a concentration of 40mg/0.8mL or 40mg/0.4mL depending on regional availability) in a single-use syringe.

Placebo: 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (USP/Ph.Eur) quality in a 1mL PFS for sc injection.

PA0011

Placebo: 0.9% sodium chloride aqueous solution (physiological saline, preservative-free) of pharmacopoeia (US Pharmacopoeia/European Pharmacopoeia) quality in a 1mL PFS for sc injection.

Background Treatments PA0010 and PA0011

- No medication increases or additions were permitted for medications taken for PsA at baseline until Week 16. However, a decrease in dose or dosing frequency of any agent was permitted for reasons of intolerance/AEs/side-effects at any time.
- Study participants were allowed to use acetaminophen/paracetamol and mild opioids as needed, except within 24 hours of a visit with disease activity assessment.
- Study participants who were already receiving an established antidepressant regimen were on a stable dose of the antidepressant for 8 weeks prior to Baseline.
- For treatment of PSO, study participants could continue to use topical moisturizers, emollients, salicylic acid preparations, bath oils, oatmeal bath preparations, over-the-counter shampoos, mild topical steroids were permitted for use limited to the face, axillae, and/or genitalia, as needed.
- Use of psoralen and ultraviolet A light therapy for the treatment of PSO was not permitted for the first 16 weeks of both studies and was discouraged through the remainder of duration of the PA0010 study.
- Administration of live (including attenuated) vaccines was not allowed during the conduct of the study and for 20 weeks after the final dose IMP.

PA0010

- After the Week 16 Visit, the addition of topical retinoids, vitamin D analogues, coal tar preparations, and more potent topical steroids could be used as medically required to treat a flare but were not permitted to be used within 24 hours prior to a study visit.

Rescue Treatments

PA0010

After the 16-week Double-Blind Treatment Period, if the study participants were not responding adequately as per Investigators' judgement, rescue therapy was allowed.

Study participants who were rescued remained on IMP. Permitted rescue therapy for eligible study participants was at the Investigator's discretion, with the following options:

- Nonsteroidal anti-inflammatory drugs, cDMARDs (MTX, SSZ, LEF, HCQ, apremilast), and/or joint injections may be given as permitted rescue therapy if deemed appropriate by the Investigator as outlined below. Study participants may have received these add-on therapies while continuing to receive their randomized dose of IMP.
- A decrease in dose or dosing frequency of any agent for the treatment of PsA was permitted for reasons of intolerance/AEs/side-effects at any time.

PA0011

Rescue medication was not permitted in the 16-week Double-Blind Treatment Period.

Objectives

Primary Objective PA0010 and PA0011

To demonstrate the clinical efficacy of bimekizumab administered subcutaneously (sc) every 4 weeks (Q4W) for 16 weeks compared with placebo in the treatment of study participants with active PsA, as assessed by the American College of Rheumatology (ACR) 50 response.

Key Secondary Objectives PA0010 and PA0011

- efficacy of bimekizumab compared with placebo
- safety and tolerability of bimekizumab
- impact of bimekizumab on patient-reported quality of life (QoL)
- impact of bimekizumab on skin psoriasis (PSO) in the subgroup of affected study participants at Baseline
- impact of bimekizumab on functional improvement
- impact of bimekizumab on extra-articular disease manifestations (dactylitis, enthesitis)

PA0010

- impact of bimekizumab on radiographic changes in the hands and feet

Other Secondary Objectives

PA0010 and PA0011

- immunogenicity of bimekizumab

- impact of bimekizumab treatment on axial disease
- nail PSO in the subgroup of affected study participants at Baseline
- exposure response relationship of bimekizumab
- effect of bimekizumab on gene and protein expression, and explore the
- relationship between genomic, genetic, and proteomic biomarkers and disease biology, drug treatment and inflammatory and immune responses (from consenting study participants who agree to participate in the biomarker substudy)
- impact of bimekizumab on social life and work productivity

PA0010

- efficacy of bimekizumab with reference to adalimumab
- maintenance of treatment effect

Outcomes/endpoints

Primary Endpoint PA0010 and PA0011

- American College of Rheumatology 50% (ACR50) response at Week 16.

Key Secondary Endpoints PA0010 and PA0011

At Week 16:

- ACR20, ACR70,
- Health Assessment Questionnaire–Disability Index (HAQ-DI),
- 90% or greater improvement from Baseline in the Psoriasis Area and Severity Index (PASI90) in the subgroup of study participants with PSO involving at least 3% of Body Surface Area (BSA) at Baseline,
- Short-Form 36-item Health Survey Physical Component Summary (SF-36 PCS) score,
- Minimal Disease Activity (MDA),
- Proportion of study participants with an Investigator Global Assessment (IGA) score of 0 (clear) or 1 (almost clear) and at least a 2-grade reduction from Baseline at Week 4 and Week 16 in the subset of study participants with psoriatic skin lesions at Baseline
- Change from Baseline in Patient's Assessment of Arthritis Pain (PtAAP),
- Change from Baseline in Psoriatic Arthritis Impact of Disease 12 (PsAID-12),
- Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue subscale score.

PA0010 only secondary endpoints

- Structural damage assessed through the vdHmTSS
    - subgroup analysis in study participants with ≥1 bone erosion and/or hs-CRP ≥6mg/L
- Proportion of ACR50 responders at Week 16 and maintaining response at Week 52

Pooled secondary endpoints

- dactylitis and enthesitis endpoints; pooled between the 2 Phase 3 studies and assessed as part of the PA0010 hierarchy. Rationale of pooling was to provide well powered results across a more mixed population (TNFα-IR and bDMARD-naïve).
- Pool E1: data from PA0010 and PA0011, BKZ 160mg Q4W and PBO, Weeks 0-16; to investigate efficacy in selected subgroups

Other secondary endpoints PA0010 and PA0011

- Time to ACR20, ACR50, and ACR70 response from Baseline (Day 1)
- ACR20, ACR50, and ACR70 response
- PASI75, PASI90, and PASI100 response in the subgroup of study participants with PSO involving at least 3% BSA at Baseline
- Composite endpoint composed of ACR50 and PASI90 in study participants with PSO involving at least 3% BSA at Baseline
- Composite endpoint composed of ACR50 and PASI100 in study participants with PSO involving at least 3% BSA at Baseline
- Proportion of Psoriatic Arthritis Response Criteria (PsARC) responders
- Psoriatic Arthritis Disease Activity Score (PASDAS) categories
- Change from Baseline in the PASDAS
- MDA response
- Very Low Disease Activity (VLDA) response
- Proportion of study participants with an IGA score of 0 (clear) or 1 (almost clear) and at least a 2-grade reduction from Baseline in the subset of study participants with psoriatic skin lesions at Baseline
- Disease Activity Index for Psoriatic Arthritis (DAPSA) score categories
- Change from Baseline in DAPSA score
- Change from Baseline in the Disease Activity Score-28 based on C-reactive protein
- (DAS28[CRP])
- Change from Baseline in all individual ACR core components: SJC, TJC, HAQ-DI, PtAAP, Physician's Global Assessment of Psoriatic Arthritis, Patient's Global Assessment of Psoriatic Arthritis (PGA-PsA), and hs-CRP

Sample size

PA0010:

For power calculations of the primary endpoint, the sample size assumptions for bimekizumab versus placebo were based on the ACR50 response data from the Phase 2b bimekizumab study in study participants with moderate-to-severe PsA (PA0008). The median ACR50 responses of the top 3 dose groups (bimekizumab 160mg, 320mg, and 320mg [initial dose] plus 160mg) at Week 12 in the TNF-naïve population are conservatively assumed for the Week 16 endpoint. The observed median ACR50 response rate of the top 3 bimekizumab doses in the TNF-naïve population in study PA0008 was 43.8%.

The placebo ACR50 response at Week 16 is based on the TNFα-naïve population in PA0008 (6.1% at Week 12, study participants with available measurement (n)=33); Mease et al, 2015), FUTURE 2 study in the subgroup of TNFα-naïve study participants (15.9%, n=63; McInnes et al, 2014), FUTURE 3 study (11.8%, n=93; Nash et al, 2018), and FUTURE 5 study in a mixed tumor necrosis factor alpha (TNFα) exposure population (8.1% at Week 16, n=332; Mease et al, 2018). Therefore, the estimated ACR50 response at Week 16 in the placebo group is assumed to be 16%.

The sample size for showing statistical superiority of bimekizumab vs placebo was calculated using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). Assuming 420 study participants in the bimekizumab group and 280 study participants in the placebo group, the test for detecting statistical superiority of bimekizumab 160mg Q4W vs placebo based on ACR50 response at Week 16 has >99% power to detect a true treatment difference of 27.8% (OR=4.09).

The assumptions for power calculations of the secondary endpoints included in the hierarchy, and for which supporting data exists, are based on the interim results of the Phase 2b bimekizumab study PA0008 and the FUTURE 1, FUTURE 2, FUTURE 5, and SPIRIT P1 studies. All power calculations for binary endpoints were performed using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). All power calculations for continuous endpoints were performed using a 2-sided 2-group Satterthwaite t-test (Moser et al, 1989).

PA0011:

The sample size assumptions for bimekizumab versus placebo were based on the ACR50 response data in the subgroup of TNFα-IR patients from the Phase 2b bimekizumab study in a mixed prior TNFα therapy population of study participants with moderate-to-severe PsA (PA0008). Sample size calculations for a TNFα-IR population were also based on ACR50 responses at Week 16 in the SPIRIT-P2 study.

Observed ACR50 at Week 12 results in the PA0008 TNFα-IR populations were in a small number of study participants; bimekizumab 160mg (n=7), 320mg (n=8), and 320mg (initial dose) plus 160mg (n=8), and ranged from 14.3% to 37.5%.

The ixekizumab Phase 3 study SPIRIT–P2 was conducted on a similar patient population to that in this study and showed a 35% (n=122) ACR50 response at Week 16. Therefore, taking into account the range of ACR50 responses at Week 12 in PA0008, the estimated ACR50 response at Week 16 in the bimekizumab 160mg sc Q4W group was conservatively assumed to be 26%. For placebo, a similar approach as above was used. In the PA0008 TNFα-IR population, an ACR50 response of 11.1% (n=9) was observed at Week 12. The observed placebo ACR50 response at Week 16 was less than 10% in the SPIRIT-P2 study (n=118). Therefore, the estimated ACR50 response at Week 16 in the placebo group was assumed to be 10%.

The sample size for showing statistical superiority of bimekizumab versus placebo was calculated using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). Assuming 260 study participants in the bimekizumab group and 130 study participants in the placebo group, the test for detecting statistical superiority of bimekizumab 160mg versus placebo based on ACR50 response at Week 16 had 96% power to detect a true treatment difference of 16% (odds ratio of 3.16).

The assumptions for power calculations of the secondary endpoints included in the hierarchy and for which supporting data were available, in the TNFα-IR population were based on the results of PA0008 and the SPIRIT-P2 studies. All power calculations for binary endpoints were performed using a 2-sided 2-sample Chi-square test with continuity correction (Fleiss et al, 1980). All power calculations for continuous endpoints were performed using a 2-sided 2-group Satterthwaite t-test (Moser et al, 1989).

Randomisation

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

Each study participant received a 5-digit number assigned at Screening that served as the study participant identifier throughout the study. The IXRS automatically informed the Investigator or designee of the study participant's randomisation number. The IXRS allocated kit numbers to the study participant based on the study participant number during the course of the study. The randomisation number was documented in the eCRF.

Blinding (masking)

Unblinded study staff were responsible for preparation of the clinical study material, including recording the administration information on source documents, and administration of the IMP as sc injections. The unblinded personnel were not involved in the study in any way other than assuring the medication was taken from the correct kit and administering the IMP to the study participants. All study participant treatment details were allocated and maintained by IXRS system.

PA0010

Bimekizumab, adalimumab, and placebo were administered sc by unblinded study personnel at the clinical site.

Due to differences in presentation between the bimekizumab, adalimumab, and placebo treatments, special precautions were taken to ensure study blinding and study sites had blinded and unblinded personnel. As per dosing schedule for adalimumab, all study participants came to the study center for IMP administration at Baseline, Week 2, Week 4, and then Q2W thereafter. For study participants receiving bimekizumab, the IMP was administered at Baseline and Q4W thereafter; dummy/placebo treatments at Week 2 and Q4W thereafter were administered to preserve blinding and correspond to the dosing schedule for adalimumab. Adalimumab study participants received adalimumab at Baseline and Q2W thereafter.

After the 16-week Double-Blind Treatment Period, study participants entered the 36-week Active Treatment-Blind Period. Bimekizumab and adalimumab were administered sc by unblinded study personnel at the clinical site.

PA0011

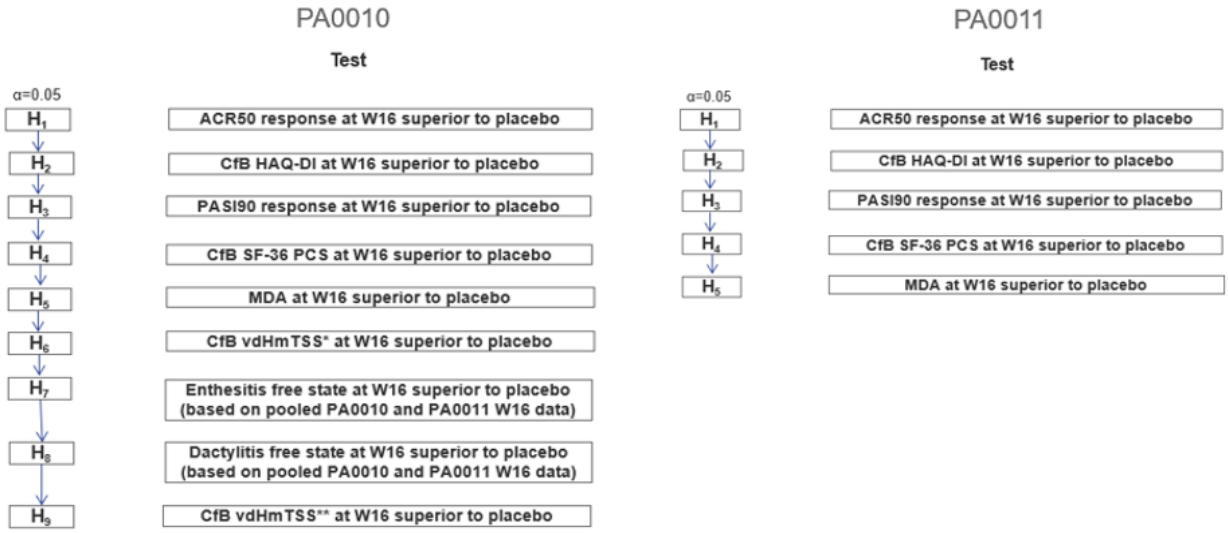
Bimekizumab and placebo were administered sc by unblinded study personnel at the clinical site. The remaining study team, including the Investigator, the Sponsor, an independent joint assessor, and study participants remained blinded.

Statistical methods

PA0010 and PA0011

For the primary efficacy endpoint and some secondary efficacy endpoints a step-down closed testing procedure was applied. The testing procedure accounted for multiplicity and controlled the family-wise type I error rate at alpha=0.05 (2-sided). 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 (i.e., if $p<0.05$). Figure 34 shows the testing order for these endpoints.



ACR=American College of Rheumatology; BKZ=bimekizumab; CfB=change from Baseline; H=hypothesis; HAQ-DI=Health Assessment Questionnaire—Disability Index; hs-CRP=high sensitivity C-reactive protein; MDA=Minimal Disease Activity; PASI=Psoriasis Area and Severity Index; PCS=Physical Component Summary; Q4W=every 4 weeks; SF-36=Short-Form 36-item Health Survey; vdHmTSS=Van der Heijde modified Total Sharp Score; W=Week

* In PA0010 study participants who were positive for elevated hs-CRP (hs-CRP ≥6mg/L) and/or had at least 1 bone erosion at Screening.

**Based on the overall population in PA0010.

Figure 34: PA0010 and PA0011 statistical testing hierarchies

Analysis Populations PA0010 and PA0011

The **Enrolled Set (ES)** was to consist of all study participants who had given informed consent. Study participant dispositions are presented on the ES.

The **Randomised Set (RS)** was to consist of all enrolled study participants that had been randomised. Demographic tables, primary, secondary and other efficacy variables are presented on the RS.

The **Safety Set (SS)** was to consist of all subjects who received at least 1 dose of the IMP. Demographic tables, study treatment compliance, exposure and safety variables are presented on the SS. Subjects in the SS were to be analysed according to the treatment they actually received.

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

The **Per-Protocol Set (PPS)** was to consist of all subjects in the RS who had no important protocol deviation (IPD), or non-PD related to prohibited medications affecting the primary efficacy variable (only IPD/non-PF related to prohibited medications observed prior to week 16 are considered for exclusion from the PPS). 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. Supportive analysis of the primary efficacy variable was performed on the PPS.

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 and not discontinuing due to COVID-19.

PA0010 only:

The **Active Medication Set (AMS)** was to consist of all study participants who received at least 1 dose of active IMP (bimekizumab or adalimumub). The AMS covers the analysis of data collected during the Active Medication Periods (AMP), i.e.:

- The Active Treatment-Blind Period for study participants randomised to placebo.
- The Double-Blind Treatment Period and the Active Treatment-Blind Period for study participants randomised to bimekizumab or adalimumab.

The AMS is used for summaries of safety during the AMP. The ADAb is also analysed on the AMS for study participants receiving bimekizumab.

The **Active Treatment-Blind Set (ATS)** was to consist of all study participants who received at least 1 dose of active treatment (bimekizumab or adalimumab) during the Active Treatment-Blind Period (Week 16 and after). Disposition, demographics, and Baseline characteristics are reported on the ATS. The ATS is also used to report data from the Active Treatment-Blind Period such as study treatment compliance and exposure, AEs, TEMA data for vital signs and laboratory data and selected efficacy analyses.

The disposition data, the primary efficacy endpoint and the secondary efficacy endpoints included in the testing hierarchy are analysed on the COVID-19-free Set.

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

Analysis of Primary Efficacy Variable PA0010 and PA0011

The primary endpoint was the ACR50 response at Week 16. The primary efficacy analysis evaluated the composite estimand in the Randomized Set (RS). The composite estimand combined the clinically meaningful improvement from Baseline in ACR50 response at Week 16 and not discontinuing IMP prior to Week 16.

The following 4 attributes described this estimand:

- **Population** = Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomised to IMP.
- **Study participant-level outcome** = ACR50 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 ACR50 at Week 16 and not discontinuing study treatment through Week 16.
- **Population-level summary measure** = Conditional OR comparing bimekizumab to placebo.

Use of prohibited or rescue medication through week 16 was not specified as in intercurrent event, but implicitly handled using a treatment policy strategy. Any use of prohibited or rescue medications through Week 16 constituted an IPD which was accounted for when the sensitivity analysis based on the PPS was performed.

Missing data at Week 16 that were not preceded by an intercurrent event (IE), and any data after an IE were imputed as non-responders. This resulted in a more traditional non-responder imputation (NRI) approach. A logistic regression model was used to assess the treatment effect on ACR50 response at Week 16. The model included a fixed effect for treatment (and in PA0011 for prior TNFα inhibitor exposure and region as stratification factors).

The suitability of including randomisation stratification variables (bone erosion at Baseline and region) was assessed using Pearson and Deviance and The Hosmer-Lemeshow Goodness-of-Fit Tests (Hosmer and Lemeshow, 2000).

Summary table results presented the adjusted responder rates and the associated 95% CIs for the 3 treatment groups, the adjusted OR and the corresponding 95% CI for the comparison of bimekizumab versus placebo, the p-value and the difference of response rate between bimekizumab and placebo and associated 95% CI. Comparisons of bimekizumab vs. placebo were made using the 2-sided Wald test at a significance level of α=0.05.

Supportive analyses of the primary efficacy variable PA0010 and PA0011

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 ACR (using two forms of hypothetical estimand where the single intercurrent event is discontinuation of study treatment prior to week 16)
- 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
- Analyses including COVID-19 impact

Analyses of Key Secondary Efficacy Variables PA0010 and PA0011

The secondary efficacy variables were analysed for all study participants in the RS by treatment group (except for vdHmTSS in PA0010, for which the analysis was performed on the Radiographic Set). For the secondary composite and non-composite binary endpoints, the same estimand structure (composite estimand) as the one defined for the primary efficacy analysis of the primary efficacy endpoint was used.

The NRI approach for handling missing data and the same analysis model was considered, and the analysis results were presented similarly, with the exceptions that the analyses performed on pooled data from PA0010 and PA0011 study participants considered the region and the study-id factor as possible covariates for the modelling.

For the secondary continuous endpoints, the analysis evaluated the hypothetical estimand as defined below:

- **Population**=Study participants enrolled according to the protocol-specified inclusion/exclusion criteria and randomised to IMP.
- **Study participant level outcome**=variable of interest.
- **IE handling**=An IE was defined as discontinuation of study treatment prior to Week 16. A hypothetical strategy for addressing IE was implemented. This estimand targeted the treatment difference in a scenario where withdrawal from study treatment did not occur, such that outcomes for study participants without an IE were as observed, and outcomes for study participants with

an IE were treated as though they had completed treatment through Week 16 but on placebo. A MI strategy was used to impute any missing data and observed data after IE which was set to missing prior to running MI. Such data were imputed using reference-based MI, in which the MI model was based on data from the placebo group.

- **Population-level summary measure**=the difference in the adjusted means between bimekizumab 160mg Q4W and placebo

For vdHmTSS in PA0010, a similar estimand structure as that defined for continuous endpoints was used with the following exception for population:

- When analysing change at Week 16 from Baseline in vdHmTSS for study participants with elevated hs-CRP or with at least 1 erosion at Baseline: Population=Study participants enrolled according to the protocol-specified inclusion/exclusion criteria, randomised to IMP, who had a valid radiographic image of the hands and feet at Baseline in the subgroup of patients with elevated CRP and with at least 1 bone erosion at Baseline.
- When analysing change at Week 16 from Baseline in vdHmTSS for all study participants: Population=Study participants enrolled according to the protocol-specified inclusion/exclusion criteria, randomised to IMP, who had a valid radiographic image of the hands and feet at Baseline.

Rules for calculation of MDA response were described in the SAP.

Enthesitis and dactylitis pooling strategy

The original PA0010 hierarchy planned to examine dactylitis (free-state) and enthesitis (change from Baseline [CfB]) while the PA0011(Phase 3 study of bimekizumab in study participants with active PsA who were TNFα inadequate responders) hierarchy does not include either. As part of a standard blinded data evaluation meeting of PA0010, after approximately 50% of study participants had enrolled, to examine Baseline characteristics and check for data quality trends, it was discovered that the number of study participants with dactylitis and/or enthesitis at Baseline was lower than anticipated. Consequently, the number of study participants was also lower than what was used for the a priori power calculation assumptions for these endpoints.

In order to provide well powered and more clinically interpretable results for dactylitis and enthesitis endpoints across a more robust mixed population (TNF-inadequate responders and bDMARD-naïve), the hierarchy was updated to remove dactylitis free-state and enthesitis (CfB) from the PA0010 study hierarchy and add pooled PA0010 and PA0011 endpoints for dactylitis free-state and enthesitis free-state, which is a more interpretable and clinically meaningful endpoint than CfB, within the PA0010 study hierarchy.

PA0011 does not have either of these variables in its hierarchy; therefore, pooling within the closed sequential testing procedure of PA0010 did not introduce any inflation of the type 1 error within the PA0010 hierarchy. As the pooling was done to achieve power similar to the original a priori power, there was no additional adjustment to the p-value to make it more conservative. In addition to showing a significant result of the pooled endpoints, for the sake of interpretation, the individual studies were required to additionally show a similar trend that bimekizumab was numerically better than placebo.

Analyses of Other Secondary Efficacy Variables PA0010 and PA0011

The time to ACR20/50/70 response was analysed for the Double-Blind Treatment Period on the treatment groups. The Kaplan-Meier plots of time to ACR20,50,70 response are presented by treatment group. For binary variables, the analysis followed the NRI approach (composite estimand).

PA0010- The analysis model was based on a logistic model with fixed effect for treatment and in PA0010, bone erosion at Baseline and region as stratification variables. For continuous variables, the MI-MCMC/monotone regression approach was applied for the imputation model on the change from Baseline (hypothetical estimand). The analysis model was based on ANCOVA with fixed effect of treatment, region, bone erosion at Baseline and Baseline value as covariates.

PA0011- For binary variables, the analysis followed the NRI approach (composite estimand). Study participants who had an IE, which was considered associated to a treatment failure, were considered as non-responders. Any missing data were also considered as non-responders (NRI approach). For categorical variables, the worst-category was imputed similarly instead of non-response. For continuous variables, the MI-MCMC/monotone regression approach was applied for the imputation model on the change from Baseline (hypothetical estimand). The analysis model was based on analysis of covariance, with fixed effect of treatment, region, and prior TNFα inhibitor exposure, and Baseline value as covariates. For responder variables, the analysis followed the NRI approach (composite estimand). The analysis model was based on a logistic model, with fixed effect for treatment and prior TNFα inhibitor exposure Baseline and region as stratification variables.

Subgroup analyses PA0010 and PA0011

Subgroup analyses were to be performed on the variables below. These variables were all assessed at Baseline except concomitant cDMARDs, concomitant MTX and ADAb status which were assessed during the 16-week Double-Blind Treatment Period.

Subgroup analyses were to be performed on the ACR50 response, the PASI90 response and the HAQ-DI response (subjects with a decrease of HAQ-DI from Baseline of at least 0.35) at Week 16.

ADAb status were also used for subgroup analysis for the PK endpoints. The variables for subgroup analyses were:

- Age (<45 years of age, ≥45 years of age)
- Gender (male, female)
- Disease duration (<1 year, ≥1 year)
- Region (eg, North America, Western Europe, Eastern Europe, Asia)
- Race (White, Black and Other)
- Body weight at Baseline (≤100 kg, >100 kg)
- Bone erosion (≥1) at Baseline (Yes, No) **– PA0010 only**
- hs-CRP at Baseline (<6mg/L, ≥6mg/L)
- Bone erosion (≥1) and/or hs-CRP ≥6mg/L at Baseline (Yes, No) **– PA0010 only**
- Prior TNF exposure (intolerance to TNFα inhibitor, inadequate response to at least 1 TNFα inhibitor, inadequate response to 2 prior or more TNFα inhibitors) **– PA0011 only**
- Prior cDMARDs (0, 1, ≥2) (taken prior to Baseline)
- Concomitantly receiving cDMARDs versus no concomitant cDMARDs
- Concomitantly receiving MTX versus no concomitant MTX
- Concomitantly receiving MTX at Baseline vs. other cDMARDs at Baseline (MTX at Baseline, no MTX at Baseline and cDMARDs at Baseline, no MTX at Baseline and no cDMARDs at Baseline)
- PSO affected BSA at Baseline (<3%, ≥3% to 10%, >10%)

- BASDAI at Baseline (<4, ≥4)
- ADAb status (positive, negative) (for the Bimekizumab 160mg Q4W group only)
- Human leukocyte antigen B27 (HLA-B27) (positive, negative).

Multicentre study

In general, the data from all centers was to be pooled for the purposes of the analysis. However, the effect of center (using a pooling of centers by region) on results was to be evaluated.

The 4 geographic regions considered for the study were those used for randomisation stratification: North America (Canada, USA), Western Europe (Belgium, France, Germany, Italy, Spain, United Kingdom), Eastern Europe (Czech Republic, Hungary, Poland, Russia), Asia (Australia, Japan) identified as "Asia" in all analyses.

Interim analyses

In PA0010, 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 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 final analysis for PA0010 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.

In PA0011, one analysis was performed prior to the final analysis at week 16. No formal alterations to the further study conduct (eg, stopping rules, sample size re-estimation, or changes to eligibility criteria) were planned for the Week 16 interim analysis. No separate SAP for the Week 16 interim analysis was provided; all analyses for Week 16 followed the planned analyses described in the study SAP. The database lock and unblinding date for the PA0011 Week 16 interim analysis used was 22 December 2021.

The final analysis for PA0011 was completed when all participants in the SFU Period completed the SFU Visit and consisted of a rerun of all analyses as well as new data from the SFU Period that were not available for the Week 16 interim analysis. The database lock date for the final analysis was 04 March 2022.

Changes to the Planned Analyses

Changes related to COVID-19 PA0010 and PA0011

The impact of the COVID-19 pandemic on study procedures/conduct as well as the efficacy and safety endpoints was investigated, and additional analysis outputs are provided as appropriate. These additional analyses were not planned as part of the original 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 (pre/during/post) as defined below:

- Pre-COVID-19 pandemic period: period prior to COVID-19 pandemic start date defined as 11-Mar-2020
- COVID-19 pandemic period: period from 11-Mar-2020 though the COVID-19 pandemic end date which is currently not defined at the time of approval of the SAP

- Post-COVID-19 pandemic period: period after the declaration of the end of the pandemic. (at the time of study conduct and data analyses, the COVID-19 pandemic was ongoing; therefore, no results were presented for the post-COVID period).

PA0010 Changes to the protocol-defined analyses

The following changes from the protocol were considered:

- An additional supportive analysis for primary endpoint based on the analysis of the individual components of ACR is performed using the Reference-Based imputation method.
- The main analyses of the secondary continuous variables included in the testing hierarchy will be performed using the Reference-Based imputation method.
- Proportion of study participants with a decrease of HAQ-DI from Baseline of at least 0.35 (HAQ-DI responders) in those study participants with HAQ-DI ≥0.35 instead of >0.35.
- An additional subgroup based on the combination of concomitant MTX and Baseline cDMARD.
- Additional subgroup analyses were performed on HAQ-DI responders at Week 16.
- Proportion of PsAID-12 responders (decrease from Baseline in PsAID-12 total score ≥3) in study participants with PsAID-12 total score ≥3 at Baseline instead of >3 at Baseline.
- The subgroup analysis on BASDAI was performed on the categories: <4 vs. ≥4 rather than ≤4 vs. >4.
- The analysis of the proportion of responding study participants at Week 52 among those who responded at Week 16 is extended to all post Week 16 visits (and not only Week 52).
- The analysis of the proportion of FACIT-Fatigue subscale responders (study participants with a minimum clinically important difference for FACIT-Fatigue subscale score defined as an increase of ≥4) is performed in study participants with FACIT-Fatigue subscale score ≤48 at Baseline.
- The time to ACR20/50/70 is exclusively analyzed using observed cases data.
- The AMS is an analysis set that has been added for the analysis of safety variables.
- The ATS is an analysis set that has been added for the analysis of data collected during the Active Treatment-Blind Period.

These changes from the protocol were reflected in the final SAP prior to unblinding.

Regarding the summary of imaging endpoints, the SAP states that for the Week 24 analysis only the first reading session will be used when generating the outputs based on the imaging data. Prior to unblinding, it was noticed that in some cases the first reading session was missing and the second reading session was non-missing. In an effort to have as much available data as possible for the Week 24 analysis, the analysis deviated from the SAP and included data from the second reading session in cases where the first reading session was missing.

PA0011 Changes to the protocol-defined analyses

The following changes from the protocol were considered:

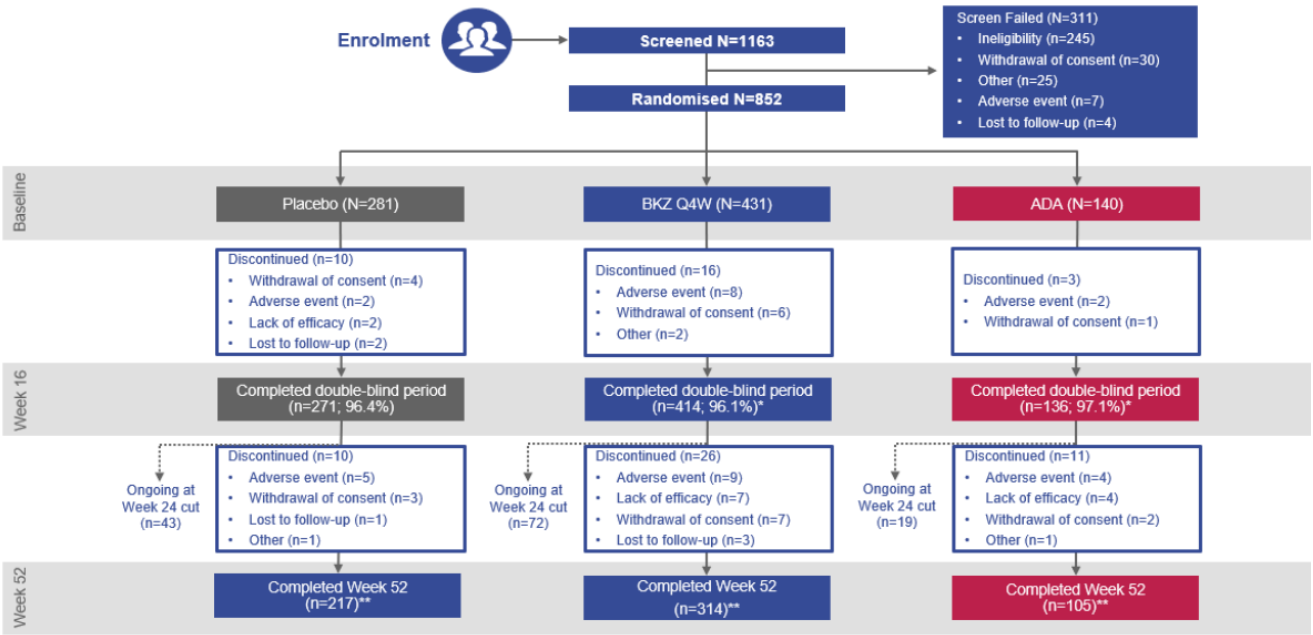
- The subgroup analysis on BASDAI was performed on the categories: <4 versus ≥4 rather than ≤4 versus >4.
- Proportion of study participants with a decrease of HAQ-DI from Baseline of at least 0.35 (HAQ-DI responders) in those study participants with HAQ-DI ≥0.35 instead of >0.35.

- Proportion of PsAID-12 responders (decrease from Baseline in PsAID-12 total score ≥3) in study participants with PsAID-12 total score ≥3 at Baseline instead of >3 at Baseline.
- An additional supportive analysis for primary endpoint based on the analysis of the individual components of ACR was performed using the Reference-Based imputation method.
- The main analyses of the secondary continuous variables included in the testing hierarchy were performed using the Reference-Based imputation method.
- Additional subgroup analyses were performed for HAQ-DI responders at Week 16.
- Additional subgroups based on the combination of concomitant MTX and baseline cDMARDs.

Results

Participant flow

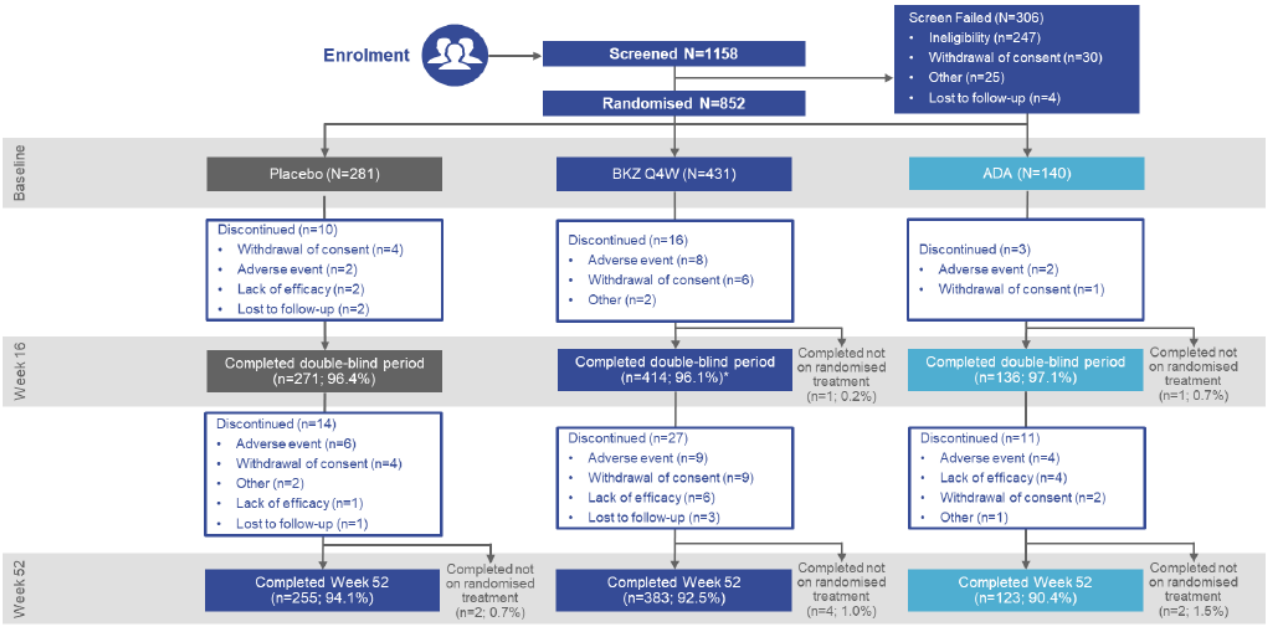
PA0010



ADA=adalimumab; BKZ=bimekizumab; Q4W=every 4 weeks
* One study participant each in the BKZ and the ADA groups completed the Double-Blind Period (but not on randomized treatment) and were not included in the completed Double-Blind Period.
** One study participant in the placebo/BKZ 160mg Q4W group, 2 study participants in the BKZ group, and 1 study participant in the ADA group completed Week 52 (but not on randomized treatment) and were not included in the completed Week 52 data.
Note: A study participant was said to have completed the Double-Blind Treatment Period if she/he had completed the last scheduled study visit of that period. Study participants who withdrew from the study medication but returned for all scheduled visits up to Week 16 visit were considered as completed the Double-Blind Treatment Period not on randomized treatment.

Figure 35: Disposition schematic

Participant flow PA0010 Final updated data:



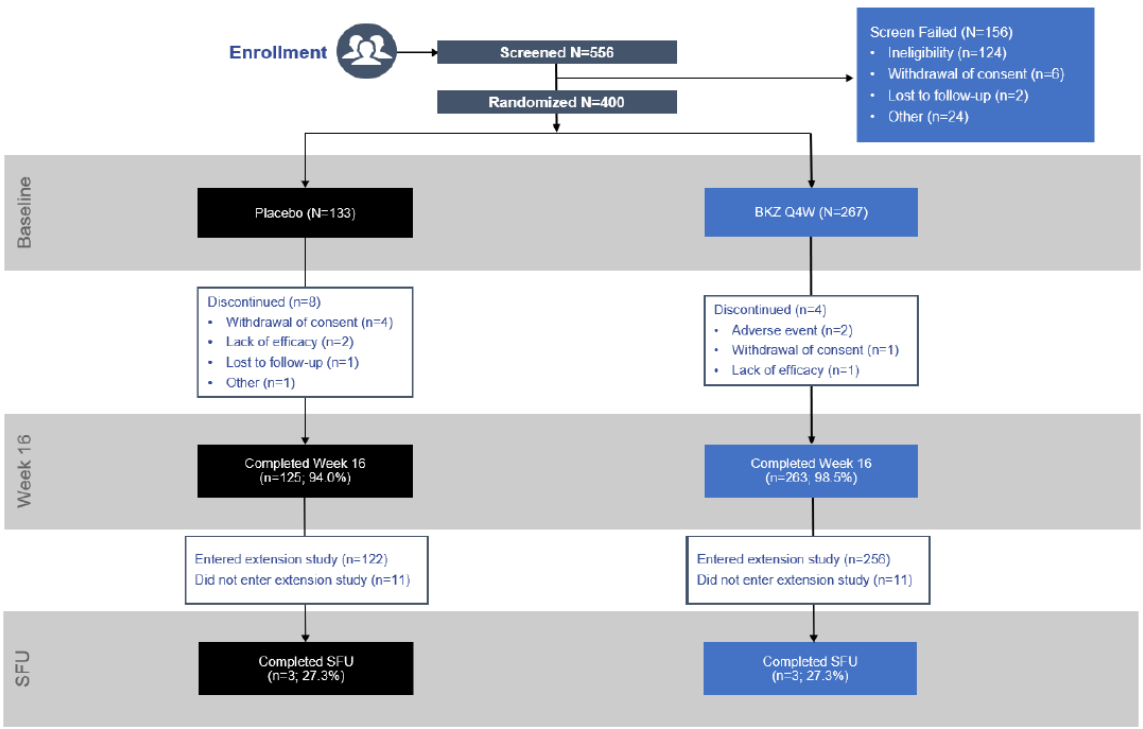
ADA=adalimumab; BKZ=bimekizumab; Q4W=every 4 weeks

* One study participant in the BKZ group completed the Double-Blind Treatment Period but the disposition was not correctly available at the time of the data cut.

Note: A study participant was said to have completed the Double-Blind Treatment Period if she/he had completed the last scheduled study visit of that period. Study participants who withdrew from the study medication but returned for all scheduled visits up to Week 16 visit were considered as completed the Double-Blind Treatment Period not on randomized treatment.

Figure 36: Disposition schematic

PA0011



BKZ=bimekizumab; IMP=investigational medicinal product; Q4W=every 4 weeks; SFU=Safety Follow-up

Note: A study participant was said to have completed the Double-Blind Treatment Period if she/he had completed the last scheduled study visit, not including the SFU visits. Study participants who withdrew from the IMP but returned for all scheduled visits up to the Week 16 visit were considered as completed the study not on randomized treatment.

Figure 37: Disposition schematic

Recruitment

During the course of this study, recruitment was halted for approximately 2 months (20 March 2020 to 22 May 2020) due to the COVID-19 worldwide pandemic. Any study participants who were in the screening process during that timeframe were captured as screen failures.

PA0010

A total of 1163 study participants signed the ICF and were screened for the study, 311 of whom were screen failures. The most common reason for being a screen failure was ineligibility (245 study participants [78.8%]).

PA0011

A total of 556 study participants signed the ICF and were screened for the study, 156 of whom were screen failures. The most common reason for being a screen failure was ineligibility (124 study participants [79.5%]).

Conduct of the study

Changes to the Conduct of the Study PA0010 and PA0011

The original PA0010 protocol (dated 28 November 2018) and PA0011 protocol (dated 29 November 2018) have undergone 2 global protocol amendments each and additional local (Japan) protocol amendments.

Global protocol amendments:

PA0010

Protocol Amendment 1 (10 January 2020) was implemented to update the completed and ongoing studies information, clarify study procedures, update the description of the IMP, and to apply a minimum percentage for enrolment of study participants who had elevated hs-CRP and/or have at least 1 bone erosion at Screening.

Protocol Amendment 2 (22 February 2021) was implemented to modify the secondary variables and fixed sequence testing procedure, update the statistical section, and make other procedural clarifications.

PA0011

Protocol Amendment 1 (14 May 2020) was implemented to update the completed and ongoing studies information, clarify study procedures, add re-screening rules, update the description of IMP, change the statistical hierarchy, and update the statistical section.

Protocol Amendment 2 (01 April 2021) was implemented to modify the secondary variables and fixed sequence testing procedure, update the statistical section, and make other procedural clarifications.

COVID-19 impact:

In accordance with the released guidance documents for clinical trial conduct during the COVID-19 pandemic by local Health Authorities, the study eCRF was updated by adding a specific page to record any COVID-19 impact on study assessments.

Additionally, a study-specific contingency plan was developed to ensure participant safety and data integrity during the pandemic. The contingency plan provided options to sites which could be applied in case of severe local COVID-19 restrictions.

Protocol Deviations

Impact of COVID-19 PA0010

No more than 2 study participants (0.2%) at any given visit had a visit not done due to COVID-19 through Week 24. No study participant permanently discontinued IMP or missed IMP administration due to COVID-19 before Week 16. Two study participants discontinued IMP after Week 16 (1 [0.2%] in the bimekizumab 160mg Q4W group at Week 20 and 1 [0.4%] in the placebo/bimekizumab 160mg Q4W group at Week 28); both were due to general circumstances around COVID-19 without infection. No more than 6 participants (0.7%) overall missed IMP administration at any given visit.

Table 30: Important protocol deviations – double blind treatment period (RS)

Category	Placebo N=281 n (%)	BKZ 160mg Q4W N=431 n (%)	ADA 40mg Q2W N=140 n (%)	All Subjects N=852 n (%)
Number of subjects with:				
No important protocol deviations	243 (86.5)	383 (88.9)	122 (87.1)	748 (87.8)
At least one important protocol deviation	38 (13.5)	48 (11.1)	18 (12.9)	104 (12.2)
Inclusion criteria deviation	3 (1.1)	3 (0.7)	1 (0.7)	7 (0.8)
Exclusion criteria deviation	0	0	0	0
Withdrawal criteria deviation	1 (0.4)	0	0	1 (0.1)
Prohibited concomitant medication use	14 (5.0)	14 (3.2)	7 (5.0)	35 (4.1)
Incorrect treatment or dose	2 (0.7)	4 (0.9)	0	6 (0.7)
Treatment non-compliance	0	0	0	0
Procedural non-compliance	17 (6.0)	22 (5.1)	6 (4.3)	45 (5.3)
COVID-19 visit deviation	3 (1.1)	7 (1.6)	5 (3.6)	15 (1.8)
COVID-19 treatment deviation	0	1 (0.2)	0	1 (0.1)
COVID-19 termination	0	0	0	0
COVID-19 other IPD	0	0	0	0

Impact of COVID-19 PA0011

No more than 1 study participant (0.3%) at any given visit missed a visit due to COVID-19. Visits were not done for these participants at Weeks 4, 8, and 12 (1 participant each). Visits out of window were reported by 1 participant (0.3%), 3 participants (0.8%), and 14 participants (3.5%) for Weeks 8, 12, and 16, respectively. One participant in the placebo group discontinued IMP due to general circumstances around COVID-19 without infection. The majority of study participants were enrolled during the pandemic (n=234) rather than before the pandemic (n=166). There was no pattern of enrollment differences between the treatment groups. Overall, only 1 study participant had efficacy assessments impacted by COVID-19.

Table 31: Important protocol deviations – double blind treatment period (RS)

Category	Placebo N=133 n (%)	BKZ 160mg Q4W N=267 n (%)	All Subjects N=400 n (%)
Number of subjects with:			
No important protocol deviations	122 (91.7)	243 (91.0)	365 (91.3)
At least one important protocol deviation	11 (8.3)	24 (9.0)	35 (8.8)
Inclusion criteria deviation	6 (4.5)	13 (4.9)	19 (4.8)
Exclusion criteria deviation	0	0	0
Withdrawal criteria deviation	0	0	0
Prohibited concomitant medication use	0	1 (0.4)	1 (0.3)
Incorrect treatment or dose	0	1 (0.4)	1 (0.3)
Treatment non-compliance	0	0	0
Procedural non-compliance	5 (3.8)	9 (3.4)	14 (3.5)
COVID-19 visit deviation	0	0	0
COVID-19 treatment deviation	0	0	0
COVID-19 termination	0	0	0
COVID-19 other IPD	0	2 (0.7)	2 (0.5)

PA0010 Double-Blind Treatment Period- Protocol Deviations

After the database lock for the Week 24 interim analysis, new important protocol deviations (IPDs) were identified which impacted the PPS. Six study participants were added to and 9 were excluded from the initial Per-Protocol Set (PPS) after the interim analysis based on the assessment of IPD by the blinded study team. The impact of this change on the efficacy in PPS was minimal, and the overall conclusions were not impacted.

Most study participants (87.8%) had no IPDs during the Double-Blind Treatment Period (Table 32). The incidence of IPDs was similar in the bimekizumab 160mg Q4W (11.1%), adalimumab (12.9%), and placebo (13.5%) groups. Overall, the most common IPDs were procedural noncompliance (5.3%) and prohibited concomitant medication use (4.1%); the incidence of these were similar across treatment groups. The most common reason for procedural noncompliance was due to a missed assessment at either Baseline or Week 16. A total of 15 study participants (1.8%) had other IPDs related to COVID-19, these were most frequently due to X-rays not collected at Week 16.

The incidence of study participants who were excluded from the PPS overall was 5.3%; the incidence was similar in the bimekizumab 160 Q4W (5.1%), placebo (5.7%), and adalimumab (5.0%) groups. No study participants in the bimekizumab 160mg Q4W group were excluded from the PK-PPS due to IPDs.

Table 32: Important protocol deviations – double blind treatment period (RS)

Category	Placebo N=281 n (%)	BKZ 160mg Q4W N=431 n (%)	ADA 40mg Q2W N=140 n (%)	All Study Participants N=852 n (%)
Study participants with no important protocol deviations	243 (86.5)	383 (88.9)	122 (87.1)	748 (87.8)
Study participants with at least 1 important protocol deviation	38 (13.5)	48 (11.1)	18 (12.9)	104 (12.2)
Inclusion criteria deviation	3 (1.1)	3 (0.7)	1 (0.7)	7 (0.8)
Exclusion criteria deviation	0	0	0	0
Withdrawal criteria deviation	1 (0.4)	0	0	1 (0.1)
Prohibited concomitant medication use	14 (5.0)	14 (3.2)	7 (5.0)	35 (4.1)
Incorrect treatment or dose	2 (0.7)	4 (0.9)	0	6 (0.7)
Treatment noncompliance	0	0	0	0
Procedural noncompliance	17 (6.0)	22 (5.1)	6 (4.3)	45 (5.3)
COVID-19 visit deviation	0	0	0	0
COVID-19 treatment deviation	0	0	0	0
COVID-19 termination	0	0	0	0
COVID-19 other IPD	3 (1.1)	7 (1.6)	5 (3.6)	15 (1.8)
Study participants excluded from PPS	16 (5.7)	22 (5.1)	7 (5.0)	45 (5.3)
Inclusion criteria deviation	3 (1.1)	2 (0.5)	0	5 (0.6)
Prohibited concomitant medication use	9 (3.2)	11 (2.6)	5 (3.6)	25 (2.9)
Incorrect treatment or dose	2 (0.7)	3 (0.7)	0	5 (0.6)
Procedural noncompliance	2 (0.7)	6 (1.4)	1 (0.7)	9 (1.1)
Exclusion from PPS due to reason other than protocol deviation	6 (2.1)	5 (1.2)	2 (1.4)	13 (1.5)
Study participants excluded from the PK-PPS	0	0	0 [a]	0
Procedural noncompliance	0	0	0 [a]	0

ADA=adalimumab; BKZ=bimekizumab; COVID-19=coronavirus disease 2019; IPD=important protocol deviation; PK=pharmacokinetic; PPS=Per-Protocol Set; PK-PPS=Pharmacokinetic Per-Protocol Set; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

PA0010 Active Treatment-Blind Period- Protocol Deviations

Most study participants (96.7%) had no important protocol deviations during the Active Treatment-Blind Period (Table 33). The incidence of important protocol deviations was similar in the bimekizumab 160mg Q4W (2.7%), adalimumab (3.7%), and placebo/bimekizumab 160mg Q4W (4.1%) groups. Overall, the most common important protocol deviations were procedural noncompliance (2.3%); the incidence of these were generally similar across treatment groups. No study participants were excluded from the PK-PPS.

Table 33: Important protocol deviations – active treatment blind period (ATS)

Category	Placebo/ BKZ 160mg Q4W N=271 n (%)	BKZ 160mg Q4W N=414 n (%)	ADA 40mg Q2W N=136 n (%)	All Study Participants N=821 n (%)
Study participants with no important protocol deviations	260 (95.9)	403 (97.3)	131 (96.3)	794 (96.7)
Study participants with at least 1 important protocol deviation	11 (4.1)	11 (2.7)	5 (3.7)	27 (3.3)
Incorrect treatment or dose	0	1 (0.2)	1 (0.7)	2 (0.2)
Procedural noncompliance	9 (3.3)	8 (1.9)	2 (1.5)	19 (2.3)
COVID-19 other IPD	0	1 (0.2)	2 (1.5)	3 (0.4)
Study participants excluded from the PK-PPS	0	0	0	0

PA0011 Protocol Deviations

Most study participants (91.0%) had no IPDs during the study (Table 34). The incidence of IPDs was similar in the bimekizumab 160mg Q4W (9.0%) and placebo (8.3%) groups. Overall, the most common IPDs were inclusion criteria deviation and procedural noncompliance; the incidence of these was similar between treatment groups. The most common reasons for inclusion criteria deviation were that the participant was not on a stable dose of NSAID or oral corticosteroid, or MTX prior to Baseline and remained on a stable dose throughout the duration of the study. Four study participants did not meet the criteria of having a proper washout period after prior TNF.

A total of 2 study participants (0.5%) had other IPDs related to COVID-19: an out of window visit at Week 16 and PK samples not collected at Week 12 (1 participant each).

The incidence of study participants who were excluded from the PPS was low overall (4.5%) with the same incidences in the bimekizumab 160mg Q4W and placebo groups (4.5%). Two study participants (0.5%; 1 participant from each treatment group) were excluded from the PK-PPS. The reasons for exclusion from the PK-PPS were due to procedural noncompliance and COVID-19 other important protocol deviation (1 study participant each).

Table 34: Important protocol deviations (RS)

Category	Placebo N=133 n (%)	BKZ 160mg Q4W N=267 n (%)	All study participants N=400 n (%)
Study participants with no IPDs	122 (91.7)	243 (91.0)	365 (91.3)
Study participants with at least 1 IPD	11 (8.3)	24 (9.0)	35 (8.8)
Inclusion criteria deviation	6 (4.5)	13 (4.9)	19 (4.8)
Exclusion criteria deviation	0	0	0
Withdrawal criteria deviation	0	0	0
Prohibited concomitant medication use	0	1 (0.4)	1 (0.3)
Incorrect treatment or dose	0	1 (0.4)	1 (0.3)
Treatment noncompliance	0	0	0
Procedural noncompliance	5 (3.8)	9 (3.4)	14 (3.5)
COVID-19 visit deviation	0	0	0
COVID-19 treatment deviation	0	0	0
COVID-19 termination	0	0	0
COVID-19 other IPD	0	2 (0.7)	2 (0.5)
Study participants excluded from PPS	6 (4.5)	12 (4.5)	18 (4.5)
Inclusion criteria deviation	5 (3.8)	12 (4.5)	17 (4.3)
Exclusion criteria deviation	0	0	0
Withdrawal criteria deviation	0	0	0
Prohibited concomitant medication use	0	1 (0.4)	1 (0.3)
Incorrect treatment or dose	0	0	0
Treatment noncompliance	0	0	0
Procedural noncompliance	1 (0.8)	1 (0.4)	2 (0.5)
COVID-19 visit deviation	0	0	0
COVID-19 treatment deviation	0	0	0
COVID-19 termination	0	0	0
COVID-19 other IPD	0	0	0
Exclusion from PPS due to reason other than protocol deviation	0	0	0
Study participants excluded from the PK-PPS	1 (0.8)	1 (0.4)	2 (0.5)
Inclusion criteria deviation	0	0	0
Exclusion criteria deviation	0	0	0
Withdrawal criteria deviation	0	0	0
Prohibited concomitant medication use	0	0	0
Incorrect treatment or dose	0	0	0
Treatment noncompliance	0	0	0
Procedural noncompliance	1 (0.8)	0	1 (0.3)
COVID-19 visit deviation	0	0	0
COVID-19 treatment deviation	0	0	0
COVID-19 termination	0	0	0
COVID-19 other IPD	0	1 (0.4)	1 (0.3)
Exclusion from PK-PPS due to reason other than protocol deviation	0	0	0

BKZ=bimekizumab; COVID-19=Coronavirus Disease-2019; IPD=important protocol deviation; PPS=Per-Protocol Set; PK-PPS=Pharmacokinetics Per-Protocol Set; Q4W=every 4 weeks; RS=Randomized Set
Note: Study participants with IPDs affecting the primary efficacy variable were excluded from the PPS.
Note: Study participants with IPDs affecting the plasma concentration were excluded from the PK-PPS.

Baseline data

Demography

A total of 1112 study participants with active PsA were randomised to receive either bimekizumab or placebo in the Phase 3 studies PA0010 and PA0011. In PA0010, there were an additional 140 study participants with PsA randomised to receive adalimumab in the active reference arm. All study participants came from the regions of North America, Europe, and Asia.

The mean age of study participants was 49.3 years and approximately half the study participants (51.6%) were in the age category 45 to <65 years of age. The majority of study participants were female

(53.4%) and White (95.7%) with a mean body weight and mean BMI of 85.33kg and 29.50kg/m2, respectively.

Baseline Disease Characteristics (Overall)

Overall, the mean time since diagnosis of PsA was 7.15 years (range: 0.0 to 56.0 years). In PA0010, the mean time since diagnosis of PsA was 5.87 years overall (range: 0.0 to 49.8 years), while in PA0011, the mean time since diagnosis of PsA was longer (9.50 years overall [range: 0.4 to 56 years]), given that study participants in PA0011 had more advanced disease by study design.

Approximately 10% of study participants in Pool E1 had moderate to severe PSO disease. The mean time since diagnosis of PSO was 15.94 years overall (range: 0.0 to 58.5 years) The mean PASI score was 8.71, and 55.9% of participants had ≥3% of BSA affected by PSO.

Study participants had active disease across multiple domains of PsA including dactylitis, enthesitis, and skin and nail disease. Overall, 57.7% of study participants had nail PSO, 12.3% of study participants had dactylitis, and approximately one-third had enthesitis (38.6% by SPARCC and 31.9% by LEI).

Study participants with different subtypes of PsA were enrolled across the bDMARD naïve and TNFα-IR populations in bimekizumab studies. In both study populations, the majority of study participants had polyarticular arthritis (63.5%) with oligoarticular arthritis as the second largest group (25.9%).

Baseline Disease Characteristics- PA0010

The majority of study participants were White (95.4%) and over half of the participants were female (53.2%). The mean age of all study participants was 48.65 years of age, mean body weight and mean body mass index (BMI) overall were 84.63kg and 29.20kg/m2, respectively.

The mean time since diagnosis of PSO was 15.13 years overall (range: 0.0 to 57.0 years). The mean PASI score was 8.14 and 49.9% of participants had ≥3% of BSA affected by PSO. Overall, 55.8% of study participants had nail PSO, 11.7% of study participants had dactylitis and approximately one-third had enthesitis (35.2% by SPARCC and 29.2% by LEI).

In the Double-Blind Treatment Period, 78.3% of the study participants had prior exposure to one or more conventional DMARDs (cDMARDs). At Baseline, the majority of study participants were using nonsteroidal anti-inflammatory drug therapy (58.6%) and/or cDMARDs (69.5%, primarily methotrexate [58.2%]).

Approximately three-quarters of study participants (77.0% overall) had ≥1 bone erosion at Baseline (actual stratum), and 84.2% of study participants had ≥1 bone erosion and/or hs-CRP ≥6mg/mL at Baseline.

Active-Treatment Blind Period- At the time of the data cut date for this Week 24 CSR, the percentages of study participants who completed the Active Treatment-Blind Period were similar in the bimekizumab 160mg Q4W (76.3%), the adalimumab (77.9%), and the placebo/bimekizumab 160mg Q4W (80.4%) groups. At the time of the Week 24 data cut, 640 study participants had completed the study, of which at least 631 study participants (98.6%) had entered the OLE study. The demographics and baseline disease characteristics of study participants who entered the Active Treatment-Blind Period were similar to the demographics of those in the Double-Blind Treatment Period.

Notable differences in Baseline characteristics across treatment groups include:

- The proportion of study participants with PsA subtype of polyarticular symmetric arthritis at Baseline was numerically higher in the bimekizumab 160mg Q4W (62.9%) and placebo (64.4%) groups compared with the adalimumab group (51.4%). Conversely, the proportion of study participants with PsA subtype of oligoarticular asymmetric arthritis was numerically lower in the

bimekizumab 160mg Q4W (27.4%) and placebo (27.0%) groups compared with the adalimumab group (37.9%).

- The mean HAQ-DI score at Baseline was numerically higher in the placebo group (0.8906) and adalimumab (0.8589) groups compared with the bimekizumab 160mg Q4W group (0.8189).
- The proportion of study participants with enthesitis, whether determined by SPARCC or LEI, was numerically higher in the bimekizumab 160mg Q4W group (38.5% and 33.2%, respectively) and adalimumab (31.4% and 25.7%, respectively) groups compared with the placebo group (32.0% and 24.9%, respectively).

A summary of PsA and PSO history and other baseline disease characteristics are presented for the RS in Table 35:

Table 35: PsA and PSO history and other Baseline disease characteristics (RS)

Variable Statistic	Placebo N=281	BKZ 160mg Q4W N=431	ADA 40mg Q2W N=140	All Study Participants N=852
PsA subtype, n (%)				
Polyarticular symmetric arthritis	181 (64.4)	271 (62.9)	72 (51.4)	524 (61.5)
Oligoarticular asymmetric arthritis	76 (27.0)	118 (27.4)	53 (37.9)	247 (29.0)
Distal interphalangeal joint predominant	12 (4.3)	17 (3.9)	9 (6.4)	38 (4.5)
Spondylitis predominant	10 (3.6)	15 (3.5)	4 (2.9)	29 (3.4)
Arthritis mutilans	1 (0.4)	8 (1.9)	2 (1.4)	11 (1.3)
Missing	1 (0.4)	2 (0.5)	0	3 (0.4)
Bone erosion at Baseline ≥1, n (%)				
Actual stratum [a]				
Yes	210 (74.7)	341 (79.1)	105 (75.0)	656 (77.0)
No	59 (21.0)	79 (18.3)	30 (21.4)	168 (19.7)
Missing	12 (4.3)	11 (2.6)	5 (3.6)	28 (3.3)
Bone erosion at Baseline ≥1 and/or hs-CRP ≥6mg/mL, n (%) [b]				
Yes	236 (84.0)	365 (84.7)	116 (82.9)	717 (84.2)
No	45 (16.0)	66 (15.3)	24 (7.1)	135 (15.8)
BSA affected by PSO, n (%)				
<3%	141 (50.2)	214 (49.7)	72 (51.4)	427 (50.1)
≥3% to ≤10%	92 (32.7)	144 (33.4)	42 (30.0)	278 (32.6)
>10%	48 (17.1)	73 (16.9)	26 (18.6)	147 (17.3)
PASI score [c]				
Mean (SD)	7.89 (5.64)	8.16 (6.84)	8.53 (7.60)	8.14 (6.59)
Median (min, max)	6.45 (1.2, 33.6)	6.00 (0.3, 46.0)	5.70 (1.2, 35.0)	6.00 (0.3, 46.0)
PASI score, n (%) [c]				
<10	102 (36.3)	160 (37.1)	50 (35.7)	312 (36.6)
10 to 20	34 (12.1)	44 (10.2)	13 (9.3)	91 (10.7)
>20	4 (1.4)	13 (3.0)	5 (3.6)	22 (2.6)
TJC [d]				
Mean (SD)	17.08 (12.51)	16.79 (11.75)	17.52 (13.08)	17.01 (12.22)
Median (min, max)	13.00 (3.0, 64.0)	14.00 (3.0, 66.0)	13.00 (4.0, 68.0)	14.00 (3.0, 68.0)
SJC [d]				
Mean (SD)	9.46 (7.26)	8.96 (6.18)	9.65 (7.10)	9.24 (6.70)
Median (min, max)	7.00 (3.0, 56.0)	7.00 (3.0, 48.0)	7.00 (3.0, 48.0)	7.00 (3.0, 56.0)
hs-CRP (mg/L) [e]				
Geometric mean (CV%)	4.359 (2.6)	3.715 (2.4)	2.989 (2.1)	3.778 (2.4)
Median (min, max)	4.650 (0.15, 204.12)	3.630 (0.11, 99.08)	2.870 (0.15, 80.43)	3.855 (0.11, 204.12)
hs-CRP, n (%) [e]				
<6mg/L	160 (56.9)	273 (63.3)	96 (68.6)	529 (62.1)
≥6mg/L	121 (43.1)	158 (36.7)	44 (31.4)	323 (37.9)
Dactylitis, n (%)				
Yes	33 (11.7)	56 (13.0)	11 (7.9)	100 (11.7)
No	247 (87.9)	368 (85.4)	128 (91.4)	743 (87.2)
Missing	1 (0.4)	7 (1.6)	1 (0.7)	9 (1.1)
Enthesitis (SPARCC), n (%)				
Yes	90 (32.0)	166 (38.5)	44 (31.4)	300 (35.2)
No	191 (68.0)	259 (60.1)	95 (67.9)	545 (64.0)
Missing	0	6 (1.4)	1 (0.7)	7 (0.8)
Enthesitis (LEI), n (%)				
Yes	70 (24.9)	143 (33.2)	36 (25.7)	249 (29.2)
No	211 (75.1)	282 (65.4)	103 (73.6)	596 (70.0)
Missing	0	6 (1.4)	1 (0.7)	7 (0.8)

Baseline Disease Characteristics- PA0011

The mean age of all study participants was 50.52 years of age with a range of 20.0 to 85.0 years of age. Slightly over half of the participants were female (52.5%), and the majority of study participants were White (96.0%), and not of Hispanic or Latino ethnicity (99.0%). The mean body weight and mean BMI overall were 85.99kg and 29.76kg/m2, respectively. For both treatment groups, the proportions of study participants enrolled in each region were similar (region was a stratification factor for randomisation).

The mean time since diagnosis of PsA was 9.50 years overall (range: 0.4 to 56 years). The majority of study participants had the polyarticular symmetric arthritis subtype of PsA (63.5%). Treatment groups were generally well balanced with respect to PsA-related and other Baseline disease characteristics. The mean time since diagnosis of PSO was 17.41 years overall (range: 0.0 to 58.5 years). The mean PASI score was 9.58 and 66.0% of participants had ≥3% of BSA affected by PSO. Overall, 60.5% of study

participants had nail PSO, 12.0% of study participants had dactylitis, and approximately 40% had enthesitis (43.3% by SPARCC and 35.5% by LEI).

Notable differences in Baseline disease characteristics across treatment groups included:

- The proportion of study participants with >10% BSA affected by PSO at Baseline was numerically higher in the bimekizumab 160mg Q4W group (25.1%) compared with the placebo group (18.8%).
- The proportion of study participants with PASI score <10 at Baseline was numerically lower in the bimekizumab 160mg Q4W group (41.9%) compared with the placebo group (50.4%).
- The proportion of study participants with enthesitis, whether determined by SPARCC or LEI was numerically higher in the bimekizumab 160mg Q4W group (45.7% and 39.7%, respectively) compared with the placebo group (38.3% and 27.1%, respectively).
- A numerically lower proportion of participants in the bimekizumab160mg Q4W group reported NSAID therapy at Baseline (53.6%) compared with the placebo group (60.2%).
- A numerically higher proportion of participants in the bimekizumab 160mg Q4W group reported MTX at Baseline (44.6%) compared with the placebo group (38.3%).

A summary of PsA and PSO history and other Baseline disease characteristics are presented for the RS in Table 36:

Table 36: PsA and PSO history and other Baseline disease characteristics (RS)

Variable Statistic	Placebo N=133	BKZ 160mg Q4W N=267	All study participants N=400
PsA subtype, n (%)			
Polyarticular symmetric arthritis	86 (64.7)	168 (62.9)	254 (63.5)
Oligoarticular asymmetric arthritis	32 (24.1)	62 (23.2)	94 (23.5)
DIP joint predominant	7 (5.3)	13 (4.9)	20 (5.0)
Spondylitis predominant	7 (5.3)	15 (5.6)	22 (5.5)
Arthritis mutilans	0	8 (3.0)	8 (2.0)
Missing	1 (0.8)	1 (0.4)	2 (0.5)
Time since first diagnosis of PSO (years)			
n	133	266	399
Mean (SD)	17.89 (11.815)	17.17 (13.380)	17.41 (12.869
Median (min, max)	16.10 (0.4, 48.5)	14.50 (0.0, 58.5)	14.70 (0.0, 58.5)
Missing	0	1	1
Actual stratum:			
Prior TNFα inhibitor exposure [a]			
Inadequate response to 1 TNFα inhibitor	103 (77.4)	203 (76.0)	306 (76.5)
Inadequate response to 2 TNFα inhibitors	15 (11.3)	30 (11.2)	45 (11.3)
Intolerance to TNFα inhibitors	15 (11.3)	34 (12.7)	49 (12.3)
BSA affected by PSO, n (%)			
<3%	45 (33.8)	91 (34.1)	136 (34.0)
≥3% to ≤10%	63 (47.4)	109 (40.8)	172 (43.0)
>10%	25 (18.8)	67 (25.1)	92 (23.0)
PASI score [b]			
n	88	176	264
Mean (SD)	8.46 (6.590)	10.15 (9.077)	9.58 (8.357)
Median (min, max)	6.50 (0.9, 36.0)	7.15 (0.4, 49.0)	7.05 (0.4, 49.0)

Variable Statistic	Placebo N=133	BKZ 160mg Q4W N=267	All study participants N=400
Nail PSO, n (%)			
Yes	83 (62.4)	159 (59.6)	242 (60.5)
No	49 (36.8)	108 (40.4)	157 (39.3)
Missing	1 (0.8)	0	1 (0.3)
Dactylitis, n (%)			
Yes	14 (10.5)	34 (12.7)	48 (12.0)
No	118 (88.7)	233 (87.3)	351 (87.8)
Missing	1 (0.8)	0	1 (0.3)
Enthesitis (SPARCC), n (%)			
Yes	51 (38.3)	122 (45.7)	173 (43.3)
No	81 (60.9)	145 (54.3)	226 (56.5)
Missing	1 (0.8)	0	1 (0.3)
Enthesitis (LEI), n (%)			
Yes	36 (27.1)	106 (39.7)	142 (35.5)
No	96 (72.2)	161 (60.3)	257 (64.3)
Missing	1 (0.8)	0	1 (0.3)

Prior and concomitant diseases

PA0010

Overall, the majority (87.8%) of study participants in the SS reported a previous and ongoing medical condition at Baseline. The most frequently reported conditions/diseases at Baseline were in the SOCs of Metabolism and nutrition disorders (54.3%), Musculoskeletal and connective tissue disorders (39.7%), and Vascular disorders (39.4%). The incidences of previous or ongoing medical conditions/diseases at Baseline by SOC were generally similar across treatment groups.

Overall, the most frequently reported conditions/diseases at Baseline by PT were hypertension (36.0%), obesity (35.9%), and osteoarthritis (14.8%). The incidences of previous or ongoing medical conditions/diseases at Baseline by PT were generally similar across treatment groups.

PA0011

Overall, the majority (89.2%) of study participants in the SS reported a previous and ongoing medical condition at Baseline. This was generally similar across the bimekizumab 160mg Q4W (88.4%) and placebo (90.9%) groups.

The most frequently reported conditions/diseases at Baseline were in the SOCs of Metabolism and nutrition disorders (52.6%), Vascular disorders (44.6%), and Musculoskeletal and connective tissue disorders (34.8%). The incidences of previous or ongoing medical conditions/diseases at Baseline by SOC were generally similar between treatment groups. Overall, the most frequently reported conditions/diseases at Baseline by PT were hypertension (39.1%), obesity (34.6%), and osteoarthritis (13.3%). The incidences of previous or ongoing medical conditions/diseases at Baseline by PT were generally similar between treatment groups.

Previous Medications and Procedures

Prior cDMARDs were used by 72.9% of study participants. At Baseline, 62.5% of study participants were using cDMARDs (MTX or other cDMARDs), 52.5% were using MTX alone or with other cDMARDS, and 37.5% of study participants were using no cDMARDs. Nonsteroidal anti-inflammatory drug (NSAID) therapy was used by 57.8% of study participants at Baseline.

PA0010: In the Double-Blind Treatment Period, 78.3% of the study participants had prior exposure to one or more conventional DMARDs (cDMARDs). At Baseline, the majority of study participants were using

nonsteroidal anti-inflammatory drug therapy (58.6%) and/or cDMARDs (69.5%, primarily methotrexate [58.2%]).

Week 24 Analysis in Study PA0010

Table 37: Concomitant Medications Analysis Set: Safety Set

WHODD MARCH 2021 Anatomical Main Group [Level 1] Pharmacological Subgroup [Level 3] Preferred Term	Placebo/ BKZ 160mg Q4W N=281 n (%)	BKZ 160mg Q4W N=431 n (%)	ADA 40mg Q2W N=140 n (%)	All Subjects N=852 n (%)
Immunosuppressants	182 (64.8)	286 (66.4)	92 (65.7)	560 (65.7)
Methotrexate	141 (50.2)	228 (52.9)	78 (55.7)	447 (52.5)
Methotrexate Sodium	24 (8.5)	28 (6.5)	4 (2.9)	56 (6.6)
Leflunomide	16 (5.7)	26 (6.0)	8 (5.7)	50 (5.9)
Apremilast	5 (1.8)	10 (2.3)	2 (1.4)	17 (2.0)
Etanercept	0	1 (0.2)	0	1 (0.1)
Ustekinumab	0	1 (0.2)	0	1 (0.1)
Ciclosporin	1 (0.4)	0	0	1 (0.1)
Hydroxychloroquine	1 (0.4)	0	0	1 (0.1)
Other Antineoplastic Agents	0	1 (0.2)	0	1 (0.1)
Indole-3-Carbinol	0	1 (0.2)	0	1 (0.1)

Summary baseline therapies are presented for the RS in Table 38:

Table 38: PsA and PSO history and other Baseline disease characteristics (RS)

Variable Statistic	Placebo N=281	BKZ 160mg Q4W N=431	ADA 40mg Q2W N=140	All Study Participants N=852
NSAID therapy at Baseline, n (%)				
Yes	165 (58.7)	255 (59.2)	79 (56.4)	499 (58.6)
No	116 (41.3)	176 (40.8)	61 (43.6)	353 (41.4)
Past cDMARD therapy, n (%) [e]				
Yes	117 (41.6)	196 (45.5)	56 (40.0)	369 (43.3)
No	164 (58.4)	235 (54.5)	84 (60.0)	483 (56.7)
Prior cDMARDs, n (%) [f]				
0	61 (21.7)	92 (21.3)	32 (22.9)	185 (21.7)
1	185 (65.8)	270 (62.6)	90 (64.3)	545 (64.0)
≥2	35 (12.5)	69 (16.0)	18 (12.9)	122 (14.3)
cDMARDs at Baseline, n (%)				
Yes	192 (68.3)	301 (69.8)	99 (70.7)	592 (69.5)
No	89 (31.7)	130 (30.2)	41 (29.3)	260 (30.5)
Methotrexate at Baseline, n (%)				
Yes	162 (57.7)	252 (58.5)	82 (58.6)	496 (58.2)
No	119 (42.3)	179 (41.5)	58 (41.4)	356 (41.8)
Oral corticosteroids at Baseline, n (%)				
Yes	57 (20.3)	79 (18.3)	28 (20.0)	164 (19.2)
No	224 (79.7)	352 (81.7)	112 (80.0)	688 (80.8)

PA0011: The majority of participants had an inadequate response to 1 TNFα inhibitor (76.5%) with the remaining participants having had an inadequate response to 2 TNFα inhibitors (11.3%) or intolerance to TNFα inhibitors (12.3%). Overall, 63.0% of the study participants had prior exposure to one or more conventional disease-modifying antirheumatic drugs (cDMARDs). At Baseline, the majority of study participants were using nonsteroidal anti-inflammatory drug therapy (55.8%) and/or cDMARDs (50.5%, primarily methotrexate [42.5%]).

The most common prior medications used overall were folic acid (48.1%) and MTX (46.9%; also taken as MTX sodium [7.3%]). Prior anti-TNFs used by study participants included ADA (50.4%), ETN (32.3%), and GOL (12.5%) (Table 39). Other anti-TNFs used included IFX (7.8%), CZP (7.5%), certolizumab (2.8%), and TNFα-inhibitors (0.3%). Prior medications are defined as medications that started prior to the start date of study medication (or randomization date for subjects randomized but not treated).

Final – Week 16 Analysis in Study PA0011

Table 39: Prior Anti-TNFs Analysis Set: Safety Set

WHODD MAR/2021 Anatomical Main Group [Level 1] Pharmacological Subgroup [Level 3] Preferred Term	Placebo N=132 n (%)	BKZ 160mg Q4W N=267 n (%)	All Subjects N=399 n (%)
Any prior Anti-TNFs	132 (100)	267 (100)	399 (100)
ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS	132 (100)	267 (100)	399 (100)
Immunosuppressants	132 (100)	267 (100)	399 (100)
Adalimumab	64 (48.5)	137 (51.3)	201 (50.4)
Etanercept	42 (31.8)	87 (32.6)	129 (32.3)
Golimumab	22 (16.7)	28 (10.5)	50 (12.5)
Infliximab	8 (6.1)	23 (8.6)	31 (7.8)
Certolizumab Pegol	12 (9.1)	18 (6.7)	30 (7.5)
Certolizumab	2 (1.5)	9 (3.4)	11 (2.8)
Tumor Necrosis Factor Alpha (Tnf-) Inhibitors	0	1 (0.4)	1 (0.3)

The use of concomitant medications was generally similar across the bimekizumab 160mg Q4W (98.1%) and placebo (96.2%) groups overall and by individual concomitant medication. The most common concomitant medications used during the study were folic acid (45.4%) and MTX (37.3%; also taken as MTX sodium [5.5%]). Additionally, 59.6% of study participants used NSAIDs during the study.

Table 40: PsA and PSO history and other Baseline disease characteristics (RS)

Variable Statistic	Placebo N=133	BKZ 160mg Q4W N=267	All study participants N=400
Prior cDMARDs, n (%)			
0	50 (37.6)	98 (36.7)	148 (37.0)
1	68 (51.1)	150 (56.2)	218 (54.5)
≥2	15 (11.3)	19 (7.1)	34 (8.5)
cDMARDs at Baseline, n (%)			
Yes	63 (47.4)	139 (52.1)	202 (50.5)
No	70 (52.6)	128 (47.9)	198 (49.5)
Methotrexate at Baseline, n (%)			
Yes	51 (38.3)	119 (44.6)	170 (42.5)
No	82 (61.7)	148 (55.4)	230 (57.5)
Oral corticosteroids at Baseline, n (%)			
Yes	21 (15.8)	38 (14.2)	59 (14.8)
No	112 (84.2)	229 (85.8)	341 (85.3)
HLA-B27, n (%)			
Positive	21 (15.8)	55 (20.6)	76 (19.0)
Negative	106 (79.7)	206 (77.2)	312 (78.0)
Missing	6 (4.5)	6 (2.2)	12 (3.0)
NSAID therapy at Baseline, n (%)			
Yes	80 (60.2)	143 (53.6)	223 (55.8)
No	53 (39.8)	124 (46.4)	177 (44.3)

Rescue Medications

PA0010

Rescue medication use was permitted after Week 16 (in the Active Treatment-Blind Period). As of the data cut for this Week 24 CSR, only 4.6% of study participants were taking any rescue therapies [Placebo to BKZ group 17 (6.3%), BKZ Q4 group 18 (4.3%), and ADA Q2 group 3 (2.2%)].

PA0010

The use of rescue medications through Week 16 were constituted as an important protocol deviation.

Numbers analysed

Analysis Sets PA0010

Table 41: Disposition of Analysis Sets (RS)

Disposition	Placebo/ BKZ 160mg Q4W N=281 n (%)	BKZ 160mg Q4W N=431 n (%)	ADA 40mg Q2W N=140 n (%)	All Study Participants N=852 n (%)
RS	281 (100)	431 (100)	140 (100)	852 (100)
SS	281 (100)	431 (100)	140 (100)	852 (100)
FAS	280 (99.6)	426 (98.8)	139 (99.3)	845 (99.2)
PPS	265 (94.3)	409 (94.9)	133 (95.0)	807 (94.7)
ATS	271 (96.4)	414 (96.1)	136 (97.1)	821 (96.4)
AMS	271 (96.4)	431 (100)	140 (100)	842 (98.8)
RAS	261 (92.9)	416 (96.5)	131 (93.6)	808 (94.8)
PK-PPS	267 (95.0)	430 (99.8)	0	697 (81.8)
CFS	272 (96.8)	419 (97.2)	134 (95.7)	825 (96.8)

Analysis Sets PA0011

Table 42: Disposition of Analysis Sets (RS)

Disposition	Placebo N=133 n (%)	BKZ 160mg Q4W N=267 n (%)	All study participants N=400 n (%)
RS	133 (100)	267 (100)	400 (100)
SS	132 (99.2)	267 (100)	399 (99.8)
FAS	132 (99.2)	267 (100)	399 (99.8)
PPS	125 (94.0)	255 (95.5)	380 (95.0)
PK-PPS	0	266 (99.6)	266 (66.5)
COVID-19-free Set	125 (94.0)	249 (93.3)	374 (93.5)

BKZ=bimekizumab; COVID-19=Coronavirus Disease-2019; FAS=Full Analysis Set; PK-PPS=Pharmacokinetics Per-Protocol Set; PPS=Per-Protocol Set; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set

Treatment Compliance PA0010

The allowed injection sites for the sc administration of bimekizumab for this study were the lateral abdominal wall and upper outer thigh. Compliance was defined as the number of actual injections/expected injections taken at the appropriate time in the study.

Double-Blind Treatment Period: Treatment compliance was high and similar across treatment groups (Table 43). Overall, 97.8% of study participants had ≥75% compliance.

Table 43: Treatment Compliance During the Double-Blind Treatment Period (SS)

	Placebo N=281	BKZ 160mg Q4W N=431	ADA 40mg Q2W N=140	All Study Participants N=852
Overall compliance (%), n	281	431	140	852
Mean (SD)	97.04 (9.086)	96.99 (8.454)	97.49 (8.912)	97.09 (8.734)
Median	100.00	100.00	100.00	100.00
Min, max	12.5, 100.0	33.3, 100.0	37.5, 100.0	12.5, 100.0
Overall compliance				
<75%, n (%)	6 (2.1)	9 (2.1)	4 (2.9)	19 (2.2)
≥75%, n (%)	275 (97.9)	422 (97.9)	136 (97.1)	833 (97.8)

Active Treatment-Blind Period: Treatment compliance was high and similar across treatment groups (Table 44). Overall, 94.9% of study participants had ≥75% compliance.

Table 44: Treatment Compliance During the Active Treatment-Blind Period (ATS)

	Placebo/BKZ 160 mg Q4W N=271	BKZ 160mg Q4W N=414	BKZ 160mg Q4W Total N=685	ADA 40mg Q2W N=136	All Study Participants N=821
Overall compliance (%), n	271	414	685	136	821
Mean (SD)	95.02 (8.970)	95.35 (9.784)	95.22 (9.465)	93.94 (11.610)	95.01 (9.856)
Median	100.00	100.00	100.00	100.00	100.00
Min, max	38.9, 100.0	33.3, 100.0	33.3, 100.0	27.8, 100.0	27.8, 100.0
Overall compliance					
<75%, n (%)	13 (4.8)	22 (5.3)	35 (5.1)	7 (5.1)	42 (5.1)
≥75%, n (%)	258 (95.2)	392 (94.7)	650 (94.9)	129 (94.9)	779 (94.9)

Treatment Compliance PA0011

The allowed injection sites for the sc administration of bimekizumab for this study were the abdominal wall, thigh, or upper outer arm without massage. Compliance was defined as the number of actual injections/expected injections taken at the appropriate time in the study.

Overall, 98.5% of study participants had ≥75% compliance. Treatment compliance was high and similar across treatment groups (Table 45).

Table 45: Treatment Compliance (SS)

	Placebo N=132	BKZ 160mg Q4W N=267	All study participants N=399
Overall compliance (%), n			
Mean (SD)	99.05 (6.483)	98.13 (7.891)	98.43 (7.459)
Median (min, max)	100.00 (50.0, 100.0)	100.00 (50.0, 100.0)	100.00 (50.0, 100.0)
Overall compliance			
≤75%, n (%)	2 (1.5)	4 (1.5)	6 (1.5)
>75%, n (%)	130 (98.5)	263 (98.5)	393 (98.5)

BKZ=bimekizumab; max=maximum; min=minimum; Q4W=every 4 weeks; SD=standard deviation; SS=Safety Set.

Outcomes and estimation

The primary endpoint and ranked secondary endpoints were evaluated using a fixed-sequence testing procedure to account for multiplicity. According to this procedure, the statistical testing of an endpoint was investigated only if the null hypothesis for the previous endpoint had been rejected (i.e., if $p<0.05$).

For both PA0010 and PA0011, the RS was the primary analysis set for efficacy analyses, but analyses were also repeated on the FAS and the PPS for the primary efficacy endpoint. The FAS analysis evaluated whether there were differences in the efficacy analysis between randomised study participants and randomised study participants with a Baseline assessment, while the PPS analysis evaluated the effect of IPD on the analysis.

Primary Efficacy Endpoints

PA0010 ACR50 responder rate at Week 16

The primary objective was met. Bimekizumab 160mg Q4W treatment demonstrated a superior ACR50 responder rate at Week 16 compared with the placebo group (43.9% vs 10.0%, respectively). This difference was considered clinically meaningful, with a statistically significant odds ratio versus placebo of 7.082 ($p<0.001$).

Table 46: ACR50 responder rate at Week 16 including logistic regression (RS [NRI])

Variable	Placebo N=281	BKZ 160mg Q4W N=431	ADA 40mg Q2W N=140
Responders, n (%)	28 (10.0)	189 (43.9)	64 (45.7)
Adjusted responder rate (%) [a]	8.5	39.7	41.8
95% CI	5.7, 12.5	33.9, 45.9	33.1, 50.9
Difference vs placebo	-	31.226	-
95% CI for difference	-	25.174, 37.278	-
Odds ratio vs placebo [b]	-	7.082	-
95% CI for odds ratio	-	4.583, 10.943	-
p-value	-	<0.001	-

ACR50=American College of Rheumatology 50% improvement criteria; ADA=adalimumab; BKZ=bimekizumab; CI=confidence interval; NRI=nonresponder imputation; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: Study participants who had missing ACR50 data at Week 16 or who discontinued study treatment before Week 16 regardless of whether they had data or not were considered as nonresponders.

Note: In the n (%) row, n represents the number of responder cases at Week 16, and percentages were calculated by treatment group on the number of study participants in the referenced population.

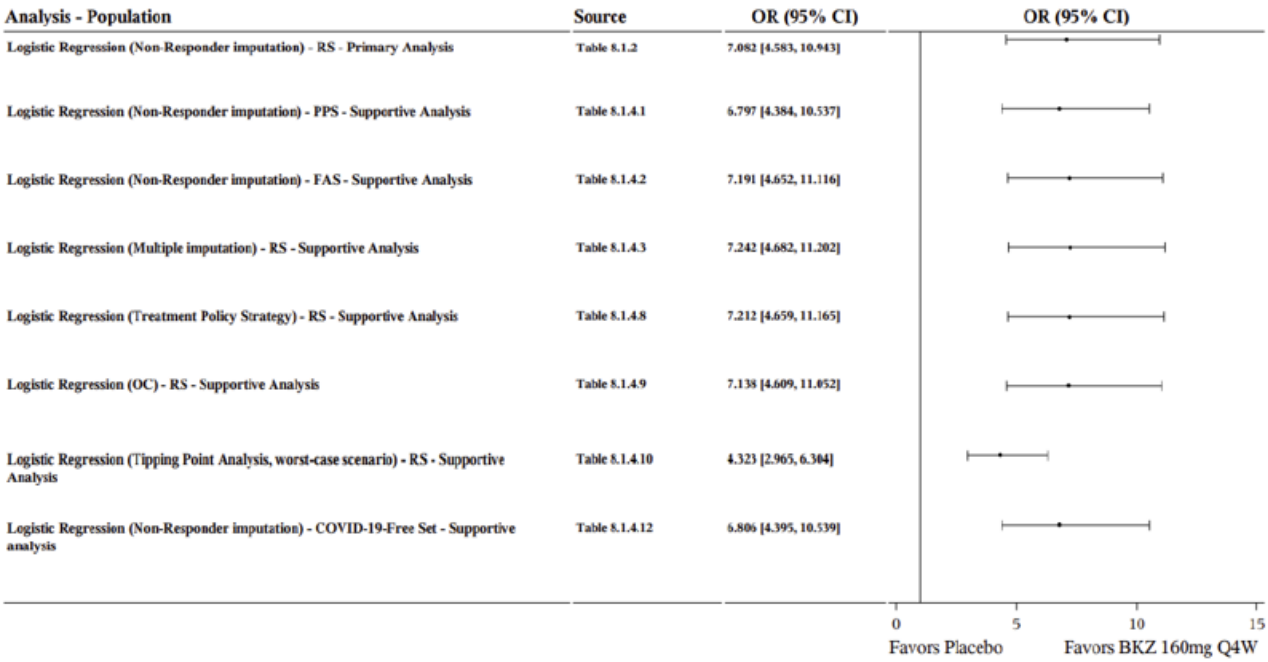
[a] Adjusted responder rates and CIs by treatment group, difference of adjusted response rates and CI were calculated using a logistic regression model with factors for treatment, bone erosion at Baseline, and region.

[b] Odds ratio, CI and p-value were calculated using the same logistic regression model.

Sensitivity/Supportive Analysis

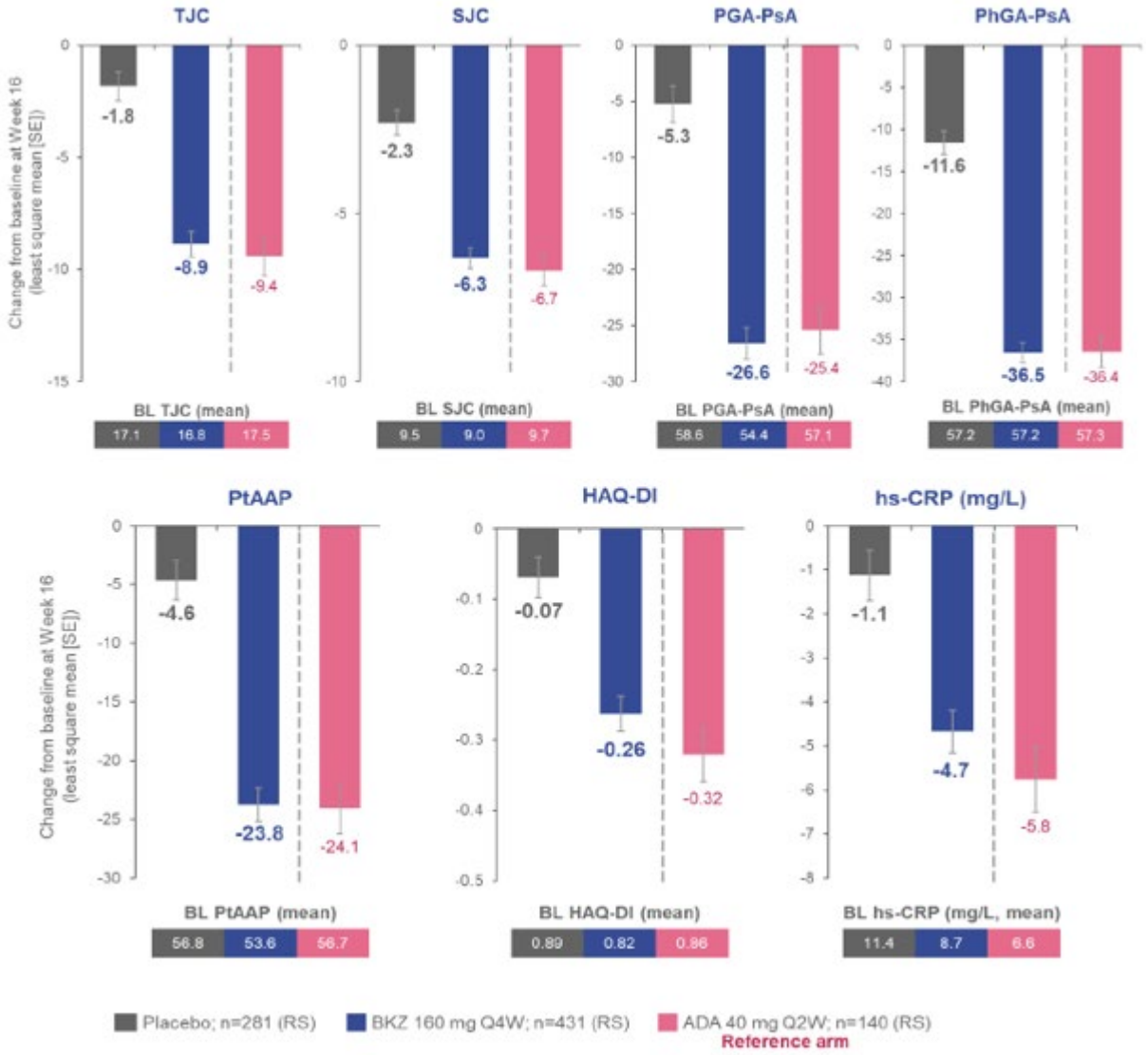
The results of all supportive analyses of the primary efficacy variable confirmed the primary efficacy results (Figure 38), even in the worst-case scenario where all missing data in the placebo group were treated as response and all missing data in the bimekizumab group were treated as non-response. The COVID-19 pandemic had a minimal impact on the primary efficacy results.

Figure 38: Forest plot of OR of ACR50 response at Week 16 (BKZ 160mg Q4W versus placebo) comparing primary and supportive analysis



Supportive analyses of individual ACR components (TJC, SJC, PGA-PsA, PhGA-PsA, PtAAP, HAQ-DI, and hs-CRP) at Week 16 were also conducted. The trend in ACR50 responder rate observed overall for bimekizumab compared with placebo was supported by that observed for each individual component both using reference-based imputation and MI (all nominal $p<0.001$). Results also showed that none of the individual ACR components drove the overall ACR50 response at Week 16 (Figure 39).

Figure 39: Change from Baseline in individual ACR components at Week 16 (RS [MI])



PA0011 ACR50 responder rate at Week 16

The primary objective was met. Treatment with bimekizumab 160mg Q4W demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.4% vs 6.8%, respectively). This difference was considered clinically meaningful, with a statistically significant odds ratio versus placebo of 11.139 ($p<0.001$).

Table 47: ACR50 responder rate at Week 16 including logistic regression (RS [NRI])

Variable	Placebo N=133	BKZ 160mg Q4W N=267
Responders, n (%)	9 (6.8)	116 (43.4)
Adjusted responder rate (%) [a]	4.3	33.3
95% CI	2.0, 8.9	24.8, 43.1
Difference versus placebo	-	29.028
95% CI for difference	-	21.874, 36.183
Odds ratio versus placebo [b]	-	11.139
95% CI for responder rate	-	5.402, 22.969
p-value	-	<0.001

ACR50=American College of Rheumatology 50% improvement criteria; BKZ=bimekizumab; CI=confidence interval; IMP=investigational medicinal product; NRI=nonresponder imputation; Q4W=every 4 weeks; RS=Randomized Set; TNFα=tumor necrosis factor alpha

Note: Study participants who had missing ACR50 data at Week 16 or who discontinued IMP before Week 16 regardless of whether they had data or not were considered as nonresponders.

Note: In the n (%) row, n represents the number of responder cases at Week 16, and percentages were calculated by treatment group on the number of study participants in the referenced population.

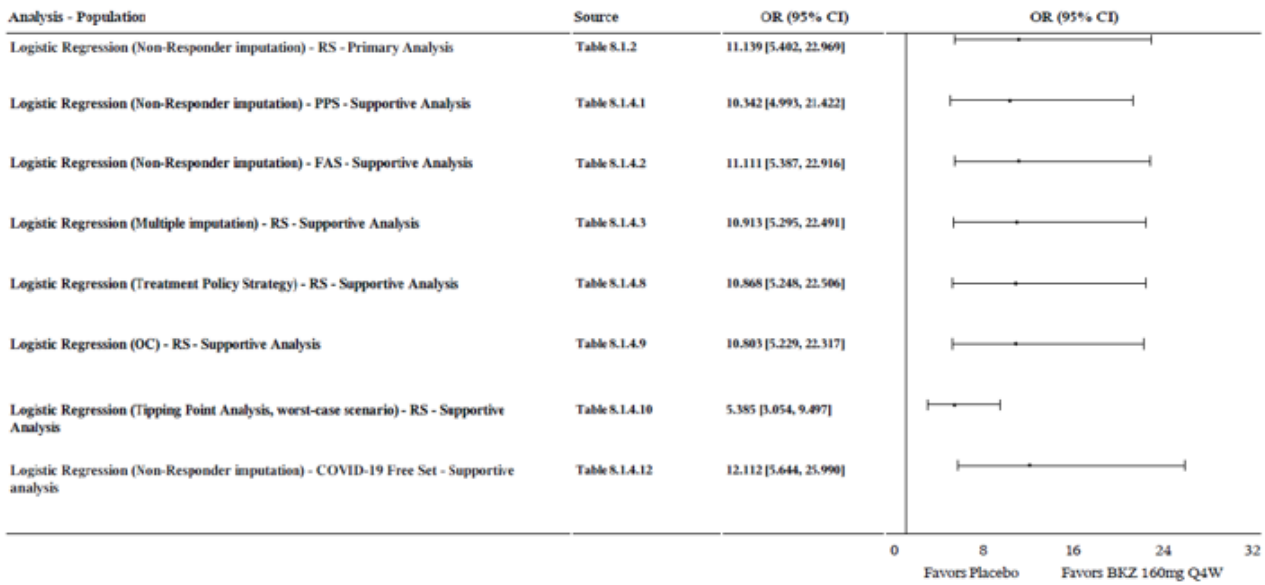
[a] Adjusted responder rates, CIs by treatment group, difference of adjusted response rates, and CI were calculated using a logistic regression model with factors for treatment, prior TNFα inhibitor exposure at Baseline, and region.

[b] Odds ratio, CI, and p-value were calculated using the same logistic regression model.

Sensitivity/Supportive Analysis

The results of all supportive analyses of the primary efficacy variable were consistent with the primary efficacy results (Figure 40), even in the worst-case scenario where all missing data in the placebo group were treated as response, and all missing data in the bimekizumab group were treated as nonresponse. The COVID-19 pandemic had a minimal impact on the primary efficacy results.

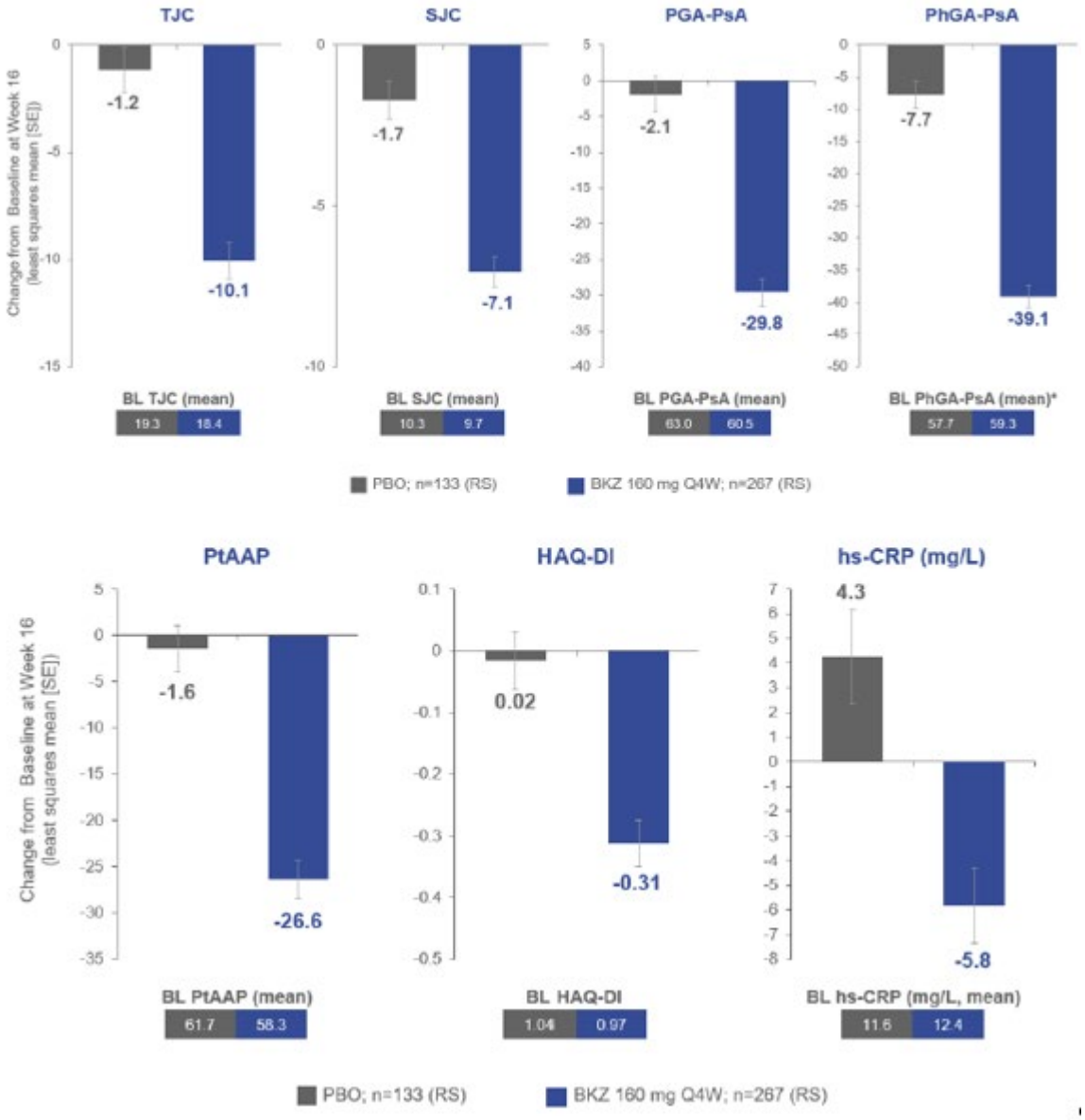
Figure 40: Forest plot of odds ratio for ACR50 Response at Week 16 (BKZ 160mg Q4W versus placebo comparing primary and supportive analyses (RS)



Supportive analyses of individual ACR components (TJC, SJC, PhGA-PsA, PGA-PsA, PtAAP, HAQ-DI, and hs-CRP) at Week 16 were also conducted. The trend in ACR50 responder rate observed overall for bimekizumab 160mg Q4W compared with placebo was supported by that observed for each individual

ACR component using reference-based imputation and MI (all nominal p<0.001). Results also showed that none of the individual ACR components drove the overall ACR50 response at Week 16 (Figure 41).

Figure 41: Change from Baseline in individual ACR components at Week 16 (RS [MI])



Ranked Secondary Efficacy Endpoints

In both Phase 3 studies, treatment with bimekizumab 160mg Q4W demonstrated clinically meaningful and statistically superior response rates for the primary efficacy variable (ACR50 response at Week 16) and all ranked secondary efficacy variables compared with placebo.

Change from Baseline HAQ-DI superior to Placebo

PA0010

At Week 16 the bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in HAQ-DI compared with the placebo group at Week 16 (-0.2567 vs -0.0880, respectively; p<0.001).

PA0011

At Week 16 the bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in HAQ-DI compared with the placebo group (-0.3751 vs -0.0701, respectively; p<0.001).

PASI90 Response superior to Placebo

PASI90 response at Week 16 (study participants with PSO involving at least 3% BSA at Baseline).

PA0010

At Week 16 the bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group at Week 16 (61.3% vs 2.9%, respectively; p<0.001) and 41.2% in the adalimumab arm. Differences with both control treatments are considered clinically relevant improvements.

PA0011

At Week 16 the bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group (68.8% vs 6.8%, respectively; p<0.001) in study participants with PSO involving at least 3% BSA at Baseline.

Change from Baseline SF-36 PCS superior to Placebo

PA0010

At Week 16 the bimekizumab 160mg Q4W group had a greater increase from Baseline (ie, improvement) in SF-36 PCS score compared with the placebo group at Week 16 (LS Mean 6.2 vs 0.1, respectively; p<0.001).

PA0011

At Week 16 the bimekizumab 160mg Q4W group had a greater increase from Baseline (ie, improvement) in SF-36 PCS compared with the placebo group (LS mean 6.3 vs 0.9, respectively; p<0.001).

MDA superior to Placebo

PA0010

At Week 16 the bimekizumab 160mg Q4W group had a higher MDA responder rate compared with the placebo group at Week 16 (45.0% vs 13.2%, respectively; p<0.001), and 45.0% in the adalimumab arm.

PA0011

At Week 16 the bimekizumab 160mg Q4W group had a higher MDA responder rate compared with theplacebo group (44.2% vs 6.0%, respectively; p<0.001).

Change from Baseline vdHmTSS* superior to Placebo on study participants with elevated hs-CRP and/or with at least one bone erosion (hs-CRP ≥6mg/L and/or erosion-positive)

PA0010 only

At Week 16 the bimekizumab 160mg Q4W group had a minimal change from Baseline in vdHmTSS at Week 16, indicating inhibition of structural progression, whereas the placebo group worsened (0.04 vs 0.36, respectively; p<0.001) in study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline.

Enthesitis-free state superior to Placebo

-based on pooled PA0010 and PA0011 W16 data

-based on LEI at Week 16 (study participants with enthesitis at Baseline)

The bimekizumab 160mg Q4W group had a higher proportion of study participants in the enthesitis-free state compared with placebo at Week 16 (49.8% vs 34.9%, respectively; p=0.008) in study participants with enthesitis at Baseline in the pooled PA0010/PA0011 population.

Dactylitis-free state superior to Placebo

-based on pooled PA0010 and PA0011 W16 data

The bimekizumab 160mg Q4W group had a higher proportion of study participants in the dactylitis-free state compared with placebo at Week 16 (75.6% vs 51.1%, respectively; p=0.002) in study participants with dactylitis at Baseline in the pooled PA0010/PA0011 population.

Enthesitis and dactylitis pooling strategy

In study participants with enthesitis at Baseline in the pooled PA0010/PA0011 population, the bimekizumab 160mg Q4W group had a higher proportion of study participants in the enthesitis free state compared with placebo at Week 16 (49.8% vs 34.9%, respectively; p=0.008); this difference was statistically significant and considered clinically meaningful. In study participants with enthesitis at Baseline in the PA0010 population alone, a similar trend was observed. The bimekizumab 160mg Q4W group had a numerically higher proportion of study participants in the enthesitis-free state compared with placebo at Week 16 (50.3% vs 41.4%, respectively). The proportions of study participants in the enthesitis-free state were similar between the bimekizumab 160mg Q4W and the adalimumab groups at Week 16 in PA0010 (50.3% vs 50.0%, respectively).

In study participants with dactylitis at Baseline in the pooled PA0010/PA0011 population, the bimekizumab 160mg Q4W group had a higher proportion of study participants in the dactylitis free state compared with placebo at Week 16 (75.6% vs 51.1%, respectively; p=0.002). In study participants with dactylitis at Baseline in the PA0010 population alone, a similar trend was observed. The bimekizumab 160mg Q4W group had a higher proportion of study participants in the dactylitis-free state compared with placebo at Week 16 (78.6% vs 54.5%, respectively; nominal p=0.010); this difference was considered clinically meaningful. The proportions of study participants in the dactylitis-free state were similar between the bimekizumab 160mg Q4W and the adalimumab groups at Week 16 in PA0010 (78.6% vs 81.8%, respectively).

Change from Baseline vdHmTSS superior to Placebo**

PA0010 only

The bimekizumab 160mg Q4W group had a minimal change from Baseline in vdHmTSS, whereas the placebo group worsened at Week 16 (0.04 vs 0.32, respectively; p=0.001) in all study participants.

Non-Ranked Secondary Efficacy Endpoints

Numerically greater improvements compared with placebo were observed for the non-ranked secondary efficacy endpoints following bimekizumab treatment. Any testing outside of the fixed sequential testing procedure was labelled as nominal and was neither powered nor controlled for multiplicity.

PASI90 response at Week 4

-study participants with PSO involving ≥3% BSA at Baseline

PA0010

The bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group at Week 4 (19.8% vs 4.3%, respectively; nominal p<0.001).

PA0011

Not listed.

ACR20 response at Week 16

PA0010

The bimekizumab 160mg Q4W group had a higher ACR20 responder rate compared with the placebo group (62.2% vs 23.8%, respectively; nominal p<0.001) and 68.6% in the adalimumab arm.

PA0011

The bimekizumab 160mg Q4W group had a higher ACR20 responder rate compared with the placebo group (67.0% vs 15.8%, respectively; nominal p<0.001).

ACR70 response at Week 16

PA0010

The bimekizumab 160mg Q4W group had a higher ACR70 responder rate compared with the placebo group (24.4% vs 4.3%, respectively; nominal p<0.001) and 27.9% in the adalimumab arm.

PA0011

The bimekizumab 160mg Q4W group had a higher ACR70 responder rate compared with the

placebo group (26.6% vs 0.8%, respectively; nominal p<0.001).

IGA 0/1 response at Week 4 and Week 16

-study participants with psoriatic skin lesions at Baseline and PSO involving ≥3% BSA at Baseline

PA0010

The bimekizumab 160mg Q4W group had a higher IGA responder rate compared with the placebo group at Week 16 (50.5% vs 3.9%, respectively; nominal p<0.001).

PA0011

The bimekizumab 160mg Q4W group had a higher IGA 0 (clear)/1 (almost clear) responder rate compared with the placebo group (30.7% vs 1.2%, respectively; nominal p<0.001)

PtAAP change from Baseline at Week 16

PA0010

The bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in PtAAP compared with the placebo group (-23.6 vs -6.2, respectively; nominal p<0.001).

PA0011

The bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in PtAAP compared with the placebo group (-27.7 vs -4.5, respectively; nominal p<0.001).

Enthesitis-free state at Week 16

-study participants with SPARCC>0 at Baseline

The bimekizumab 160mg Q4W group had a higher proportion of study participants in the enthesitis-free state compared with placebo at Week 16 (50.0% vs 35.6%, respectively; nominal p=0.043) in study participants with SPARCC>0 at Baseline.

PsAID-12 total score change from Baseline at Week 16

PA0010

The bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in PsAID-12 total score compared with the placebo group (-1.83 vs -0.53, respectively; nominal p<0.001).

PA0011

The bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in PsAID-12 total score compared with the placebo group (-2.24 vs -0.32, respectively; nominal p<0.001).

Other Efficacy Endpoints

In PA0010, treatment with bimekizumab 160mg Q4W demonstrated improvements over time, compared with placebo (often reported the first post-Baseline assessment) and maintained over time (ie, up to the Week 24 cut-off) across the spectrum of other efficacy variables.

Efficacy outcomes from the completed PA0010 study (up to Week 52)

PA0010 vdHmTSS change from Baseline by visit (Week 52)

For the Radiographic Set (MI), in the subset of study participants with elevated hs-CRP and/or with at least 1 bone erosion at Baseline, the bimekizumab 160mg Q4W group had a minimal mean change from Baseline in vdHmTSS, whereas the placebo group worsened at Week 16 (0.03 vs 0.29, respectively); this difference indicated inhibition of structural progression after treatment with bimekizumab. The mean change from Baseline at Week 16 in vdHmTSS for adalimumab was -0.14 (PA0010 Final CSR Table 48).

Final – Week 52 Analysis in Study PA0010

Table 48: VdHmTSS Absolute Values and Changes from Baseline (Subjects with Elevated hs-CRP and/or With at Least One Bone Erosion at Baseline) – Analysis of Other Efficacy Endpoints (Multiple Imputation) Analysis Set: Radiographic Set

	Result						Change From Baseline Result						
Treatment Group Visit, Week (Descriptor)	n	Mean	SE	Median	Min	Max	n	BL Mean	Mean	SE	Median	Min	Max
Placebo / BKZ 160mg Q4W (N=227)													
Visit 2, Baseline (Day 1)	227	14.54	1.58	5.50	0	159.0							
Visit 10, Week 16	227	14.83	1.58	5.51	0	156.5	227	14.54	0.29	0.09	0	-4.5	9.0
Visit 28, Week 52	227	14.73	1.58	5.70	0	154.0	227	14.54	0.19	0.13	0	-8.5	13.5

Table 8.4.34.3
VdHmTSS Absolute Values and Changes from Baseline (Subjects with Elevated hs-CRP and/or With at Least One Bone Erosion at Baseline) - Analysis of Other Efficacy Endpoints (Multiple Imputation)
Analysis Set: Radiographic Set

	Result						Change From Baseline Result						
Treatment Group Visit, Week (Descriptor)	n	Mean	SE	Median	Min	Max	n	BL Mean	Mean	SE	Median	Min	Max
BKZ 160mg Q4W (N=361)													
Visit 2, Baseline (Day 1)	361	14.36	1.68	4.50	0	405.5							
Visit 10, Week 16	361	14.40	1.69	4.59	0	405.0	361	14.36	0.03	0.05	0	-7.0	4.1
Visit 28, Week 52	361	14.47	1.70	4.86	0	405.5	361	14.36	0.10	0.08	0	-7.0	14.0

Treatment Group Visit, Week (Descriptor)	Result						Change From Baseline Result						
	n	Mean	SE	Median	Min	Max	n	BL Mean	Mean	SE	Median	Min	Max
ADA 40mg Q2W (N=112)													
Visit 2, Baseline (Day 1)	112	16.46	2.69	8.75	0	227.0							
Visit 10, Week 16	112	16.33	2.66	8.35	0	226.5	112	16.46	-0.14	0.10	0	-5.0	3.1
Visit 28, Week 52	112	16.29	2.68	8.69	0	227.4	112	16.46	-0.17	0.13	0	-6.0	6.5

¶

Note: Placebo subjects switched to BKZ 160mg Q4W at/after Week 16.
Note: BL Mean is defined as the Baseline results for those subjects who were also assessed at the specified visit.
Note: Missing data and non-missing data preceded by a study treatment discontinuation are imputed using multiple imputation based on Markov Chain Monte Carlo (for intermittent missing data) followed by monotone regression (for monotone missing data).
Note: To ensure that unnecessary bias is not introduced, data from the same reading session will be used within a given analysis: For the analysis involving data up to Week 16 only (Week 24 interim analysis), the first set of reads will be used for all subjects. For the analysis involving data up to Week 52 as above, the second set of reads will be used for all subjects.

At Week 52, the mean change from Baseline in vdHmTSS for the bimekizumab 160mg Q4W group was 0.10, indicating that the inhibition of structural progression observed with bimekizumab treatment was sustained. In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the mean change from Baseline in vdHmTSS at Week 52 was 0.19 (PA0010, Table 48).

The mean change from Baseline at Week 52 in vdHmTSS for adalimumab was -0.17 (PA0010, Table 48).

PA0010 Proportion with no radiographic joint damage progression

At Week 16, the proportion of study participants in the RAS with no radiographic joint damage progression (defined as a change from Baseline in vdHmTSS ≤0.5) was numerically higher for the bimekizumab 160mg Q4W group compared with the placebo group at Week 16 both overall (84.8% vs 82.5%, respectively) and in the subset of study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline (82.8% vs 81.9%, respectively) (Table 49). At Week 52, the proportion was similar between study participants in the bimekizumab 160mg Q4W group and the study participants who switched to bimekizumab 160mg Q4W from the placebo group overall (77.6% vs 77.0%, respectively) and in the subset of study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline, the proportion was numerically higher for the bimekizumab 160mg Q4W group compared with the placebo group (76.5% vs 74.0%, respectively).

At Week 16, the proportion of study participants in the RAS with no radiographic joint damage progression was numerically higher for the bimekizumab 160mg Q4W group compared with the adalimumab group overall (84.8% vs 80.7%) and was similar in the subset of study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline (82.8% vs 83.0%, respectively). At Week 52, the proportion was numerically higher for the adalimumab group compared with the bimekizumab 160mg Q4W group both overall (82.2% vs 77.6%, respectively) and in the subset of study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline (85.7% vs 76.5%, respectively). A summary of the proportion of study participants with no radiographic joint damage progression by visit for the RAS (NRI) is presented in Table 49.

Table 49: Proportion of study participants with no radiographic joint damage progression (change from Baseline in vdHmTSS<=0.55) at Week 16 (Overall; RAS [NRI])

	Placebo/BKZ 160mg Q4W	BKZ 160mg Q4W	ADA 40mg Q2W
Overall			
Week 16, N	269	420	135
Week 16, n (%)	222 (82.5)	356 (84.8)	109 (80.7)
Week 52, N	269	420	135
Week 52, n (%)	207 (77.0)	326 (77.6)	111 (82.2)
Study participants with elevated hs-CRP and/or with at least 1 bone erosion at Baseline			
Week 16, N	227	361	112
Week 16, n (%)	186 (81.9)	299 (82.8)	93 (83.0)
Week 52, N	227	361	112
Week 52, n (%)	168 (74.0)	276 (76.5)	96 (85.7)

ADA=adalimumab; BKZ=bimekizumab; hs-CRP=high sensitivity C-reactive protein; NRI=nonresponder imputation; Q2W=every 2 weeks; Q4W=every 4 weeks; RAS=Radiographic Set; vdHmTSS=van der Heijde modified Total Sharp Score

Note: Placebo study participants switched to BKZ 160mg Q4W at/after Week 16.

Note: NRI used the estimand approach. Missing data or data after study treatment discontinuation were set to nonresponse.

Note: In the n (%) rows, n represents the number of study participants with change from Baseline in vdHmTSS≤0.5 at the given week, and percentages were calculated by treatment group on the number of study participants in the referenced population.

ACR 20/50/70 response by visit

In both PA0010 and PA0011, the ACR 20/50/70 responder rate at Week 4 was higher in the bimekizumab 160mg Q4W group compared with the placebo group across all variables. The differences were considered clinically meaningful with nominally significant p values. The ACR 20/50/70 responder rate for study participants in the bimekizumab 160mg Q4W group increased through Week 16 and was higher compared with the placebo group at each time point. The ACR 20/50/70 response with bimekizumab treatment was maintained up to Week 24 in PA0010 and Week 16 in PA0011.

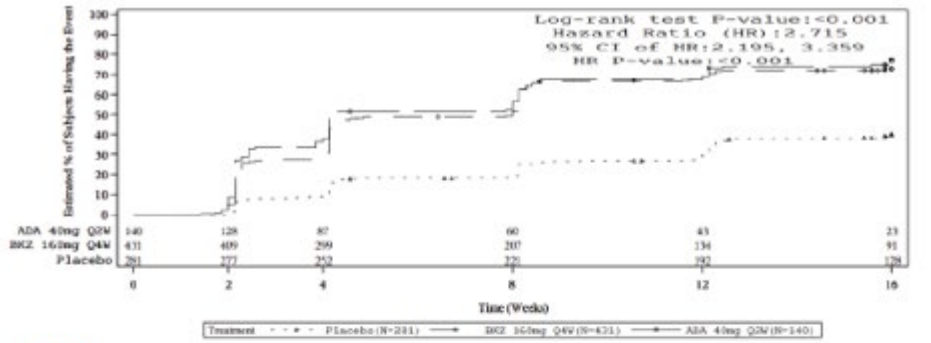
In study PA0010 participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the ACR 20/50/70 responder rate increased from Week 16 to Week 24. ACR 20/50/70 responder rate at Week 16 was reported as 62.2%/ 43.9%/ 24.4% respectively. The ACR 20/50/70 responder rate was similar between the bimekizumab 160mg Q4W and adalimumab groups over time.

At Week 52 in Study PA0010, the ACR20/50/70 response with bimekizumab treatment was sustained up to Week 52 (71.2%/ 54.5%/ 39.2% respectively) and was similar to the bimekizumab 160mg Q4W and adalimumab groups by Week 52.

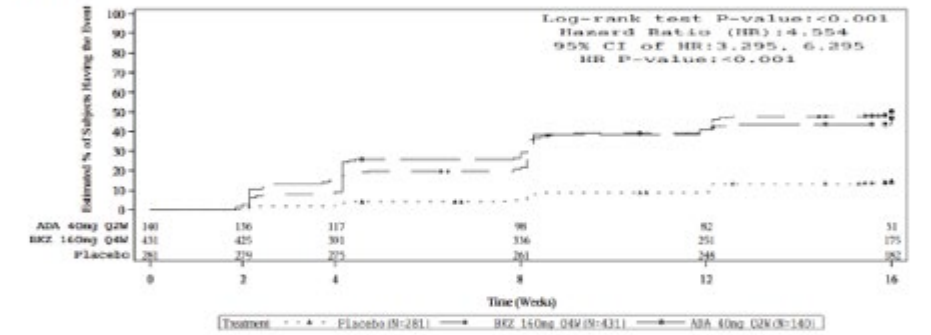
PA0010

Figure 42: Kaplan-Meier curves for time to ACR20, ACR50, and ACR70 response (Double-Blind Treatment Period; RS [OC])

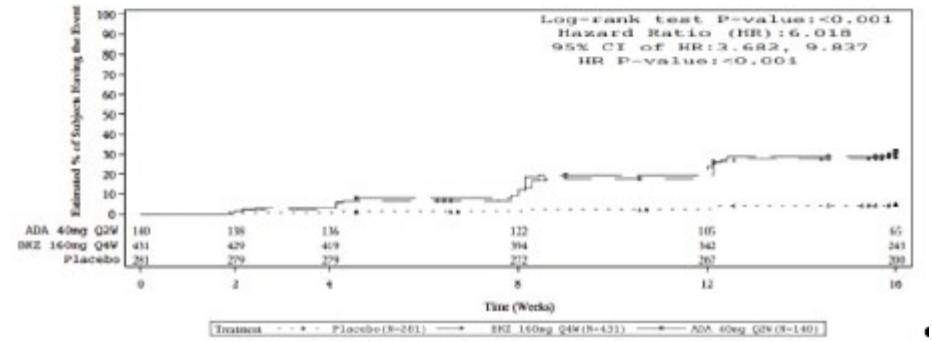
ACR20



ACR50

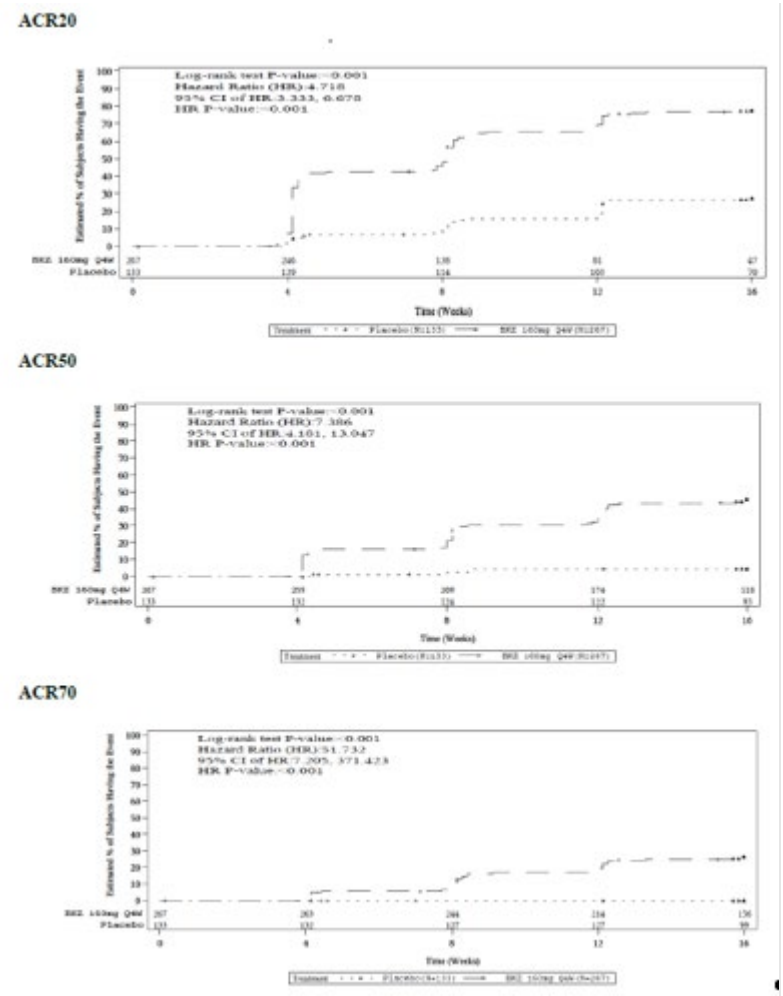


ACR70



PA0011

Figure 43: Kaplan-Meier curves for time to ACR20, ACR50, and ACR70 response (RS [OC])



Completed PA0010 study (up to Week 52)

Figure 44: ACR20 response by visit (Overall; RS [NRI]) (PA0010)

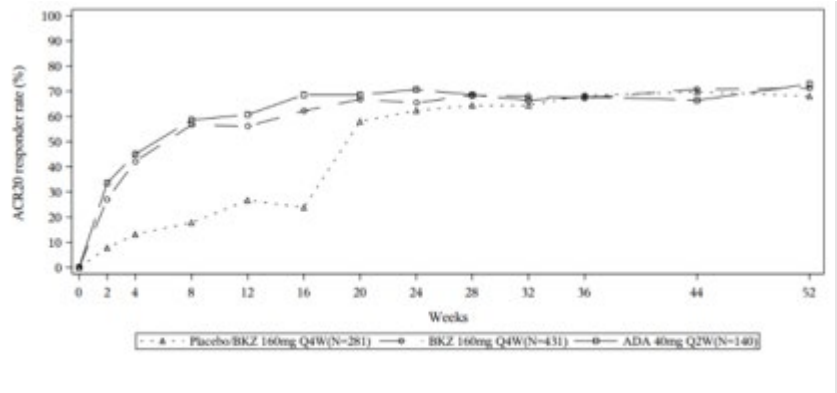


Figure 45: ACR50 response by visit (Overall; RS [NRI]) (PA0010)

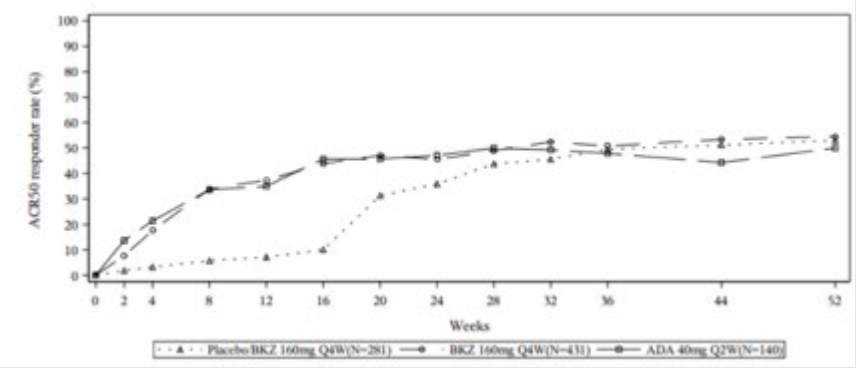
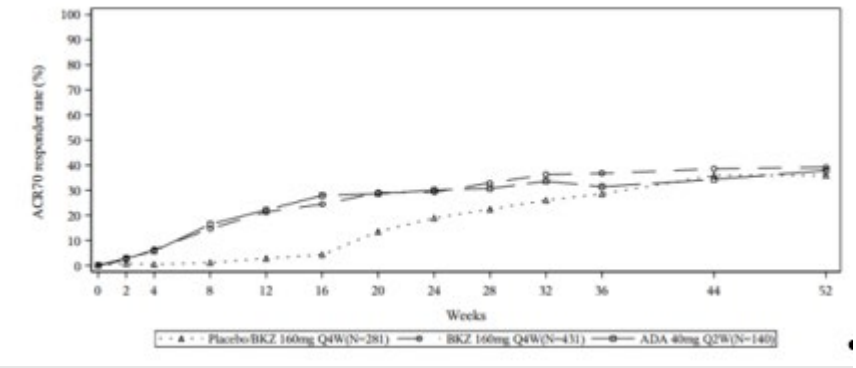


Figure 46: ACR70 response by visit (Overall; RS [NRI]) (PA0010)



Proportion of ACR50 responders at Week 16 and maintaining response at Week 52

For study participants with an observed response at Week 16, the ACR50 response was maintained in 87.2% of responders up to Week 52 in the bimekizumab 160mg Q4W group and 79.7% of responders in the adalimumab group.

HAQ-DI change from Baseline by visit

PA0010, For the Randomised Set (RS) (MI),

- Mean Baseline HAQ-DI scores across the placebo, bimekizumab 160mg Q4W, and adalimumab groups were 0.8906, 0.8197, and 0.8589, respectively
- Week 2, bimekizumab 160mg Q4W group compared with the placebo group (-0.0534 vs 0.0371, respectively)
- Week 16 (-0.2583 vs -0.0858, respectively) ranked secondary endpoint
- After Week 16, the mean decreases observed in HAQ DI score with bimekizumab treatment continued to improve to Week 24 (-0.3046).
- In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the mean decrease in HAQ-DI score improved from Week 16 (-0.0858) to Week 24 (-0.2839).
- After Week 16, the mean reduction observed in HAQ-DI score with bimekizumab treatment was sustained up to Week 52 (-0.3376), D92 completed PA0010 study (up to Week 52)

- In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the mean reduction in HAQ-DI score improved from Week 16 (-0.0856) to Week 52 (-0.3758).

The mean reduction in HAQ-DI scores was similar between the bimekizumab 160mg Q4W (range: -0.0542 to -0.3473) and adalimumab (range: -0.0519 to -0.4105) groups over time.

PASI75/90/100 response by visit

In both PA0010 and PA0011 studies, participants with PSO involving at least 3% BSA at Baseline, the PASI75/90/100 responder rate at Week 2 was higher in the bimekizumab 160mg Q4W group compared with the placebo group; the differences were considered clinically meaningful. The PASI75/90/100 responder rate for study participants in the bimekizumab 160mg Q4W group increased through Week 16 and was higher compared with the placebo group at each time point (all nominal $p<0.001$, in PA0011 PASI90/100 Week 4: p-value was not evaluable).

In PA0010, the PASI75/90/100 responses with bimekizumab treatment was maintained up to Week 24. As per the D92 completed PA0010 study data (up to Week 52), the PASI75/90/100 responses with bimekizumab treatment continued to improve to Week 52.

In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the PASI75/90/100 responder rate increased from Week 16 to Week 24 and was similar to the bimekizumab 160mg Q4W group by Week 52. The PASI75/90/100 responder rate was consistently numerically higher for the bimekizumab 160mg Q4W group compared with the adalimumab group over time.

ACR50/PASI100

PA0010

In study participants with PSO involving at least 3% BSA at Baseline, at Week 16, the composite ACR50 and PASI100 responder rate was numerically higher in the bimekizumab 160mg Q4W group compared with the placebo group (27.6% vs 16.2%, respectively; Table 50)

Composite ACR50 and PASI100 response with bimekizumab treatment continued to improve to Week 52.

In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the composite ACR50 and PASI100 responder rate increased rapidly from Week 16, and the efficacy was similar to bimekizumab 160mg Q4W group by Week 52.

The composite ACR50 and PASI100 responder rate was consistently numerically higher for the bimekizumab 160mg Q4W group compared with the adalimumab group over time.

Table 50: Composite ACR50 and PASI100 response by visit (Overall; RS [NRI] [study participants with PSO involving at least 3% BSA at Baseline])

Visit	Placebo/BKZ 160mg Q4W N=140 n (%)	BKZ 160mg Q4W N=217 n (%)	ADA 40mg Q2W N=68 n (%)
Week 2	0	0	0
Week 4	0	12 (5.5)	0
Week 8	1 (0.7)	32 (14.7)	4 (5.9)
Week 12	0	50 (23.0)	11 (16.2)
Week 16	0	60 (27.6)	11 (16.2)
Week 20	16 (11.4)	73 (33.6)	15 (22.1)
Week 24	32 (22.9)	68 (31.3)	17 (25.0)
Week 36	57 (40.7)	92 (42.4)	19 (27.9)
Week 52	65 (46.4)	102 (47.0)	24 (35.3)

ACR50=American College of Rheumatology 50% improvement criteria; ADA=adalimumab; BKZ=bimekizumab; BSA=body surface area; NRI=nonresponder imputation; PASI100=Psoriasis Area and Severity Index 100%; PSO=psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: Placebo study participants switched to BKZ 160mg Q4W at/after Week 16.

Note: NRI used the estimand approach. Missing data or data after study treatment discontinuation were set to nonresponse.

Note: In the n (%) rows, n represents the number of responder cases at the given week, and percentages were calculated by treatment group on the number of study participants in the referenced population.

PA0011

In study participants with PSO involving at least 3% BSA at Baseline, the composite ACR50 and PASI90 responder rate was numerically higher in the bimekizumab 160mg Q4W group compared with the placebo with a clinically meaningful difference observed at Week 16 (33.5% vs 1.1%, respectively; nominal $p<0.001$).

PASI100

PA0010

In study participants with PSO involving at least 3% BSA at Baseline, at Week 4, the PASI100 responder rate was higher in the bimekizumab 160mg Q4W group compared with the placebo group (12.9% vs 4.3%, respectively; nominal $p=0.007$; this difference was considered clinically meaningful. The PASI100 responder rate for study participants in the bimekizumab 160mg Q4W group increased from Week 4 to Week 16 and was higher compared with the placebo group at each timepoint (all nominal $p\leq0.006$). The PASI100 response with bimekizumab treatment continued to improve to Week 52.

In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the PASI100 responder rate increased rapidly from Week 16, and the efficacy was similar to bimekizumab 160mg Q4W group by Week 52.

The PASI100 responder rate was consistently numerically higher for the bimekizumab 160mg Q4W group compared with the adalimumab group over time.

Table 51: PASI100 response by visit (Overall; RS [NRI] [study participants with PSO involving at least 3% BSA at Baseline])

Visit	Placebo/BKZ 160mg Q4W N=140 n (%)	BKZ 160mg Q4W N=217 n (%)	ADA 40mg Q2W N=68 n (%)
Week 2	1 (0.7)	9 (4.1)	0
Week 4	6 (4.3)	28 (12.9)	3 (4.4)
Week 8	3 (2.1)	64 (29.5)	13 (19.1)
Week 12	4 (2.9)	91 (41.9)	16 (23.5)
Week 16	3 (2.1)	103 (47.5)	14 (20.6)
Week 20	28 (20.0)	120 (55.3)	20 (29.4)
Week 24	60 (42.9)	122 (56.2)	26 (38.2)
Week 36	90 (64.3)	129 (59.4)	23 (33.8)
Week 52	91 (65.0)	132 (60.8)	33 (48.5)

ADA=adalimumab; BKZ=bimekizumab; BSA=body surface area; NRI=nonresponder imputation; PASI100=Psoriasis Area and Severity Index 100%; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set

Note: Placebo study participants switched to BKZ 160mg Q4W at/after Week 16.

Note: NRI used the estimand approach. Missing data or data after study treatment discontinuation were set to nonresponse.

Note: In the n (%) rows, n represents the number of responder cases at the given week, and percentages were calculated by treatment group on the number of study participants in the referenced population.

PA0011

In study participants with PSO involving at least 3% BSA at Baseline, the PASI100 responder rate was numerically higher in the bimekizumab 160mg Q4W group compared with the placebo group with a clinically meaningful difference observed at week 16 (58.5% vs 4.5%, respectively; nominal p<0.001).

FACIT-Fatigue subscale

The mean Baseline FACIT-Fatigue subscale scores were generally similar across treatment groups. Consistently greater mean increases from Baseline in FACIT-Fatigue subscale score (i.e., improvement) were observed in the bimekizumab 160mg Q4W group compared with the placebo group at Week 4 that continued through Week 16 (both nominal p<0.001).

After Week 16, the improvement observed in mean FACIT-Fatigue subscale score with bimekizumab treatment was generally maintained up to Week 24. In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the mean FACIT-Fatigue subscale score improved from Week 16 to Week 24.

Clinically meaningful improvements in FACIT-Fatigue subscale score were observed at Week 24 across all treatment groups as indicated by the mean changes that are all above the 4-point threshold for within-patient clinically meaningful improvement (Cella et al, 2019).

The FACIT-Fatigue subscale response with bimekizumab treatment was sustained up to Week 52. In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the FACIT-Fatigue subscale responder rate increased rapidly from Week 16 and was sustained up to Week 52.

The FACIT-Fatigue subscale responder rate was similar between the bimekizumab 160mg Q4W and adalimumab groups over time.

The results reported in the "FACIT-Fatigue subscale score change from Baseline by visit" were mirrored in "FACIT-Fatigue subscale response by visit" results (i.e., improvement observed in the bimekizumab 160mg Q4W group compared with the placebo group at all time points.

DAPSA score categories

PA0010

From Week 2, the DAPSA rate for LDA or better response was higher in the bimekizumab 160mg Q4W group compared with the placebo group (17.4% vs 3.6%, respectively; nominal p<0.001); this difference was considered clinically meaningful. The DAPSA rate for LDA or better response for study participants in the bimekizumab 160mg Q4W group increased through Week 16 and was higher compared with the placebo group at each timepoint (all nominal p<0.001). The DAPSA rate for LDA or better response with bimekizumab treatment was maintained up to Week 24.

In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the DAPSA rate for LDA or better response increased from Week 16 to Week 24. The DAPSA rate for LDA or better response was similar between the bimekizumab 160mg Q4W and adalimumab groups over time.

PA0011

From Week 4, the DAPSA rates for low disease activity and REM response were higher in the bimekizumab 160mg Q4W group (18.7% and 1.1%, respectively) compared with the placebo group (5.3% and 0%, respectively); and nominal p<0.001; these differences were considered clinically meaningful. The DAPSA rates for low disease activity and REM response for study participants in the bimekizumab 160mg Q4W group increased through Week 16 and were higher compared with the placebo group at each time point (all nominal p<0.001).

The mean reduction in DAPSA scores showed similar improvements in the bimekizumab 160mg Q4W group compared with the placebo group.

mNAPSI resolution from Baseline by visit

PA0010

In study participants with psoriatic nail disease at Baseline (mNAPSI score >0), the proportion of study participants achieving mNAPSI resolution was numerically greater in the bimekizumab 160mg Q4W group compared with the placebo group at Week 12 (26.6% vs 18.6%, respectively) with a difference considered clinically meaningful observed between groups at Week 16 (33.6% vs 18.6%, respectively) (Table 52). The proportion of study participants achieving mNAPSI resolution with bimekizumab treatment continued to improve to Week 52 (65.6%).

Final – Week 52 Analysis in Study PA0010

Table 52: mNAPSI Resolution from Baseline – Analysis of Other Efficacy Endpoints (Non-Responder Imputation, Observed Cases and Multiple Imputation)
Analysis Set: Randomized Set (subjects with psoriatic nail disease at Baseline (mNAPSI score>0))

Visit, Week	Missing data Imputation method		Placebo/ BKZ 160mg Q4W N=156	BKZ 160mg Q4W N=244	ADA 40mg Q2W N=75
Visit 14, Week 24	NRI	n (%)	61 (39.1)	134 (54.9)	35 (46.7)
	OC	n/Nsub (%)	61/147 (41.5)	134/222 (60.4)	35/70 (50.0)
	MI	Mean proportion of Responders [95% CI]	40.3 [32.5, 48.1]	57.8 [51.5, 64.2]	47.9 [36.5, 59.4]
Visit 20, Week 36	NRI	n (%)	88 (56.4)	145 (59.4)	41 (54.7)
	OC	n/Nsub (%)	88/145 (60.7)	145/226 (64.2)	41/67 (61.2)
	MI	Mean proportion of Responders [95% CI]	59.1 [51.3, 67.0]	61.3 [55.1, 67.5]	55.9 [44.5, 67.3]
Visit 28, Week 52	NRI	n (%)	111 (71.2)	160 (65.6)	45 (60.0)
	OC	n/Nsub (%)	111/146 (76.0)	160/225 (71.1)	45/69 (65.2)
	MI	Mean proportion of Responders [95% CI]	73.2 [66.1, 80.3]	66.6 [60.6, 72.5]	60.0 [NE, NE]

In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the proportion of study participants achieving mNAPSI resolution increased rapidly from Week 16 (18.6%), and the efficacy was similar to bimekizumab 160mg Q4W group by Week 52 (71.2%).

The proportion of study participants achieving mNAPSI resolution was similar between the bimekizumab 160mg Q4W (range: 10.7% to 65.6%) and adalimumab (range: 14.7% to 60.0%) groups over time.

Psoriatic Arthritis Response Criteria (PsARC)

PA0010

The PsARC responder rate for study participants in the bimekizumab 160mg Q4W group increased through Week 16 and was higher compared with the placebo group at each timepoint (all nominal $p<0.001$). The PsARC response with bimekizumab treatment was sustained up to Week 52 (Table 53).

Table 53: PsARC response by visit (Overall; RS [NRI])

Visit	Placebo/BKZ 160mg Q4W N=281 n (%)	BKZ 160mg Q4W N=431 n (%)	ADA 40mg Q2W N=140 n (%)
Week 2	65 (23.1)	211 (49.0)	73 (52.1)
Week 4	77 (27.4)	276 (64.0)	89 (63.6)
Week 8	101 (35.9)	314 (72.9)	101 (72.1)
Week 12	118 (42.0)	332 (77.0)	114 (81.4)
Week 16	113 (40.2)	346 (80.3)	115 (82.1)
Week 20	206 (73.3)	350 (81.2)	110 (78.6)
Week 24	214 (76.2)	333 (77.3)	112 (80.0)
Week 28	219 (77.9)	346 (80.3)	112 (80.0)
Week 32	217 (77.2)	344 (79.8)	112 (80.0)
Week 36	225 (80.1)	347 (80.5)	112 (80.0)
Week 44	226 (80.4)	352 (81.7)	105 (75.0)
Week 52	224 (79.7)	341 (79.1)	116 (82.9)

ADA=adalimumab; BKZ=bimekizumab; MDA=Minimal Disease Activity; NRI=nonresponder imputation; Q2W=every 2 weeks; Q4W=every 4 weeks; RS=Randomized Set
Note: Placebo study participants switched to BKZ 160mg Q4W at/after Week 16.
Note: NRI used the estimand approach. Missing data or data after study treatment discontinuation were set to nonresponse.
Note: In the n (%) rows, n represents the number of responder cases at the given week, and percentages were calculated by treatment group on the number of study participants in the referenced population.

In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the PsARC responder rate increased rapidly from Week 16, and the efficacy was similar to bimekizumab 160mg Q4W and adalimumab groups up to Week 52

The PsARC responder rate was similar between the bimekizumab 160mg Q4W and adalimumab groups over time.

PA0011

At Week 16, the PsARC responder rate was higher in the bimekizumab 160mg Q4W group compared with the placebo group (85.4% vs 30.8%, respectively) Table 54 and nominal p<0.001.

Table 54: PsARC response by visit (RS [NRI])

Visit	Placebo N=133 n (%)	BKZ 160mg Q4W N=267 n (%)
Week 4	32 (24.1)	165 (61.8)
Week 8	39 (29.3)	195 (73.0)
Week 12	41 (30.8)	200 (74.9)
Week 16	41 (30.8)	228 (85.4)

BKZ=bimekizumab; IMP=investigational medicinal product; NRI=nonresponder imputation; PsARC= Psoriatic Arthritis Response Criteria; Q4W=every 4 weeks; RS=Randomized Set
Note: The NRI used the estimand approach. Missing data or data after IMP discontinuation were set to nonresponse.
Note: In the n (%) rows, n represents the number of responder cases at the given week, and percentages were calculated by treatment group on the number of study participants in the referenced population.

Ancillary analyses

Subgroup analysis PA0010 and PA0011

Subgroups analysed include the following assessed at Baseline: age, gender, disease duration, geographical region, race, body weight, hs-CRP, prior cDMARDs, PSO affected BSA, BASDAI, and HLA-B27. Additionally, subgroups of concomitant cDMARD use, concomitant MTX, and ADAb positive/negative status during the study were included.

The PA0010 subgroup analyses also included bone erosion and bone erosion and/or hs CRP≥6mg/L, both assessed at Baseline.

The PA0011 subgroup analysis also included prior inadequate or intolerant response to TNF inhibitors.

PA0010

Subgroup analyses were conducted at Week 16 for ACR50 response, PASI90 response, and HAQ DI response across the following subgroups: age (<45 years of age, ≥45 years of age), gender (male, female), disease duration (<1 year, ≥1 year), region (North America, Western Europe, Eastern Europe, Asia), race (White, Other), body weight at Baseline (≤100kg, >100kg), bone erosion (≥1) at Baseline (Yes, No), hs-CRP at Baseline (<6mg/L, ≥6mg/L), bone erosion (≥1) and/or hs-CRP ≥6mg/L at Baseline (Yes, No), prior cDMARDs (0, 1, ≥2), concomitantly receiving cDMARDs vs no concomitant cDMARDs, concomitantly receiving MTX vs no concomitant MTX, concomitantly receiving MTX vs. cDMARDs at Baseline (concomitant MTX, no concomitant MTX and cDMARDs at Baseline, no concomitant MTX and no cDMARDs at Baseline), PSO affected BSA at Baseline (<3%, ≥3% to 10%, >10%), BASDAI at Baseline (<4, ≥4), antidrug antibody (ADAb) status (positive, negative) (for the bimekizumab 160mg Q4W group only), human leukocyte antigen B27 (HLA B27) (positive, negative).

Improvements in ACR50, PASI90, and HAQ-DI responses at Week 16 were observed for the bimekizumab 160mg Q4W group compared with the placebo group across all subgroups that were generally considered clinically meaningful.

A higher response was observed in study participants <45 years old than those ≥45 years old and for males than females in the bimekizumab 160mg Q4W group for all 3 endpoints; these differences were not observed in the placebo group. Similar improvements in efficacy were observed in study participants irrespective of whether they were receiving concomitant cDMARDs (MTX or other cDMARDs) or no cDMARDs.

PA0011

Subgroup analyses were conducted at Week 16 for ACR50 response, PASI90 response, and HAQ DI response, across the following subgroups: age (<45 years of age, ≥45 years of age), gender (male, female), disease duration (<1 year, ≥1 year), region (Asia, Eastern Europe, North America, Western Europe), race, body weight at Baseline (≤100kg, >100kg), hs CRP at Baseline (<6mg/L, ≥6mg/L), prior TNFα inhibitor exposure, prior cDMARDs (0, 1, ≥2), concomitantly receiving cDMARDs vs no concomitant cDMARDs, concomitantly receiving MTX vs no concomitant MTX, concomitantly receiving MTX vs no concomitant MTX at Baseline vs other cDMARDs at Baseline (MTX at Baseline, no MTX at Baseline and cDMARDs at Baseline, no MTX at Baseline and no cDMARDs at Baseline), PSO affected BSA at Baseline (<3%, ≥3% to 10%, >10%), BASDAI at Baseline (<4, ≥4), ADAb status (positive, negative; for the bimekizumab 160mg Q4W group only), and HLA B27 (positive, negative).

Clinically meaningful improvements were observed for the bimekizumab 160mg Q4W group compared with the placebo group across all subgroups. Higher ACR50, PASI90, and HAQ-DI responses were observed in study participants <45 years old than those ≥45 years old and more males than females had higher ACR50 and HAQ-DI responses in the bimekizumab 160mg Q4W group compared with the placebo group. Similar improvements in efficacy were observed in study participants irrespective of whether they were receiving concomitant cDMARDs (MTX or other cDMARDs) or no cDMARDs.

Dose Rationale

Dosing recommendation in patients with active PsA

- bimekizumab 160mg Q4W

Pooled efficacy data from Pool E1

Results of the Phase 3 pooled efficacy data from Pool E1 (PA0010 and PA0011) showed that a bimekizumab 160mg dose Q4W in the Initial Treatment Period demonstrated a statistically significant and clinically meaningful separation from placebo at Week 16 on the primary efficacy variable ACR50. Overall, 43.7% of study participants receiving bimekizumab were ACR50 responders at Week 16 compared with 8.9% of study participants on placebo (nominal p<0.001). Consistent, clinically meaningful improvements in ACR50 and PASI90 response were observed for the bimekizumab 160mg Q4W group compared with the placebo group at Week 16 across all subgroups.

Combined PK-PD model of the ER relationship between bimekizumab concentrations and ACR responses.

Using the combined ACR response data from Phase 2 (PA0008) and Phase 3 studies (PA0010 and PA0011), a PK/PD analysis was conducted to describe the relationship between bimekizumab concentration and ACR responses. The simulation results confirm that bimekizumab 160mg Q4W is the appropriate dose regimen for maximal ACR response, since the majority of patients with PsA will maintain steady-state concentrations with this dose at or near the plateau of the exposure-ACR relationship.

Exposure-Response relationships for Safety

Bimekizumab plasma trough concentrations following 160mg Q4W in Phase 3 studies were not associated with clinically-relevant increases in incidences of TEAEs or infection TEAEs. Bimekizumab doses up to 320mg Q4W were tested in the Phase 2b study PA0008 and all doses were consistent with the known safety profile.

Dosing recommendation in patients with active PsA who have moderate to severe plaque PSO

- bimekizumab 320mg Q4W for the first 16 weeks and Q8W thereafter.
- body weight ≥120kg, continued dosing with 320mg Q4W after Week 16 may be considered.

- After 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160mg every 4 weeks can be considered.

Subgroup analysis PA0010- PSO affected % BSA at Baseline

A trend toward lower response was observed in study participants with ≥3 to 10% BSA at Baseline than in those with BSA>10% for the bimekizumab 160mg Q4W group (57.6% vs 68.5%, respectively). Small differences between subgroups were observed for the placebo (4.3% vs 0%, respectively) and adalimumab groups (42.9% vs 38.5%, respectively).

A summary of PASI90 response at Week 16 by subgroup is provided for the RS (non-responder imputation and observed case) in Table 55.

Week 24 Analysis in Study PA0010

Table 55: PASI90 Responder Rate at Week 16 by Subgroups – Subgroup Analysis of the Secondary Efficacy Endpoints (Observed Cases and Non-Responder Imputation) Analysis Set: Randomized Set (subjects with PSO involving at least 3% BSA at Baseline)

Subgroup: PSO affected BSA at Baseline

Category	Placebo N=92	BKZ 160mg Q4W N=144	ADA 40mg Q2W N=42
PSO affected BSA at Baseline >=3% to 10%			
n/Nsub (%)	4/85 (4.7)	83/136 (61.0)	18/41 (43.9)
n (%)	4 (4.3)	83 (57.6)	18 (42.9)

Category	Placebo N=48	BKZ 160mg Q4W N=73	ADA 40mg Q2W N=26
PSO affected BSA at Baseline >10%			
n/Nsub (%)	0/46	50/71 (70.4)	10/24 (41.7)
n (%)	0	50 (68.5)	10 (38.5)

For comparison PA0010: Ranked secondary endpoint- In study participants with PSO involving at least 3% BSA at Baseline, the bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group at Week 16 (61.3% vs 2.9%, respectively; p<0.001)

Subgroup analysis PA0011- PSO affected % BSA at Baseline

For the bimekizumab 160 mg Q4W group, a numerically higher response was observed in study participants with ≥3% to 10% BSA at Baseline compared with those with BSA >10% for (71.6% vs 64.2%, respectively). Similar differences between subgroups were observed for the placebo group (9.5% vs 0%, respectively).

Final – Week 16 Analysis in Study PA0011

Table 56: PASI90 Responder Rate at Week 16 by Subgroups – Subgroup Analysis of Secondary Efficacy Endpoint (Observed Cases and Non-Responder Imputation)
Analysis Set: Randomized Set (subjects with PSO involving at least 3% BSA at Baseline)

Subgroup: PSO affected BSA at Baseline

Category	Placebo N=63	BKZ 160mg Q4W N=109
PSO affected BSA at Baseline >=3% to 10%		
n/Nsub (%)	6/55 (10.9)	78/108 (72.2)
n (%)	6 (9.5)	78 (71.6)

Category	Placebo N=25	BKZ 160mg Q4W N=67
PSO affected BSA at Baseline >10%		
n/Nsub (%)	0/24	43/66 (65.2)
n (%)	0	43 (64.2)

For comparison: Ranked secondary endpoint PA0011- In study participants with PSO involving at least 3% BSA at Baseline, the bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group at Week 16 (68.8% vs 6.8%, respectively; p<0.001).

Pooled efficacy data from Pool E1

Results of the Phase 3 pooled efficacy data from Pool E1 (PA0010 and PA0011) showed that among study participants with PSO involving at least 3% BSA at Baseline, 64.6% of study participants receiving bimekizumab were PASI90 responders at Week 16 (a secondary efficacy variable) compared with 4.4% on placebo (nominal p<0.001)

Baseline body weight covariate analysis

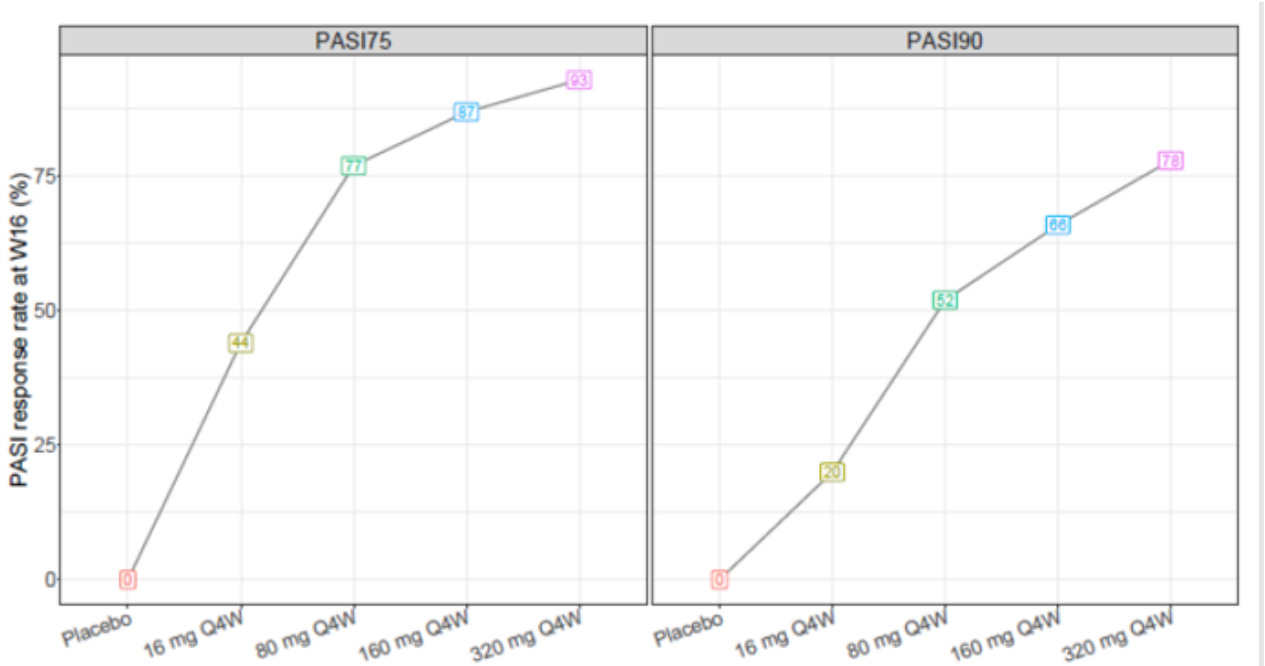
Baseline body weight was the covariate that had the largest impact on PK and PASI responses, respectively. Bimekizumab exposure decreased with increasing body weight, and the PASI90 response appeared to be more sensitive to body weight changes compared with PASI75. Simulations based on the final PASI model in study participants with PsA showed that participants weighing ≥120kg had a ~12% lower PASI90 response rate at Week 48 compared with participants weighing <120kg following bimekizumab 160mg Q4W continuous dosing. These results suggest patients with PsA and concomitant moderate to severe PSO weighing ≥120kg may benefit from an increased dose or dosing frequency to maintain maximal PASI90 responses.

Combined PK-PD model of the ER relationship between bimekizumab concentrations and PASI score.

Using combined PASI score data from Phase 2 (PA0008) and Phase 3 studies (PA0010 and PA0011), a PK/PD analysis was conducted to describe the relationships between bimekizumab concentration and PASI scores, and to evaluate potential covariates that may impact the PASI response of bimekizumab in participants with PsA.

Compared to 160 mg Q4W, the simulations showed more prominent effect for the higher dose regimen of 320 mg Q4W on week 16 PASI90 than PASI75 response rates. The time course of PASI90 response rate also demonstrated faster onset of response after treatment initiation with 320 mg Q4W compared with 160 mg Q4W. These results provide support for the proposed dose of 320 mg Q4W for treatment initiation in patients with PsA and concomitant moderate to severe PSO.

Figure 47: Predicted median Week 16 PASI75 and PASI90 response rates versus dose (CL0540)



PASI=Psoriasis Area and Severity Index; PASI75/90=75%/90% improvement in PASI; Q4W=every 4 weeks; W16=Week 16

Note: The labels indicate the median response rates for each dose. These simulation results represent the median predictions in the study population which is defined by ≥3% body surface area of psoriasis at Baseline, a median body weight of 85.5kg (CL0540 Table 4), and no prior biologics use for 61.6% of study participants

PK and PK/PD modeling with bimekizumab 320mg Q8W on ACR responses.

Pharmacokinetic simulations demonstrated substantial overlap in the distributions of simulated trough concentrations with bimekizumab 320mg Q8W and bimekizumab 160mg Q4W. This may suggest limited risk in a small proportion of patients with PsA and concomitant moderate to severe PSO.

The potential risk of reduced ACR responses with bimekizumab 320mg Q8W is further mitigated by the current flexibility in the recommended dose for patients with moderate to severe PSO. This allows some patients weighing ≥120kg to continue dosing with 320mg Q4W after Week 16, thereby resulting in similar or higher bimekizumab exposure than with 160mg Q4W and limiting potential impact on ACR response (see discussion).

Clinical and PK/PD modelling results in PSO development programme

PK/PD evidence from study participants with moderate to severe PSO in the PSO development program showed that the majority of study participants' average bimekizumab concentrations at Week 16 were at or close to the top of the exposure-response curve with 320mg Q4W. A 160mg Q4W dose resulted in lower plasma concentrations in approximately half of all study participants, which is predicted to lead to a lower response at Week 16. Thus, bimekizumab 320mg Q4W was selected as the appropriate dose for maximal PASI response during initial treatment for patients with moderate to severe PSO. Similarly, previous PK/PD modeling of PASI in study participants with moderate to severe PSO indicated that bimekizumab 320mg Q8W is appropriate for the maintenance of response in the majority of participants. The observed bimekizumab 90th percentile concentration range for the 320mg Q8W dose generally overlapped the 320mg Q4W dose at Week 56 (providing similar coverage of the exposure-response curve), except at the lower end of the concentration range where study participants tended to have higher body weights. Furthermore, simulations showed that the median predicted PASI90 and PASI100

response rates for study participants with body weights ≥120kg started to diverge after 16 weeks for the 2 tested Phase 3 dosing regimens (ie, continuous 320mg Q4W and 320mg Q4W up to Week 16 followed by 320mg Q8W). This was more evident with patient-preferred and clinically meaningful endpoints, such as PASI100, indicating that some study participants ≥120kg are likely to benefit from continued dosing with bimekizumab 320mg Q4W after Week 16.

Summary of main studies

The following tables 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).

Summary of Efficacy for trial PA0010

<table>
<tr><td colspan="4"><u>Title</u>: A Phase 3, Multicenter, Randomised, Double-Blind, Placebo Controlled, Active-Reference Study Evaluating the Efficacy and Safety of Bimekizumab in Study Participants with Active Psoriatic Arthritis</td></tr>
<tr><td>Study identifier</td><td colspan="3">PA0010
EudraCT Number: 2017-002322-20
NCT03895203</td></tr>
<tr><td>Design</td><td colspan="3">PA0010 is a multicenter study consisting of a 16 week, randomised, double blind, placebo-controlled, active-reference Treatment Period followed by a 36-week Active Treatment Blind Period to evaluate the efficacy and safety of bimekizumab in adult study participants with active PsA. After the 36-week Active Treatment Blind Period, study participants were allowed to enroll in the open-label extension study, PA0012.
PA0010 included an active (adalimumab) reference arm, in addition to the placebo control. No formal statistical comparisons were conducted versus adalimumab.</td></tr>
<tr><td></td><td colspan="2">Duration of initial treatment phase:
Duration of Active Treatment Blind phase:
Duration of Safety Follow up (SFU):</td><td>16 weeks
36 weeks
SFU Visit was planned 20 weeks after the final dose of bimekizumab (for study participants not enrolling in open-label study PA0012)</td></tr>
<tr><td>Hypothesis</td><td colspan="3">Superiority to placebo</td></tr>
<tr><td rowspan="5">Treatments groups</td><td rowspan="3">Double-Blind Treatment Period (Weeks 0-16)</td><td>Bimekizumab (BKZ) 160mg every 4 weeks (Q4W)</td><td>BKZ 160mg administered Q4W
431 randomised</td></tr>
<tr><td>Placebo Q4W</td><td>Placebo administered Q4W
281 randomised</td></tr>
<tr><td>Adalimumab (ADA) 40mg every 2 weeks (Q2W)</td><td>ADA 40mg administered Q2W
140 randomised</td></tr>
<tr><td rowspan="2">Active-Treatment Blind Period (Weeks 16-52)</td><td>BKZ 160mg Q4W</td><td>BKZ 160mg Q4W
414 continued</td></tr>
<tr><td>Placebo/BKZ 160mg Q4W</td><td>Placebo Q4W 16 weeks and switched to BKZ 160mg Q4W in Active-Treatment Blind Period
271 continued</td></tr>
<tr><td></td><td>ADA 40mg every 2 weeks (Q2W)</td><td>ADA 40mg Q2W</td></tr>
</table>

			136 continued
Endpoints and definitions	Primary endpoint	American College of Rheumatology 50% response criteria (ACR50) at Week 16	Proportion of participants who achieved an ACR50 response at Week 16
	Major secondary endpoints (in pre-defined testing hierarchy)	Change from Baseline (CfB) in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 16	CfB in HAQ-DI at Week 16
		Reduction of 90% from Baseline in Psoriasis Area and Severity index (PASI90) at Week 16	Proportion of study participants who achieved a PASI90 response at Week 16 in the subgroup of study participants with psoriasis (PSO) involving at least 3% of Body Surface Aria (BSA) at Baseline
		CfB in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16	CfB in the SF-36 PCS at Week 16
		Minimal Disease Activity (MDA) response at Week 16	Proportion of study participants who achieved MDA response at Week 16
		CfB in van der Heijde modified Total Sharp Score (vdHmTSS) at Week 16	CfB in vdHmTSS at Week 16 in study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline
		Enthesitis-free state based on the Leeds Enthesitis Index (LEI) at Week 16	Proportion of study participants who reach Enthesitis-free state based on the LEI at Week 16 in the subgroup of study participants with enthesitis at Baseline in the pooled population of PA0010 and PA0011
		Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16	Dactylitis-free state based on the Leeds Dactylitis Index (LDI) at Week 16 in the subgroup of study participants with dactylitis at Baseline in the pooled population of PA0010 and PA0011
		CfB in van der Heijde modified Total Sharp Score (vdHmTSS) at Week 16	CfB in vdHmTSS at Week 16 in the overall population
Database lock	Interim analysis clinical cutoff after all study participants completed Week 24 (25 Oct 2021). Upon CHMP's request, the final CSR (with data up to week 52) was also submitted by the MAH. Last study participant completed date: 11 July 2022. Final Report date: 02 Dec 2022		

Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (Randomised Set) Week 16			
Descriptive statistics and estimate variability	Treatment group	BKZ 160mg Q4W	Placebo	ADA 40mg Q2W
	Number of participants	431	281	140
	ACR 50 Wk16 n/N (%)	189/431 (43.9)	28/281 (10.0)	64/140 (45.7)
Effect estimate per comparison	Primary endpoint	Comparison groups	BKZ vs placebo	
		p-value	p <0.001	
Notes	The primary endpoint at Week 16 was highly statistically significant demonstrating superiority over placebo with p <0.001. No statistical comparisons were performed vs the ADA reference arm.			
Analysis description	**Secondary analysis (Major secondary endpoints)**			
Analysis population and time point description	Intent to treat (Randomised Set) Week 16			
Descriptive statistics and estimate variability	Treatment group	BKZ 160mg Q4W	Placebo	ADA 40mg Q2W
	Number of participants	431	281	140
	CfB in HAQ-DI Week 16 Mean (Standard Error [SE])	-0.2567 (0.0208)	-0.0880 (0.0273)	NA
	PASI90 response Week 16 n/N (%)	133 (61.3)	4 (2.9)	28 (41.2)
	CfB SF-36 PCS Week 16 Mean (SE)	6.219 (0.402)	2.326 (0.478)	NA
	MDA response Week 16 n/N (%)	194 (45.0)	37 (13.2)	63 (45.0)
	CfB in vdHmTSS (with elevated hs-CRP and/or at least 1 bone erosion at Baseline) Week 16 Mean (SE)	0.04 (0.05)	0.36 (0.10)	NA

	Enthesitis-free state (LEI) (pooled PA0010 and PA0011 population) Week 16 n/N (%)	124 (49.8)	37 (34.9)	NA
	Dactylitis-free state (LDI) (pooled PA0010 and PA0011 population) Week 16 n/N (%)	68 (75.6)	24 (51.1)	NA
	CfB in vdHmTSS (overall population) Week 16 Mean (SE)	0.04 (0.04)	0.32 (0.09)	NA
Effect estimate per comparison	Major secondary endpoints (in pre-defined testing hierarchy)	Comparison groups		BKZ vs placebo at Week 16
		p value		p <0.01
Notes	No statistical comparisons were performed vs adalimumab. NA=not applicable; ADA data are not available for the primary analyses of these endpoints, as reference-based multiple imputation was used for continuous endpoints.			

Summary of Efficacy for trial PA0011

Title: A Multicenter, Phase 3, Randomised, Double-Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Bimekizumab in the Treatment of Subjects with Active Psoriatic Arthritis		
Study identifier	PA0011 EudraCT Number: 2017-002804-29 NCT03896581	
Design	PA0011 was a Phase 3, multicenter, randomised, double blind, placebo-controlled study to evaluate the efficacy and safety of bimekizumab administered subcutaneously every 4 weeks for 16 weeks in study participants with active PsA. Study participants who completed Week 16 were allowed to enroll in the open-label extension study, PA0012. This final report presents an analysis of all available data (including efficacy, safety, and pharmacokinetics) through the Safety Follow Up Period (20 weeks after the final dose of investigational medicinal product).	
	Duration of initial treatment phase: Duration of Safety Follow up (SFU):	16 weeks SFU Visit was planned 20 weeks after the final dose of bimekizumab (for study participants not enrolling in open-label study PA0012)
Hypothesis	Superiority to placebo	
Treatments groups	Bimekizumab (BKZ) 160mg every 4 weeks (Q4W)	BKZ 160mg administered Q4W 267 randomised
	Placebo Q4W	Placebo administered Q4W 133 randomised

Endpoints and definitions	Primary endpoint	American College of Rheumatology 50% response criteria (ACR50) at Week 16	Proportion of participants who achieved an ACR50 response at Week 16
	Major secondary endpoints (in pre-defined testing hierarchy)	Change from Baseline (CfB) in Health Assessment Questionnaire – Disability Index (HAQ-DI) at Week 16	CfB in HAQ-DI at Week 16
		Reduction of 90% from Baseline in Psoriasis Area and Severity index (PASI90) at Week 16	Proportion of study participants who achieved a PASI90 response at Week 16 in the subgroup of study participants with psoriasis (PSO) involving at least 3% of Body Surface Aria (BSA) at Baseline
		CfB in the Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) at Week 16	CfB in the SF-36 PCS at Week 16
		Minimal Disease Activity (MDA) response at Week 16	Proportion of study participants who achieved MDA response at Week 16
Database lock	04 March 2022		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Randomised Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	BKZ 160mg Q4W	Placebo
	Number of participants	267	133
	ACR 50 Wk16, n (%)	116 (43.4)	9 (6.8)
Effect estimate per comparison	Primary endpoint	Comparison groups	BKZ vs placebo
		p-value	p <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 (Major secondary endpoints)**		
Analysis population and time point description	Intent to treat (Randomised Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	BKZ 160mg Q4W	Placebo
	Number of participants	267	133
	CfB in HAQ-DI Week 16 Mean (Standard Error [SE])	-0.3751 (0.0286)	-0.0701 (0.0432)
	PASI90 response Week 16 n/N (%)	121/176 (68.8)	6/88 (6.8)
	CfB SF-36 PCS Week 16 Mean (SE)	7.258 (0.531)	1.413 (0.714)
	MDA response Week 16 n/N (%)	118/267 (44.2)	8/133 (6.0)
Effect estimate per comparison	Major secondary endpoints (in pre-defined testing hierarchy)	Comparison groups	BKZ vs placebo at Week 16
		p value	p <0.001
Notes			

Analysis performed across trials (pooled analyses and meta-analysis)

Pool E1: data from PA0010 and PA0011

Table 57: Overview of efficacy pool

Pool name	Studies included in pool	Treatment groups included in pool	Treatment Periods included in pool	Purpose of pool
E1	PA0010, PA0011	Study participants randomized to: BKZ 160mg Q4W PBO	Initial Treatment Period (Weeks 0-16)	Investigate subgroups; add precision to treatment effect (BKZ vs PBO)

BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks

The eligibility criteria of these 2 studies were the same, with the exception that PA0010 required study participants to be bDMARD-naïve and be able to receive adalimumab, while PA0011 required study participants to have a history of inadequate response or intolerance to 1 or 2 prior TNFα inhibitors (TNFα-

IR) for either PsA or PSO. Both studies used the same dose, dosage form, and dosing schedule of bimekizumab from Week 0 to Week 16.

PA0010 study participants randomised to adalimumab were excluded from this pool. Study participants from PA0007 (Phase 1b) and PA0008 (Phase 2b) were excluded from pooling due to multiple study design differences compared with the 2 pivotal Phase 3 studies.

No formal analysis of efficacy results across studies was submitted as part of the PA0010 updated efficacy data, up to Week 52.

Pool E1 efficacy variables

Table 58: Efficacy variable classification across the 2 Phase 3 bimekizumab PsA studies

Variable	PA0010	PA0011	Included in Pool E1
ACR50 response at Week 16[a]	Primary	Primary	Yes
Change from Baseline in HAQ-DI score at Week 16[a]	Secondary	Secondary	Yes
PASI90 response at Week 16[a e]	Secondary	Secondary	Yes
Change from Baseline in SF-36 PCS score at Week 16[a]	Secondary	Secondary	Yes
MDA response at Week 16[a]	Secondary	Secondary	Yes
Enthesis-free state at Week 16 using LEI[b g]	Secondary	Other	Yes
Dactylitis-free state at Week 16 using LDI[b f]	Secondary	Other	Yes
Change from Baseline in vdHmTSS at Week 16[bc]	Secondary	Not included in the study	No
ACR20 at Week 16	Secondary	Secondary	Yes
ACR70 at Week 16	Secondary	Secondary	Yes
IGA response clear (0) almost clear (1) response at Week 16[h]	Secondary	Secondary	Yes
Change from Baseline in PtAAP at Week 16	Secondary	Secondary	Yes
Change from Baseline in PsAID-12 total score at Week 16	Secondary	Secondary	Yes
Enthesis-free state at Week 16 using SPARCC[i]	Secondary	Other	Yes
Change from Baseline in vdHmTSS at Week 16[bd]	Secondary	Not included in the study	No

[a] Included in the study hierarchy of both PA0010 and PA0011.
[b] Included in the study hierarchy of PA0010 only. For the efficacy variables of enthesitis-free state (based on LEI) and dactylitis-free state (based on LDI) pooled data from PA0010 and PA0011were analyzed (see Section 2.1.1.2.6 and Section 2.1.1.2.7).
[c] For study participants with elevated hs-CRP and/or with at least 1 bone erosion at Baseline.
[d] For study participants overall.
[e] Performed on participants with BSA≥3% at Baseline.
[f] Performed on participants with LDI>0 at Baseline.
[g] Performed on participants with LEI>0 at Baseline.
[h] Performed on participants with at least 2 psoriatic skin lesions and with BSA≥3% at Baseline.
[i] Performed on participants with SPARCC>0 at Baseline.

Additionally, the following efficacy variables over the time were described:

- Percentage of study participants achieving PASI75/100 in those with PSO involving at least 3% BSA at Baseline
- Percentage of study participants achieving an improvement from Baseline, i.e., change from Baseline in HAQ-DI of at least 0.35 (HAQ-DI response) in study participants with Baseline HAQ DI ≥0.35.
- Change from Baseline in BASDAI

All analyses and outputs based on PASI, IGA, Leeds Dactylitis Index (LDI), LEI, and SPARCC, were based on study participants with PSO involving at least 3% BSA, psoriatic lesions at Baseline, Baseline LDI>0, Baseline LEI>0, and SPARCC>0, respectively.

Analyses of Pool E1 efficacy data

The analysis methods for Pool E1 were the same as those described for the individual studies (PA0010 and PA0011) and followed the estimand structure outlined for those variables. The only difference was that the stratification variables for the imputation model and for the statistical model were region and study.

For all endpoints examined over time, statistical testing was performed at each time point. The associated p-values were considered nominal and not controlled for multiplicity.

For continuous variables, the MI-MCMC/monotone regression approach was applied for the imputation model on the change from Baseline (hypothetical estimand). The analysis model was based on ANCOVA with fixed effect of treatment, region, study ID, and Baseline value as covariates.

For responder variables, the analysis followed the NRI approach (composite estimand). The analysis model was based on a logistic model with fixed effect for treatment, region, and study ID as stratification variables.

The missing data methods applied in PA0010, PA0011, and Pool E1 are identical in principle. Different approaches were used to handle missing data, including how the intercurrent events were to be considered. An intercurrent event was defined as a discontinuation from study treatment prior to the given week of interest

Pool E1 subgroup analysis

Consistency of treatment effect for the primary efficacy variable (ACR50 response at Week 16) and for select secondary efficacy variables (HAQ-DI, PASI90, and MDA responses at Week 16) were evaluated within individual subgroups of study participants based on Pool E1. Subgroup analyses were also performed on the other efficacy variables of ACR20 and ACR70 responses at Week 16. The complete list of subgroups considered is provided in Table 59, variables were the same as those that were analysed in both PA0010 and PA0011, with the addition of subgroups for Baseline BMI, moderate/severe PSO (defined as BSA >10% and IGA ≥3 and PASI ≥12) at Baseline, and NAb status during the study.

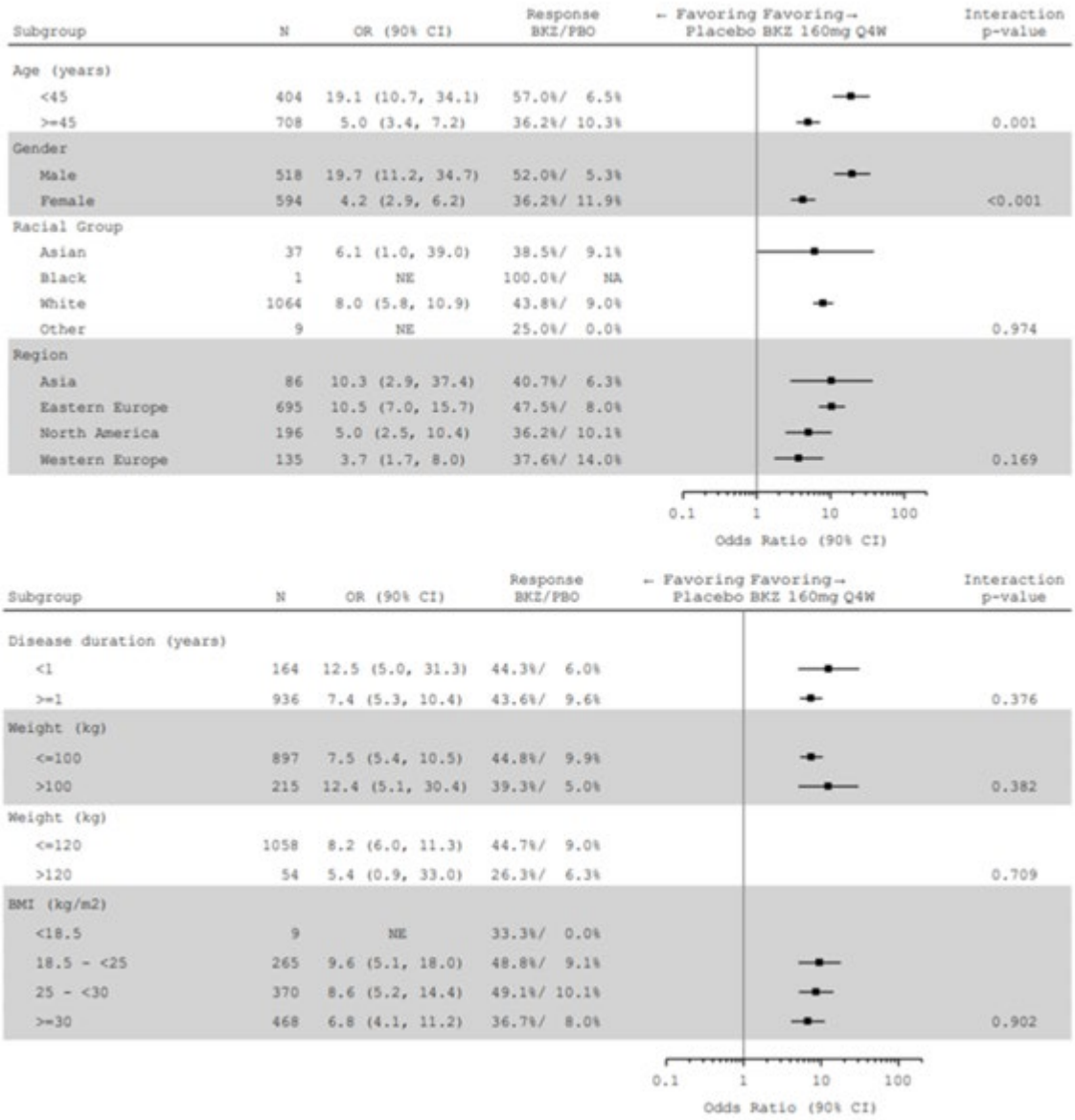
Table 59: Categories of variable for subgroup analyses

Subgroup	Categories
Age (years)	<45, ≥45
Gender	male, female
Race	Black, Asian, White, other
Region	Asia, Eastern Europe, North America, Western Europe
Disease duration (years)	<1, ≥1
Weight	≤100kg, >100kg
Weight	≤120kg, >120kg
BMI (kg/m^2)	<18.5, ≥ 18.5 to <25, ≥ 25 to <30, ≥30
hs-CRP level	<6 mg/L, ≥6 mg/L
Number of prior cDMARDs	0, 1, ≥2
Concomitantly receiving cDMARDs at Baseline	Yes, No
Concomitantly receiving MTX at Baseline	Yes, No
Concomitantly receiving MTX vs other cDMARDs at Baseline	MTX, other cDMARDs, No MTX nor other cDMARDs
PSO affected BSA at Baseline	<3%, ≥3% to ≤10%, >10%
Moderate/severe PSO at Baseline	yes (BSA>10 and IGA≥3 and PASI≥12)/no
BASDAI at Baseline	<4, ≥4
HLA-B27 positivity	yes/no
ADAb status (see definitions in ISAP Section 4.6.2.1)	positive, negative, missing
NAb status (see definitions in ISAP Section 4.6.3.1)	ADAb negative, NAb positive, ADAb positive/NAb negative, NAb missing

Pool E1 Results

There were minor differences in study participant disposition across the subgroups. The differences varied, and no trends were apparent. Overall, in Pool E1, more study participants <45 years (4.0%) discontinued from the Initial Treatment Period compared with participants ≥45years (3.1%), <65years (3.6%), and ≥65 years (2.2%). In study participants <45 years Initial Treatment Period discontinuation rate was slightly lower in the bimekizumab 160mg Q4W group (2.8%) than in the placebo group (5.9%). The most common reason for discontinuation across treatment groups in this subgroup was withdrawal by participant (0.8% and 3.3% in the bimekizumab 160mg Q4W and placebo groups, respectively), In all other age groups, the reasons for discontinuation occurred at a similar and low incidence across the treatment groups.

Figure 48: ACR50 response rate at Week 16 by subgroups age, gender, race, geographical region, disease duration, Baseline body weight, and Baseline BMI (NRI; Pool E1)



Bimekizumab demonstrated similar levels of response in both bDMARD naïve (PA0010) and TNFα-IR (PA0011) patient populations across multiple joint and skin domains. In both Phase 3 studies, treatment with bimekizumab demonstrated clinically meaningful and statistically superior response rates ($p<0.001$) for the primary efficacy variable (ACR50 at Week 16) and all ranked secondary efficacy variables (all $p \leq 0.008$) in their respective statistical hierarchies.

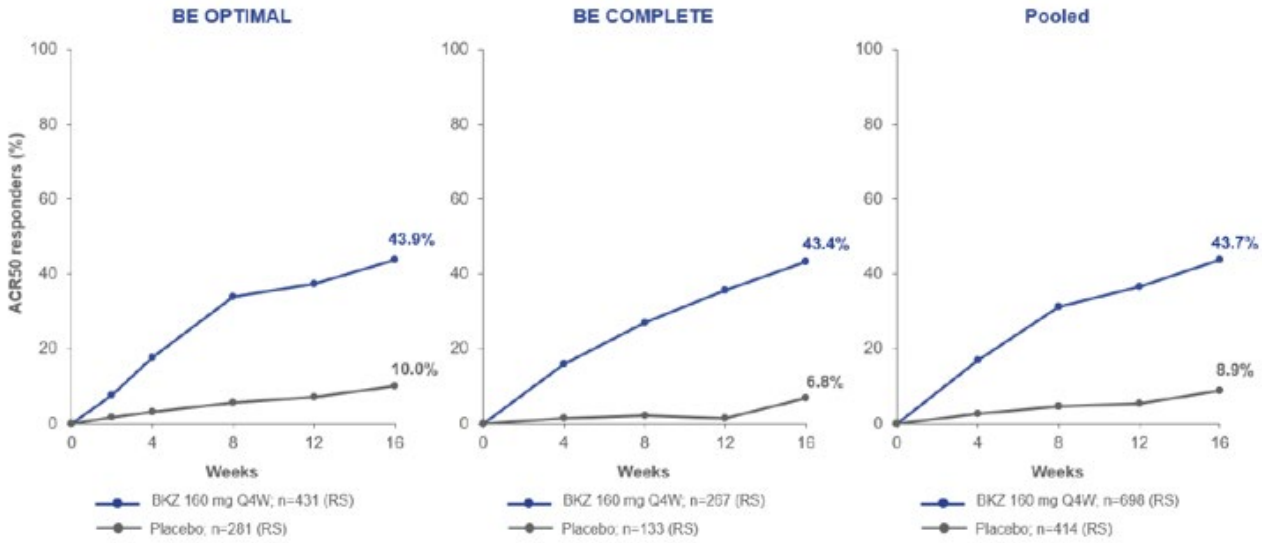
Pooled analyses based on Pool E1 were performed as prespecified in the ISAP. Results for the efficacy analyses of Pool E1 were consistent with the results for the individual studies: bimekizumab 160mg Q4W treatment was superior compared with placebo for the primary efficacy variable (ACR50 response at Week 16) and all secondary efficacy variables at Week 16 (Table 60). Overall, these results were considered clinically meaningful.

Table 60: Overview of primary and secondary efficacy variables in Pool E1

Efficacy Variables	Time point	Missing data imputation method	Point Estimate	BKZ 160mg vs Placebo 95% CI	p-value [a]	Efficacy observation
ACR50 response	Week 16	NRI	8.037	(5.548, 11.643)	<0.001	Primary
HAQ-DI change from Baseline	Week 16	RBMI	-0.236	(-2.87, -0.185)	<0.001	Secondary
PASI90 response [b]	Week 16	NRI	42.441	(21.648, 83.203)	<0.001	Secondary
SF-36 PCS score change from Baseline	Week 16	RBMI	4.890	(3.979, 5.802)	<0.001	Secondary
MDA response	Week 16	NRI	6.792	(4.808, 9.594)	<0.001	Secondary
Dactylitis-free state (based on LEI) [c]	Week 16	NRI	3.437	(1.559, 7.574)	0.002	Secondary
Enthesitis-free state (based on LEI) [d]	Week 16	NRI	1.904	(1.180, 3.074)	0.008	Secondary
ACR20 response	Week 16	NRI	6.794	(5.109, 9.034)	<0.001	Secondary
ACR70 response	Week 16	NRI	10.526	(5.899, 18.783)	<0.001	Secondary
IGA (clear/almost clear) response [e]	Week 16	NRI	31.377	(14.990, 65.676)	<0.001	Secondary
PtAAP change from Baseline	Week 16	RBMI	-20.776	(-23.716, -17.835)	<0.001	Secondary
PsAID-12 change from Baseline	Week 16	RBMI	-1.526	(-1.729, -1.324)	<0.001	Secondary
Enthesitis-free state (based on SPARCC) [f]	Week 16	NRI	2.095	(1.363, 3.222)	<0.001	Secondary

Comparison of the primary efficacy endpoint results for primary studies

Table 61: ACR50 responder rate through Week 16 including logistic regression (NRI) (PA0010, PA0011, and Pool E1)

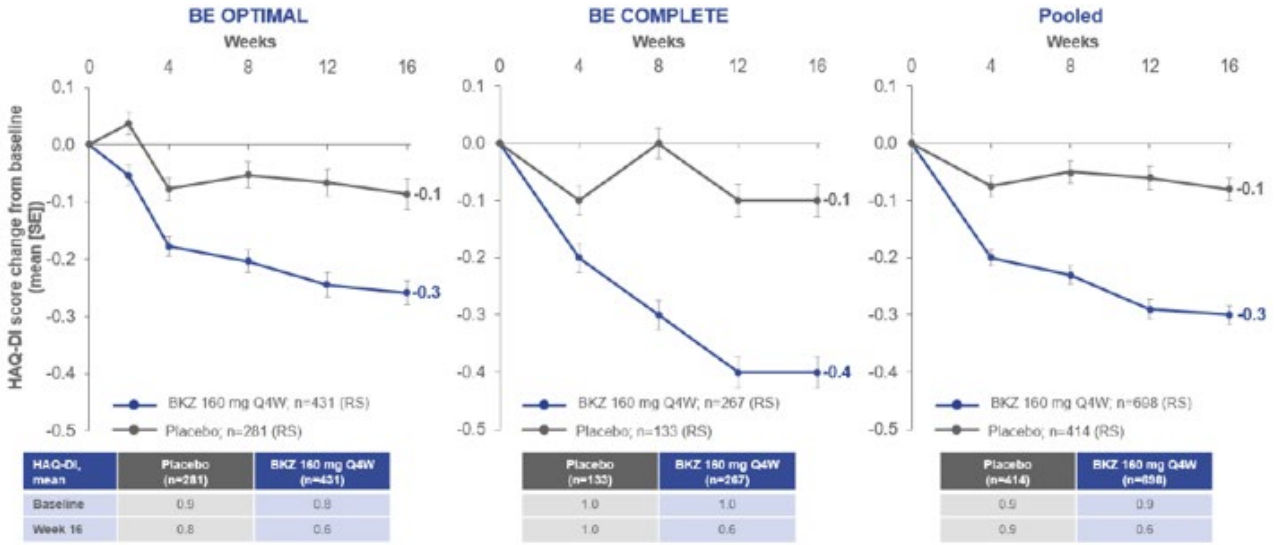


ACR50=American College of Rheumatology 50% improvement criteria; BKZ=bimekizumab; CI=confidence interval; NRI=nonresponder imputation; Q4W=every 4 weeks; RS=Randomized Set
Note: PA0010 is named BE OPTIMAL; PA0011 is named BE COMPLETE.

Supportive analyses of individual ACR components (TJC, SJC, PGA-PsA, PhGA-PsA, PtAAP, HAQ-DI, and hs-CRP) at Week 16 were also conducted. The trend in ACR50 responder rate observed overall for bimekizumab compared with placebo was supported by that observed for each individual component using reference-based multiple imputation, multiple imputation, reference-based multiple imputation including ANCOVA and MI including ANCOVA (all nominal $p<0.001$).

Comparison of the secondary efficacy endpoint results for primary studies

Figure 49: Change from Baseline in HAQ-DI Score through Week 16 (MI) (PA0010), PA0011, and Pool E1)



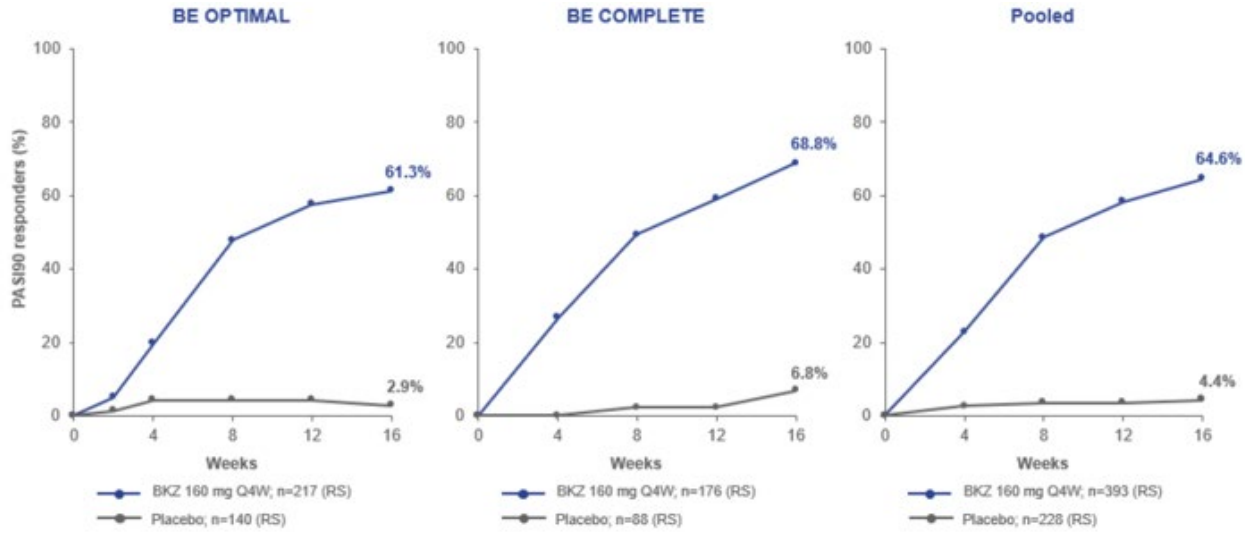
HAQ-DI, mean	Placebo (n=281)	BKZ 160 mg Q4W (n=431)
Baseline	0.9	0.8
Week 16	0.8	0.6

Placebo (n=133)	BKZ 160 mg Q4W (n=267)
1.0	1.0
1.0	0.6

Placebo (n=414)	BKZ 160 mg Q4W (n=698)
0.9	0.9
0.9	0.6

BKZ=bimekizumab; MI=multiple imputation; HAQ-DI=Health Assessment Questionnaire-Disability Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SE=standard error

Figure 50: PASI90 response rate through Week 16 (NRI) (PA0010, PA0011, and Pool E1)



BKZ=bimekizumab; BSA=body surface area; NRI=nonresponder imputation; PASI90=≥90% improvement in Psoriasis Area Severity Index; Q4W=every 4 weeks; RS=Randomized Set
Note: PASI90 was assessed in those study participants with PSO involving ≥3% BSA at Baseline.

Table 62: Summary of clinical responses across the Phase 3 studies and Pool E1 in the Initial Treatment Period (Week 16) (RS)

	PA0010 (BE OPTIMAL) (bDMARD-naïve study participants)			PA0011 (BE COMPLETE) (TNFα-IR study participants)			Pool E1		
Efficacy variables	PBO N=281	BKZ 160mg Q4W N=431	p-value	PBO N=133	BKZ 160mg Q4W N=267	p-value	PBO N=414	BKZ 160mg Q4W N=698	p-value[a]
Response, n (%)									
ACR50 response	28 (10.0)	189 (43.9)	<0.001	9 (6.8)	116 (43.4)	<0.001	37 (8.9)	305 (43.7)	<0.001
ACR20 response[a]	67 (23.8)	268 (62.2)	<0.001	21 (15.8)	179 (67.0)	<0.001	88 (21.3)	447 (64.0)	<0.001
ACR70 response[a]	12 (4.3)	105 (24.4)	<0.001	1 (0.8)	71 (26.6)	<0.001	13 (3.1)	176 (25.2)	<0.001
MDA response	37 (13.2)	194 (45.0)	<0.001	8 (6.0)	118 (44.2)	<0.001	45 (10.9)	(312 (44.7)	<0.001
PASI90 response[b]	(N=140) 4 (2.9)	(N=217) 133 (61.3)	<0.001	(N=88) 6 (6.8)	(N=176) 121 (68.8)	<0.001	(N=228) 10 (4.4)	(N=393) 254 (64.6)	<0.001
PASI100 response[b]	(N=140) 3 (2.1)	(N=217) 103 (47.5)	≤0.006	(N=88) 4 (4.5)	(N=176) 103 (58.5)	<0.001	(N=228) 7 (3.1)	(N=393) 206 (52.4)	<0.001
IGA 0/1 response[a, c]	(N=129) 5 (3.9)	(N=204) 103 (50.5)	<0.001	(N=82) 3 (3.7)	(N=163) 99 (60.7)	<0.001	(N=211) 8 (3.8)	(N=367) 202 (55.0)	<0.001
Dactylitis-free state (LDI)[d, e]	(N=33) 18 (54.5)	(N=56) 44 (78.6)	0.010	(N=14) 6 (42.9)	(N=34) 24 (70.6)	0.048	(N=47) 24 (51.1)	(N=90) 68 (75.6)	0.002
Enthesitis-free state (LEI)[e, f]	(N=70) 29 (41.4)	(N=143) 72 (50.3)	0.301	(N=36) 8 (22.2)	(N=106) 52 (49.1)	0.007	(N=106) 37 (34.9)	(N=249) 124 (49.8)	0.008
Enthesitis-free state (SPARCC)[e, g]	(N=90) 32 (35.6)	(N=166) 83 (50.0)	0.043	(N=51) 12 (23.5)	(N=122) 56 (45.9)	-	(N=141) 44 (31.2)	(N=288) 139 (48.3)	<0.001
VLDA response[h]	3 (1.1)	63 (14.6)	-	3 (2.3)	36 (13.5)	-	NA	NA	-
ACR50/PASI100 response[a, b]	(N=140) 0	(N=217) 60 (27.6)	-	(N=88) 1 (1.1)	(N=176) 59 (33.5)	<0.001	NA	NA	
Change from Baseline, mean (SE)									
HAQ-DI	-0.0880 (0.0273)	-0.2567 (0.0208)	<0.001	-0.0701 (0.0432)	-0.3751 (0.0286)	<0.001	-0.0809 (0.0226)	-0.3014 (0.0170)	<0.001
SF-36-PCS	2.326 (0.478)	6.219 (0.402)	<0.001	1.413 (0.714)	7.258 (0.531)	<0.001	2.053 (0.390)	6.615 (0.321)	<0.001
PtAAP	-6.2 (1.5)	-23.6 (1.3)	<0.001	-4.5 (2.1)	-27.7 (1.7)	<0.001	-5.8 (1.3)	-24.9 (1.1)	<0.001
PsAID-12 total score	-0.53 (0.10)	-1.83 (0.09)	<0.001	-0.32 (0.16)	-2.24 (0.13)	<0.001	-0.48 (0.09)	-1.97 (0.08)	<0.001
FACIT-Fatigue subscale score[a]	1.54 (0.50)	3.92 (0.35)	<0.001	0.12 (0.70)	5.45 (0.61)	<0.001	1.09 (0.40)	4.52 (0.32)	-
vdHmTSS (participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline)[i]	(N=227) 0.36 (0.10)	(N=361) 0.04 (0.05)	0.001	NA	NA		NA	NA	
vdHmTSS (overall study population)[i]	(N=269) 0.32 (0.09)	(N=420) 0.04 (0.04)	0.001	NA	NA		NA	NA	

Note: ACR20/70 responses were based on at least 20/70 percent improvement from Baseline in ACR criteria; PASI90 responses were based on at least 90 percent improvement from Baseline in PASI score; IGA 0/1 response was defined as a score of 0 or 1 with at least a 2-grade reduction from Baseline.
Note: Missing data imputation methods: NRI was applied to binary endpoints; RBMI was applied to continuous endpoints.

[a] For Pool E1, p-values are nominal and not multiplicity-controlled, however, pooled LDI and LEI were included in the PA0010 hierarchy. All tests were performed at a 2-sided alpha level of 0.05. The PA0010 statistical hierarchy included ACR50, HAQ-DI, PASI90, SF-36 PCS, MDA, and vdHmTSS as well as LDI and LEI pooled with the PA0011 data. The PA0011 statistical hierarchy included ACR50, HAQ-DI, PASI90, SF-36 PCS, and MDA. P-values from the study hierarchies were multiplicity controlled and are statistically significant.

[b] Performed on participants with BSA ≥3% at Baseline. The ACR50/PASI100 composite endpoint was not included in the pooled analyses.

[c] Performed on participants with Baseline psoriatic skin lesions (IGA ≥2) and with BSA≥3% at Baseline.

[d] Performed on participants with dactylitis at Baseline (LDI>0).

[e] For individual PA0010 and PA0011 data, p-values are nominal and not multiplicity-controlled. All tests were performed at a 2-sided alpha level of 0.05 In PA0010, the pooled PA0010/PA0011 population was in the hierarchy (data not shown).

[f] Performed on participants with enthesitis at Baseline (LEI>0). In PA0010, the pooled PA0010/PA0011 population was in the hierarchy (ie, same as Pool E1).

[g] Performed on participants with enthesitis at Baseline (SPARCC>0). For Pool E1 and PA0010, p-values are nominal and not multiplicity-controlled. All tests were performed at a 2-sided alpha level of 0.05 (note: the inferential analysis was not performed in PA0011).

[h] VLDA was assessed in PA0010 and PA0011; no inferential analysis was performed. VLDA was not included in the pooled analyses.

[i] vdHmTSS was assessed in PA0010 only.

BASDAI change from Baseline by visit

In Pool E1, the bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (i.e., improvement) in BASDAI compared with the placebo group from Week 4 (-1.3 vs -0.5, respectively). The BASDAI change from Baseline for study participants in the bimekizumab 160mg Q4W group decreased further through Week 16 compared with the placebo group at each time point. Similar results were observed for the BASDAI change from Baseline by visit using OC. Comparable results were observed for the BASDAI change from Baseline by visit in the individual Phase 3 studies.

Table 63: PsA and PSO history and other Baseline disease characteristics (Pool E1)

Variable Statistic	Placebo N=414	BKZ 160mg Q4W N=698	All Study Participants N=1112
BASDAI, n (%)			
<4	105 (25.4)	182 (26.1)	287 (25.8)
≥4	309 (74.6)	515 (73.8)	824 (74.1)
Missing	0	1 (0.1)	1 (0.1)

Comparison of Pool E1 results in subgroups

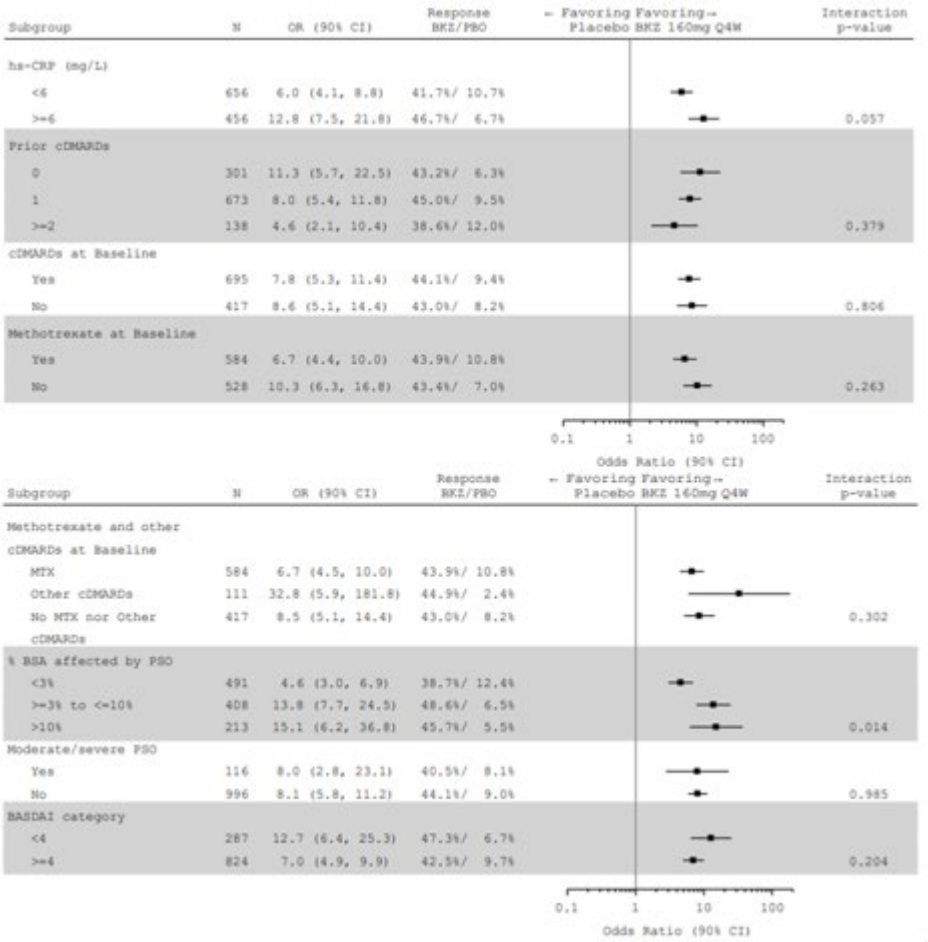
Subgroup analyses were performed on Pool E1 for the primary efficacy endpoint (ACR50 response at Week 16) and for select secondary and other efficacy endpoints (HAQ-DI, MDA, PASI90, PASI100, ACR20, and ACR70 responses at Week 16).

Consistent, clinically meaningful improvements in ACR50 response were observed for the bimekizumab 160mg Q4W group compared with the placebo group at Week 16 across all subgroups with the exception of age, gender, hs-CRP, and %BSA affected by PSO.

Response rates in the bimekizumab 160mg Q4W group were higher in participants with BMI 18.5 to<25kg/m2 (48.8%) and BMI 25 to<30kg/m2 (49.1%) compared with participants with BMI and ≥ 30kg/m2 (36.7%). Differences in response for the BMI<18.5kg/m2 subgroup were attributed to the low number of study participants (n=6). Response rates in the bimekizumab 160mg Q4W group were higher in participants weighing ≤120kg (44.7%) compared with participants weighing >120kg (26.3%). Differences in response for the >120kg subgroup were attributed to the low number of study participants (n=38).

The ACR50 response at Week 16 in the bimekizumab 160mg Q4W group was similar across subgroups irrespective of whether the study participants were receiving concomitant cDMARDs or not (44.1% and 43.0%, respectively). Moreover, even within the subgroup receiving cDMARDs, similar efficacy was demonstrated for concomitant MTX (43.9%) or other cDMARDs (including leflunomide, sulfasalazine, etc) (44.9%), although the subgroup with other cDMARDs was relatively smaller.

Figure 51: ACR50 response rate at Week 16 by subgroups for hs-CRP, prior cDMARDs, cDMARD/MTX at Baseline, % BSA affected by PSO, moderate/severe PSO, and BASDAI category (NRI; Pool E1)



Subgroup analyses for select secondary and other efficacy endpoints (HAQ-DI, MDA, PASI90, PASI100, ACR20, and ACR70 responses at Week 16) showed consistent, clinically meaningful improvements in response for the bimekizumab 160mg Q4W group compared with the placebo group at Week 16 across all subgroups. There were variations of difference seen in subgroup analysis, in the PASI responses there as the least interaction with treatment for any of the subgroups.

The responses for other select secondary endpoints at Week 16 in the bimekizumab 160mg Q4W group was similar across subgroups irrespective of whether the study participants were receiving concomitant cDMARDs or not. Moreover, even within the subgroup receiving cDMARDs, similar efficacy was demonstrated for concomitant MTX or other cDMARD.

Supportive studies

Additional supportive efficacy from Phase 2 study PA0008 and supportive long-term efficacy from Phase 2 study PA0009 (cumulatively up to 152 weeks) and data from the Phase 1b study, PA0007.

Study number/clinical development phase/study design	Study Period	Number of study participants randomized			Maximum duration of treatment
		BKZ	PBO	Active reference arm	
Supporting efficacy studies					
PA0007/Phase 1b/ multicenter, randomized, study-participant-blind, Investigator-blind, placebo-controlled, multiple-dose administration study	Double-blind Treatment Period	BKZ Loading/maintenance dose at Wk1 plus 2 maintenance doses at Wk4 and Wk7 (total of 3 doses): 240mg/160mg/160mg: 21 [d] 80mg/40mg/40mg: 6 160mg/80mg/80mg: 6 560mg/320mg/320mg: 6	12	NA	6 weeks
PA0008/ Phase 2b/ multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study	Double-blind Treatment Period	BKZ 16mg Q4W: 41 BKZ 160mg Q4W: 41 BKZ 320mg Q4W: 41 BKZ 320mg LD/160mg Q4W: 41[e]	42	NA	12 weeks
	Dose-blind Treatment Period [f]	BKZ 160mg/160mg Q4W: 40 BKZ 320mg/320mg Q4W: 41 BKZ 320mg/160mg/160mg Q4W: 37 PBO/BKZ 160mg Q4W: 20 PBO/BKZ 320mg Q4W: 20 BKZ 16mg/160mg Q4W: 22 BKZ 16mg/320mg Q4W: 19	NA	NA	36 weeks
Long-term studies					
PA0009/ Phase 2b/ multicenter, OLE study	Treatment Period	160mg Q4W: 183	NA	NA	100 weeks
PA0012/ Phase 3, multicenter, OLE study [g]	Treatment Period	160mg Q4W: NA (study is ongoing)	NA	NA	140 weeks

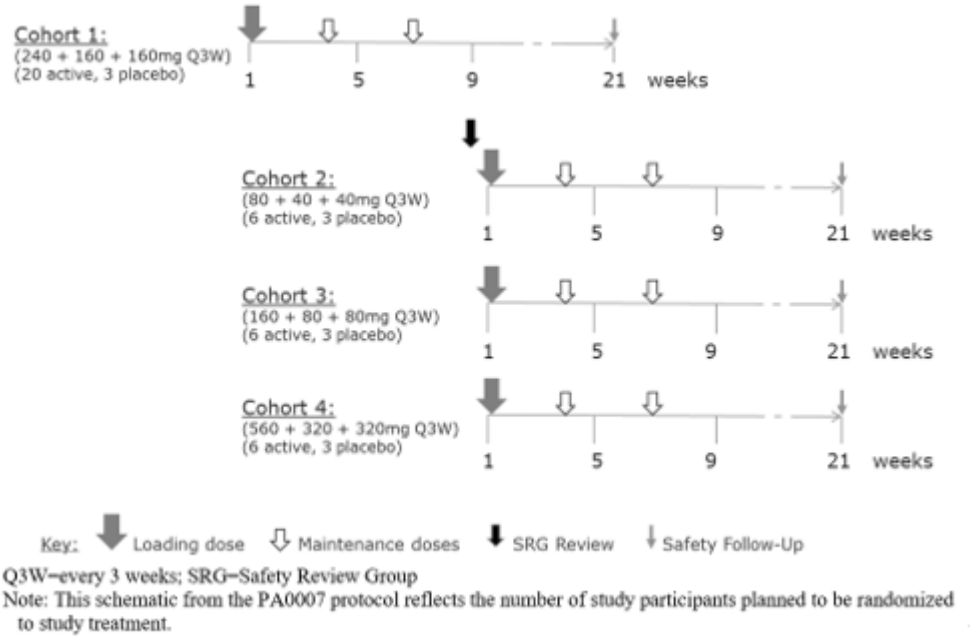
[d] In PA0007, 21 study participants were randomized to receive BKZ 240mg/160mg/160mg treatment; however, 1 participant withdrew from the study due to a pretreatment adverse event and was excluded from the Full Analysis Set.
[e] Loading dose in PA0008 was BKZ 320mg at Baseline.
[f] First dose shown reflects treatment during the PA0008 Double-blind Period. At Week 12, PBO and BKZ 16mg participants were re-randomized to either BKZ 160mg or BKZ 320mg. Participants randomized to BKZ 160mg with 320mg LD at Baseline were not re-randomized at Week 12 and remained on BKZ 160mg treatment. Participants randomized to BKZ 160mg and BKZ 320mg at Baseline were not re-randomized at Week 12 and remained on their original treatment.
[g] For PA0012, a clinical data cut was performed on 04 Jan 2022 to produce pooled data summaries of safety (described in the Integrated Summary of Safety). Efficacy data from this OLE study are not included in the pooled data summaries presented in this SCE.

PA0007 Phase 1b study

Phase 1b, randomised, study participant-blind, Investigator-blind, placebo-controlled, multiple-dose administration study to evaluate the safety, PK, and PD profiles of bimekizumab administered intravenously (iv) to study participants with active PsA who had an inadequate response to at least 1 nonbiologic DMARD and/or 1 approved bDMARD.

Bimekizumab treatment duration was 6 weeks, with study participants receiving a loading dose on Week 1 followed by a maintenance dose at Weeks 4 and 7. The loading/maintenance doses used were 80/40mg (N=6), 160/80mg (N=6), 240/160mg (N=20), and 560/320mg (N=6) (PK Per-Protocol Set analysis population). Fourteen study participants were randomised to receive placebo.

Figure 52: Schematic diagram for PA0007



Q3W=every 3 weeks; SRG=Safety Review Group
Note: This schematic from the PA0007 protocol reflects the number of study participants planned to be randomized to study treatment.

Efficacy results

The disease characteristics of the overall population at Baseline were indicative of participants with moderate to severe PsA. Overall, the mean age of participants was 43.7 years (range: 18 to 71 years); and the majority of participants (92.3%) were 19 to <65 years old. Overall, there was an equal proportion of males and females (50.0% each). Mean weight, height, and BMI were 79.54kg (range: 47.0 to 101.0kg).

Multidose administrations of the top 3 doses of bimekizumab decreased the severity of PsA, as measured by increased responder rates for ACR and mPsARC and improvements from Baseline in DAS28(CRP), and DAS28(ESR) compared with placebo. The bimekizumab top 3 dose group had consistently larger percentages of participants that achieved ACR20, ACR50, and ACR70 responses compared with the placebo group at Week 9 and Week 21. The bimekizumab top 3 dose group also had a slightly greater mean decrease in DAS28(CRP) and DAS28(ESR) compared with the placebo group and a slightly greater mean increase in mPsARC response rate. Mean decreases from Baseline in LEI (ie, improvement) were observed over time for all treatment groups; these decreases were similar for the bimekizumab top 3 dose group and the placebo group.

Multidose administrations of bimekizumab improved the clinical features of plaque psoriasis, as measured by LSS, PASI, and PGAP. The mean percent change from Baseline in the LSS was greater for the bimekizumab treatment groups compared with the placebo group. There were also greater percentages of PASI50, PASI75, and PASI90 responders and a greater reduction in median PGAP in participants treated with bimekizumab compared with those treated with placebo at all post-Baseline assessments.

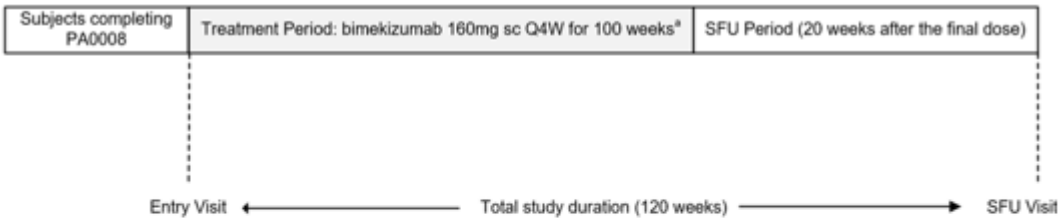
PA0008 Phase 2b

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 PsA. PA0008 study results were used to guide the selection of doses and clinical indices in the Phase 3 development. See Section 2.4.1 of AR for further information.

PA0009 Phase 2b

A Phase 2b multicenter, OLE study evaluating the long-term (up to 100 weeks [~2 years]) safety, tolerability, and efficacy of bimekizumab in study participants with PsA who completed PA0008 and were eligible to enter PA0009. At Week 48 of PA0008, all eligible study participants continuing into PA0009 underwent their final PA0008 study assessments and any nonoverlapping PA0009 entry assessments, and then received their first open-label dose of bimekizumab. At the conclusion of PA0008, study participants were either receiving bimekizumab 160mg Q4W or bimekizumab 320mg Q4W; in PA0009, all study participants received bimekizumab 160mg Q4W, regardless of the dose received in PA0008.

Figure 53: Schematic diagram for PA0009



IMP=investigational medicinal product; Q4W=every 4 weeks; sc=subcutaneous; SFU=Safety Follow-Up
Note: Self-administration was allowed after 3 months of treatment (from Week 16 onwards).
Note: Additionally, other treatments may have been used in addition to bimekizumab per Investigator discretion. Study participants not responding to treatment may be withdrawn from the study at the discretion of the Investigator.
[a] Study participants received their final dose of study drug on Week 100 and the SFU Visit was conducted 20 weeks after the last dose of IMP.

Study population disposition and baseline characteristics

A total of 184 study participants participating in PA0008 were enrolled in PA0009. Of the 183 study participants (100%) who started treatment with bimekizumab, 161 study participants (88%) completed the study. A total of 22 study participants (12.0%) discontinued the study; reasons for discontinuation were AEs and consent withdrawn (not due to AE) (9 study participants [4.9%] each), lack of efficacy (2 study participants [1.1%]) and lost to follow up and other (1 study participant [0.5%] each).

Demographics characteristics were generally well balanced across treatment groups (bimekizumab 160mg Q4W or bimekizumab 320mg Q4W at PA0008 completion). Overall, the Baseline disease characteristics in PA0008 were reflective of a population with active PsA.

The majority of study participants at Baseline in PA0008 had ≥3% PSO BSA (66.7%), and/or nail PSO (76.0%). The proportion of study participants at Baseline had enthesitis (52.5%), and/or dactylitis (27.3%). The majority of study participants at PA009 Baseline had <3% PSO BSA (92.3%). These results were as expected since all study participants had been receiving bimekizumab in PA0008; the improved parameters are reflective of efficacy observed during that period.

At Baseline in PA0009, the majority of study participants were using 1 NSAID therapy (58.5%) and/or synthetic DMARDs (62.8%, primarily MTX [58.5%]).

Overall, 24 study participants (13.1%) in the SS (Safety Set) used a concomitant rescue medication during the study. The majority of study participants who received concomitant rescue medication were taking NSAIDs at the PA0009 Entry Visit (EV) (13 study participants); of the 11 study participants who were not taking NSAIDs at the PA0009 EV, 2 study participants initiated NSAIDs in PA0009 (without COX-2 inhibitors) and 3 study participants initiated COX-2 inhibitors in PA0009. Nine study participants used MTX, and 1 study participant each used sulfasalazine and LEF in PA0009. Two study participants used a

combination of DMARDs. Two study participants received intra-articular corticosteroids. Five study participants received oral corticosteroid prednisolone during the study. One participant each started analgesics oxycodone and Vicodin. Five study participants received unclassified rescue medications; and included triamcinolone acetonide, hydrocortisone butyrate, dexamethasone sodium phosphate, amorolfine, zinalfat, and urea.

Efficacy results

There was no primary efficacy variable for this study.

The secondary efficacy variables were the ACR20, ACR50, and ACR70 response at Week 48; change from Baseline of PA0008 in MASES at Week 48; change from Baseline of PA0008 in the LDI at Week 48; and PASI75 and PASI90 response at Week 48.

Over the course of ~2 years in the study, participants maintained the substantial improvements in efficacy outcomes achieved during PA0008 through all PA0009 visits. This durability of efficacy was consistent across all efficacy variables that were assessed, indicating a sustained improvement in PsA symptoms in study participants.

Table 64: ACR20 response at PA0009 Week 48 relative to PA0008 Baseline (FAS [NRI and OC])

PA0009 Visit (Week)	BKZ dose at PA0008 completion→BKZ dose in PA0009		All PA0009 participants (BKZ 160mg [a]) N=181
	BKZ 160mg→160mg [a] N=108	BKZ 320mg→160mg [a] N=73	
Visit 7 (Week 48)			
n (%) (NRI)	80 (74.1)	63 (86.3)	143 (79.0)
n/Nsub (%) (OC)	80/100 (80.0)	63/69 (91.3)	143/169 (84.6)

ACR20=American College of Rheumatology 20% response criteria; BKZ=bimekizumab; FAS=Full Analysis Set; NRI=nonresponder imputation; OC=observed case; Q4W=every 4 weeks

Table 65: ACR50 response at PA0009 Week 48 relative to PA0008 Baseline (FAS [NRI and OC])

PA0009 Visit (Week)	BKZ dose at PA0008 completion→BKZ dose in PA0009		All PA0009 participants (BKZ 160mg [a]) N=181
	BKZ 160mg→160mg [a] N=108	BKZ 320mg→160mg [a] N=73	
Visit 7 (Week 48)			
n (%) (NRI)	64 (59.3)	53 (72.6)	117 (64.6)
n/Nsub (%) (OC)	64/100 (64.0)	53/69 (76.8)	117/169 (69.2)

Table 66: ACR70 response at PA0009 Week 48 relative to PA0008 Basline (FAS [NRI and OC])

PA0009 Visit (Week)	BKZ dose at PA0008 completion→BKZ dose in PA0009		All PA0009 participants (BKZ 160mg [a]) N=181
	BKZ 160mg→160mg [a] N=108	BKZ 320mg→160mg [a] N=73	
Visit 7 (Week 48)			
n (%) (NRI)	49 (45.4)	37 (50.7)	86 (47.5)
n/Nsub (%) (OC)	49/100 (49.0)	37/69 (53.6)	86/169 (50.9)

PASI response: Due to an error in the original PA0009 protocol schedule of assessments, the measurement of PASI in study participants with BSA affected by PSO of ≥3% at PA0008 Baseline was not performed as intended at each post-Baseline time point, as the original PA0009 protocol schedule of assessments failed to indicate this measurement should have been conducted at all visits. The protocol was subsequently updated (Amendment 3) to correct the schedule of assessments such that PASI was assessed at all visits for study participants with BSA affected by psoriasis of ≥3% at PA0008 Baseline. Thus, the number of study participants with OC data was extremely limited at some time points; however, due to the correction in Protocol Amendment 3, data was available for nearly all study participants at the Week 104 visit.

Maintenance of PASI75 response in PA0008 Week 12 responders: In participants who were PASI75 responders at Week 12 (including participants receiving placebo and bimekizumab 16mg Q4W treatment) in PA0008 (57.5%), the PASI75 responder rates in PA0009 relative to PA0008 Baseline were initially high (97.1% at PA0009 EV) (NRI). For these study participants, the PASI75 responder rate was maintained at 78.3% at Week 24 and 84.1% at PA0009 Week 104.

Maintenance of PASI90 response in PA0008 Week 12 responders: In participants who were PASI90 responders at Week 12 (including participants receiving placebo and bimekizumab 16mg Q4W treatment) in PA0008 (38.3%), the PASI90 responder rates in PA0009 relative to PA0008 Baseline were initially high (95.7% at PA0009 EV) (NRI). For these study participants, the PASI90 responder rate was maintained at 76.1% for Week 24 and 84.8% at PA0009 Week 104.

PA0012 Phase 3 OLE study

There is currently no long-term efficacy data from study PA0012, the final CSR is planned to be available in Sep 2026 and will be submitted for assessment once available (see RMP).

2.4.3. Discussion on clinical efficacy

Bimekizumab is currently approved for plaque psoriasis. This application aims to extend the indication to treatment of active psoriatic arthritis (PsA).

Design and conduct of clinical studies

The bimekizumab PsA clinical development program consisted of 2 adequate and well-controlled pivotal Phase 3 studies designed to provide confirmatory evidence of the safety and efficacy of bimekizumab through 52 weeks (PA0010) and 16 weeks (PA0011). In addition, the following supportive studies were submitted, PA0007: completed Phase 1 study, PA0008: Completed Phase 2 study and PA0009 its OLE

study, PA0012: Open-label extension study for eligible PA0010 and PA0011 completers, ongoing and DV0004: Completed Phase 3, device sub-study within the OLE study PA0012.

A sufficient number of study participants with active PsA were included in the pivotal Phase 3 studies to provide a rigorous and comprehensive evaluation of the efficacy of bimekizumab. These studies were adequately powered and representative of the targeted patient population that would be indicated for bimekizumab treatment in clinical practice. The designs were largely in line with Scientific Advice recommendations.

Bimekizumab was tested against placebo across multiple clinician-reported measures and patient-reported outcomes in both studies. PA0010 included an active reference arm (adalimumab). Both PA0010 and PA0011 investigated the effects of bimekizumab on all disease aspects, including joint and skin symptoms, peripheral and extra-articular manifestations, physical function and mobility, as well as the broader impact on the patients' ability to conduct their daily activities (including work) and health-related quality of life. The efficacy endpoints were comprehensive and representative of PsA disease.

Efficacy data and additional analyses

Dose Rationale

The recommended dose and dosing regimen tested in the Phase 3 studies of bimekizumab was selected based on safety, efficacy, and PK data from the Phase 2b study PA0008 in adult patients with PsA, as well as PK/PD modelling in that study (CL0464). While a loading dose was initially considered for faster onset of action, it was determined that higher exposures associated with the initial loading dose could result in treatment effects at an early timepoint that were not reflective of long-term efficacy of a chronic therapy. Further, the loading dose could artificially inflate the response seen at Week 16 or at Week 24, which would not be reflective of maintenance response in a chronic disease. Therefore, based on the overall data, the recommended posology of bimekizumab is as follows:

- For adult patients with PsA, the recommended dose of bimekizumab is 160mg Q4W.

The 160mg Q4W dose has been adequately supported. Further rationale has been provided to support the recommended dose.

- For adult patients with PsA and concomitant moderate to severe plaque PSO, the recommended dosing regimen of bimekizumab is the same as for PSO - 320 mg (given as 2 subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter.

To support the proposed dose bimekizumab 320mg Q4W for the first 16 weeks and Q8W thereafter, the following were provided:

- Subgroup analysis of PA0010 and PA0011 of PSO affected % BSA at Baseline, in study participants with ≥3 to 10% BSA at Baseline and those with BSA>10% for the bimekizumab 160mg Q4W group
- Pooled efficacy data from Pool E1
- Baseline body weight covariate analysis
- Combined PK-PD model of the ER relationship between bimekizumab concentrations and PASI score.
- PK and PK-PD modelling with bimekizumab 320mg Q8W on ACR responses
- Clinical and PK/PD modelling results in the PSO development programme

The parallels drawn to the endpoints generated in the plaque psoriasis (PSO) development programme cannot however be fully supported given the obvious differences of the populations and clinical trial settings; however, a lower trend of PASI90 response in the PsA development program is recognised, in both the PA0010 and PA0011 subgroup analysis and the pooled efficacy data from Pool E1.

Overall, during the initial assessment, it was concluded that there was a paucity of clinical data to support the efficacy of the 320 mg Q8W maintenance dose in patients with PsA and concomitant moderate to severe PSO. The MAH was therefore requested to discuss the benefit-risk of allowing the selection of the dose in this cohort to the discretion of the clinician, including possible risk mitigation measures in the form of clinician guidance for monitoring ACR and PASI responses/treatment targets. In response, the MAH has proposed additional clarification to be added to the proposed posology to give the clinician flexibility in the treatment of patients who do not continue to respond optimally to 320mg Q8W for joint symptoms in the maintenance phase. Overall, the MAH's proposal to consider a switch to 160 mg Q4W in patients with PsA and concomitant PSO who do not maintain a sufficient response in joints after week 16 can be accepted. It is agreed with the MAH that the risk of reduced ACR responses is small. The risk is acknowledged as more likely in patients with high body weight, with this risk being already mitigated by additional posology available for patients with PsA and concomitant PSO and weighing ≥120kg to continue dosing with 320mg Q4W after Week 16. In addition, the newly proposed wording supports the general PsA treatment goals which aim to reflect patient preferences, with patients being provided with the best information concerning relevant options and consideration of all disease domains. The section 4.2 of the SmPC was thus updated to reflect that after 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160mg every 4 weeks can be considered. In addition, the subgroup of 'psoriatic arthritis with coexistent moderate to severe psoriasis) and a body weight ≥ 120 kg' was included under the Special populations, Overweight patient subgroup, Posology sub-heading.

Pivotal trials PA0010 and PA0011

PA0010 (BE OPTIMAL) and PA0011 (BE COMPLETE) are randomised, multicenter, double-blind, parallel-group, placebo-controlled studies to evaluate the efficacy and safety of bimekizumab in adult study participants with active PsA through 52 weeks and 16 weeks, respectively. The two Phase 3 PsA clinical studies share most of the methodological aspects and thus facilitated comparative analysis.

A total of 1112 study participants with active PsA were randomised to receive either bimekizumab or placebo in the Phase 3 studies PA0010 and PA0011. In PA0010, there were an additional 140 study participants with PsA randomised to receive adalimumab in the active reference arm.

Demographic and Baseline characteristics

Demographic characteristics, PsA-related and other Baseline disease characteristics were generally well balanced across treatment groups and reflective of the populations recruited in PA0010 and PA0011 pivotal studies.

Overall, these study participant characteristics were appropriate for evaluating the efficacy of bimekizumab treatment in the target patient population of active PsA. For both studies, patients had a diagnosis of active PsA for at least 6 months based on the Classification Criteria for Psoriatic Arthritis (CASPAR) and had active disease with tender joint count (TJC) ≥3 and swollen joint count (SJC) ≥3.

Study participants had active disease across multiple domains of PsA including dactylitis, enthesitis, and skin and nail disease. Overall, 57.7% of study participants had nail PSO, 12.3% of study participants had dactylitis, and approximately one-third had enthesitis (38.6% by SPARCC and 31.9% by LEI). At baseline, 55.9% of patients had ≥ 3% Body Surface Area (BSA) with active PSO with 10.4% of patients having moderate to severe PSO. The patient demographic and baseline characteristics were largely representative of the PsA population.

Regarding the concomitant cDMARD therapy in both pivotal trials. There was insufficient representation of patients receiving concomitant treatment with cDMARDs other than methotrexate (MTX) in the pivotal studies to support B/R assessment in this patient group. In PA0010, at baseline, 58.2% of patients were receiving concomitant methotrexate (MTX), 11.3% were receiving concomitant cDMARDs other than MTX, and 30.5% were receiving no cDMARDs. In PA0011, at baseline, 42.5% of patients were receiving concomitant MTX, 8.0% were receiving concomitant cDMARDs other than MTX, and 49.5% were receiving no cDMARDs. The MAH was therefore requested to justify the benefit-risk of bimekizumab in patients receiving concomitant treatment with cDMARDs other than methotrexate, or restrict the indication to "*in combination with methotrexate*". The MAH agreed to restrict the indication to 'in combination with methotrexate as outlined in the section 4.1 of the SmPC.

Outcomes/ Results

PSA0010 and PSA0011

The primary endpoint and ranked secondary endpoints were evaluated using a fixed-sequence testing procedure to account for multiplicity. According to this procedure, the statistical testing of an endpoint was investigated only if the null hypothesis for the previous endpoint had been rejected (i.e., if $p<0.05$).

Study results for the primary and ranked secondary endpoints across PA0010 and PA0011 consistently demonstrated that treatment with bimekizumab 160mg Q4W was superior to treatment with placebo, providing robust, statistically significant, and clinically meaningful improvements for study participants with active PsA.

The primary objective was met in both pivotal studies. In PA0010, Bimekizumab 160mg Q4W treatment demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.9% vs 10.0%, respectively). This difference is considered clinically meaningful, with a statistically significant odds ratio versus placebo of 7.082 ($p<0.001$). In PA0011, treatment with bimekizumab 160mg Q4W demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.4% vs 6.8%, respectively). This difference is also considered clinically meaningful, with a statistically significant odds ratio versus placebo of 11.086 ($p<0.001$). The results of all supportive analyses of the primary efficacy variable confirmed the primary efficacy results.

PA0010 and PA0010 also met all of the ranked secondary efficacy objectives. Ranked Secondary endpoints displayed efficacy on the broader aspects of PsA disease. Efficacy was shown in skin symptoms (PASI90) and pooled data (PA0010 and PA0011) were included in the sequential testing hierarchy for the efficacy variables of enthesitis-free state and dactylitis-free state (based on LEI). Measures of physical function (HAQ-DI response and SF 36 PCS scores) and disease activity (MDA) were also significant ranked secondary endpoints.

Structural progression was assessed as part of PA0010 ranked-secondary endpoints. Of the study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline from the Radiographic Set (RAS), the bimekizumab 160mg Q4W group had a minimal mean change from Baseline in vdHmTSS, whereas the placebo group worsened at Week 16 (0.04 vs 0.36, respectively; $p=0.001$); this difference was statistically significant and indicated inhibition of structural progression after treatment with bimekizumab.

In all study participants from the RAS, the bimekizumab 160mg Q4W group had a minimal mean change from Baseline in vdHmTSS, whereas the placebo group worsened at Week 16 (0.04 vs 0.32, respectively; $p=0.001$); this difference was statistically significant and indicated inhibition of structural progression. There was no evidence of worsening after 4 months of treatment with bimekizumab 160mg Q4W.

Upon CHMP's request, further data up to week 52 were provided by the MAH. At Week 52, the mean change from Baseline in vdHmTSS for the bimekizumab 160mg Q4W group was 0.10, indicating that the inhibition of structural progression observed with bimekizumab treatment was sustained. In study participants who switched from placebo to bimekizumab 160mg Q4W at Week 16, the mean change from Baseline in vdHmTSS at Week 52 was 0.19.

Noting that higher vdHmTSS scores indicated greater radiographic damage, no radiographic joint damage progression is defined as a change from baseline in mTSS of ≤0.5.

In general, at Week 16 and Week 52 in the bimekizumab 160mg Q4W group and Placebo/BKZ 160mg Q4W group a minimal mean change from Baseline in vdHmTSS was recorded. Change from baseline in mTSS of ≤0.5 was reported indicating that there was an inhibition of structural progression observed with bimekizumab treatment.

At Week 16 and Week 52 in the adalimumab group, numerical improvement in vdHmTSS score was reported. The mean change from Baseline at Week 16 in vdHmTSS for adalimumab was -0.14 and at Week 52 was -0.17.

Non-ranked secondary endpoints displayed efficacy across signs and symptoms in joints (ACR20/50/70) and skin (PASI75/90/100 and IGA 0/1), physical function (HAQ-DI response and SF-36 PCS scores, peripheral manifestations (enthesitis-free state, dactylitis-free state, and nail PSO [mNAPSI resolution]), axial involvement (BASDAI scores), inflammation (hs-CRP levels), PROs of fatigue (FACIT-Fatigue subscale scores), health-related QoL (PsAID-12 response), and social life and work productivity (EQ-5D-3L and WPAI-SHP).

Key endpoints are presented in the SmPC section 5.1 with the Pooled E1 data group and support treatment with bimekizumab 160mg Q4W for PsA across multiple joint and skin domains.

In PA0010, study participants treated with bimekizumab achieved clinically meaningful improvement across joint symptoms (including ACR20, ACR50, ACR70) that was comparable but numerically lower than to adalimumab and was numerically higher for skin symptoms (including PASI75, PASI90, PASI100, and IGA response) compared to adalimumab within 16 weeks of treatment. No formal statistical comparisons versus adalimumab were conducted. The MAH provided adequate rationale regarding the clinical significance of the numerically lower response seen in the PA0010 Bimekizumab 160mg Q4W arm compared to the adalimumab arm in the various efficacy endpoints including but not exclusive to the primary efficacy endpoint (ACR50 responder rate at Week 16), mean decrease from Baseline in HAQ-DI and ACR20/70. The rationale is agreed that comparisons of the adalimumab arm to the bimekizumab arm should be interpreted with caution given the study was not powered to make inferential comparisons between adalimumab and bimekizumab. Moreover, the sample size ratio of bimekizumab vs adalimumab was 3:1, and the numerical treatment differences could be due to variability in the data because of the lower number of study participants in the adalimumab arm. In addition, although the responses with bimekizumab treatment for several efficacy variables (except for skin-related variables, which were numerically higher with bimekizumab) were similar to or slightly numerically lower compared with adalimumab treatment at Week 16, long-term Week 52 data demonstrated a slightly higher or similar response for bimekizumab on most joint-related endpoints compared with adalimumab including ACR20/50/70, maintenance of ACR50, Minimal Disease Activity (MDA), very low disease activity (VLDA), and Disease Activity Index for Psoriatic Arthritis (DAPSA) responses.

Bimekizumab 160mg Q4W treatment showed improvements in response over time with ACR 20/50/70 response at Week 2 and 4, maintained up to Week 24 in PA0010 and Week 16 in PA0011. In both PA0010 and PA0011 the ACR 20/50/70 Week 2 responder rate was higher in the bimekizumab 160mg Q4W group compared with the placebo group across key variables with nominally significant p values. Participants with PSO involving at least 3% BSA at Baseline in both studies, the PASI75/90/100 responder rate was

higher in the bimekizumab 160mg Q4W group compared with the placebo group at Week 2 and increased through Week 16 and was higher compared with the placebo group at each time point. In the PA0010 study data (up to Week 52), the PASI75/90/100 responses with bimekizumab treatment continued to improve to Week 52.

Bimekizumab treatment resulted in low disease activity as demonstrated by almost half of the pooled Phase 3 study participants treated with bimekizumab 160mg Q4W achieved MDA response at Week 16 compared with approximately 10% of placebo study participants; this improvement was supported by the individual study results that showed statistically significant improvements in MDA response versus placebo at Week 16. Clinically meaningful improvements were also observed after bimekizumab treatment in several composite efficacy endpoints (ACR50/PASI90, VLDA, ACR50/PASI100 DAPSA, PASDAS, and PsARC responses).

Psoriatic arthritis has a notable effect on a patient's physical function and health-related outcomes. Bimekizumab treatment produced clinically meaningful improvements in disease manifestations such as the patients' perceived PsA-related pain and fatigue, and the impact of this pain and fatigue on their ability to function in daily life. This improvement was maintained over time.

Following treatment with bimekizumab 160mg Q4W, the marked improvements compared with placebo for both physician- and participant-assessed variables observed in the initial 16-week treatment period were sustained through Week 24 (PA0010).

For both PA0010 and PA0011 subgroup analysis, improvements in ACR50, PASI90, and HAQ-DI responses at Week 16 were observed for the bimekizumab 160mg Q4W group compared with the placebo group across a large number of subgroups that were generally considered clinically meaningful. Clinically relevant differences in efficacy response are observed for age and gender in the phase 2 and phase 3 clinical studies and these might be of relevance to the prescriber. The MAH was therefore requested to discuss whether the observed differences in response with regard to age and gender subgroups were to be mentioned in the SmPC, which was not considered needed following further discussion. It is agreed with the MAH that although lower efficacy in joint outcomes was observed in females and older patients, efficacy was observed was still clinically relevant as compared with placebo. In addition, this phenomenon is well known in the literature studies with other biologics in PsA. Thus, no update to the SmPC in relation to gender or age are warranted.

Similar improvements in efficacy were observed in study participants irrespective of whether they were receiving concomitant cDMARDs (MTX or other cDMARDs) or no cDMARDs. It should be noted that the sample sizes for some of the subgroup categories in the analyses were relatively small, and therefore interpretation of these data should be made with caution.

With the submission of updated PA0010 Week 52 data, additional efficacy data collected through the 36-week, Active Treatment-Blind Period of the completed PA0010 study demonstrated that efficacy outcomes achieved at Week 16 with bimekizumab 160mg Q4W either continued to improve or were sustained up to 1 year (Week 52).

PA0008 (Dose response study)

The results indicated dose-proportional PK of bimekizumab between the dose ranges studied (16mg, 160mg and 320mg), which is consistent with other PK studies of bimekizumab in different populations. Steady state was reached between weeks 16-20, which is consistent with bimekizumab half-life of ~28 days.

The primary efficacy analysis of the dose response for the primary efficacy variable (ACR50 response at Week 12) was evaluated for statistical significance using ordered categorical analysis with a corresponding p-value. Based on this procedure, data from PA0008 demonstrated that treatment with

bimekizumab across a range of doses (16mg to 320mg) administered Q4W resulted in a statistically significant dose response in ACR50 responder rates at Week 12.

The secondary efficacy analysis of pairwise comparisons between each bimekizumab dose group and placebo for the primary efficacy variable (ACR50 response at Week 12) was evaluated for statistical significance using a fixed sequence testing procedure from highest dose to lowest dose. Significantly better ACR50 responders rates at Week 12 were observed for the bimekizumab 16mg, 160mg, and 160mg w/LD doses vs placebo. At the highest bimekizumab dose tested, 320mg, a clinically relevant difference compared with placebo was observed (24.4% vs 7.1%), although this difference was not statistically significant.

The results of all secondary endpoints were consistent and supported the findings of the primary endpoint. All bimekizumab doses were associated with a greater response compared with placebo. A significant treatment response was consistently observed for the secondary endpoints in the bimekizumab 160mg w/LD group that was not observed across all secondary endpoints for the other bimekizumab dose groups. Thus, the Phase 3 PsA program utilized bimekizumab 160mg Q4W.

PA0009

Overall, the improvement in ACR response, PASI response, BSA, MDA and DAS28(CRP) was similar in PA0009 study participants who had received bimekizumab 160mg Q4W and bimekizumab 320mg Q4W at the completion of PA0008.

The key secondary endpoints had improvements from PA0008 Baseline observed at PA0008 completion that were maintained at Week 48 of PA0009. At Week 48 of PA0009, 79.0% of study participants were ACR20 responders (NRI), 64.6% of study participants were ACR50 responders (NRI), and 47.5% of study participants were ACR70 responders (NRI).

In general, other efficacy endpoints had improvements from PA0008 Baseline observed at PA0008 completion that were maintained through PA0009 visits. The ACR20 responder rates were high at the completion of PA0008 and maintained through PA0009 visits: 80.1% at PA0009 EV, 79.0% at Week 48, and 72.9% at Week 104 (NRI).

Approximately two-thirds of the study participants were ACR50 responders at the completion of PA0008 and this was maintained through PA0009 visits: 63.5% at PA0009 EV, 64.6% at Week 48, and 60.2% at Week 104 (NRI).

Approximately half of the study participants were ACR70 responders at the completion of PA0008 and this was maintained through PA0009: 45.3% at PA0009 EV, 47.5% at Week 48, and 44.8% at Week 104 (NRI).

Due to an error in the original PA0009 protocol schedule of assessments, the number of study participants with PASI OC data was extremely limited at some time points; however due to the correction in Protocol Amendment 3, data were available for nearly all study participants at the Week 104 visit.

The PASI75, PASI190, and PASI100 responder rates were high (88.3%, 80.0%, and 70.8%, respectively) at the completion of PA0008. Data for these endpoints was limited at several PA0009 visits. For visits with a meaningful sample size of data collected,

- the PASI75, PASI190, and PASI100 responder rates were maintained for:
- PASI75 (NRI) 88.3% at PA0009 EV, 76.7% at Week 24, and 79.2% at Week 104
- PASI90 (NRI) 80.0% at PA0009 EV, 70.8% at Week 24, and 73.3% at Week 104, and
- PASI100 (NRI)70.8% at PA0009 EV, 66.7% at Week 24, and 65.8% at Week 104.

Similar results were observed with additional supporting analyses, which were performed using BSA as a proxy for PASI response.

2.4.4. Conclusions on the clinical efficacy

In adult study participants with active PsA, the individual study data and integrated analyses demonstrate the consistent and clinically meaningful benefits of bimekizumab treatment for the overall study population and across all relevant subgroups.

Overall Bimekizumab demonstrated similar levels of response in both bDMARD naïve (PA0010) and TNFα-IR (PA0011) patient populations across multiple joint and skin domains. In both pivotal Phase 3 studies, participants receiving bimekizumab 160mg Q4W showed significant improvement in signs and symptoms of PsA disease within 16 weeks of treatment regardless of whether they were bDMARD-naïve or TNFα-IR.

The magnitude of improvement was consistent across both populations. Both studies met their primary objectives and demonstrated that treatment with bimekizumab 160mg Q4W was superior to placebo in statistically significant ($p<0.001$) and clinically meaningful improvements at Week 16 in signs and symptoms of disease activity, as measured by the ACR50 response (primary efficacy variable).

Both studies also met all of their ranked secondary efficacy objectives; bimekizumab treatment resulted in clinically meaningful and statistically superior improvements for all ranked secondary efficacy variables in the statistical hierarchies compared with placebo. Additionally, numerically greater improvements compared with placebo were observed for the non-ranked secondary efficacy endpoints following bimekizumab treatment. The results of all supportive analyses of the primary and secondary efficacy variables confirmed the results of the primary analyses, and subgroup analyses demonstrated consistent efficacy over placebo at Week 16 across multiple subgroups.

Across both studies, results demonstrated that bimekizumab 160mg Q4W treatment for 16 weeks resulted in improvements in multiple aspects of PsA disease, including improvement in joint and skin symptoms, improvement in multiple disease domains (eg, physical function and peripheral disease manifestations), low disease activity, and improvement in patient-reported outcomes of fatigue, HRQoL, and social life and work productivity Inhibition of structural damage in a bDMARD-naïve population was also shown (vdHmTSS assessment) in PA0010. Updated PA0010 Week 52 efficacy data demonstrated that efficacy outcomes achieved at Week 16 either continued to improve or were sustained up to 1 year (Week 52).

The development program supports the proposed posology of bimekizumab 160mg Q4W in patients with active PsA. In patients with active PsA who have moderate to severe plaque PSO, the proposed posology of bimekizumab 320mg Q4W for the first 16 weeks and Q8W thereafter is agreed. Nevertheless, to give the clinician flexibility in the treatment of patients with PsA and concomitant PSO who may not respond optimally to 320mg Q8W for joint symptoms in the maintenance phase, a switch to 160 Q4W in such patients has been accepted.

Given that the majority of subjects enrolled were taking MTX as their cDMARD and there was insufficient representation of patients receiving concomitant treatment with other csDMARDs, the indication has been updated to be restricted to "in combination with methotrexate".

2.5. Clinical safety

Introduction

Safety Datasets

The following integrated datasets were submitted to support the safety for the current application. The safety analysis for the bimekizumab PsA program included a review of safety data from 3 integrated safety pools (SP1, SP2, and S3) and from non-pooled studies (including studies in other indications).

Pool SP1

Pool SP1, the primary safety pool, compares bimekizumab 160mg (n=698) every 4 weeks (Q4W) with placebo (N=413) through Week 16 in 2 Phase 3 studies conducted in the PsA population. Combined data from the Initial Treatment Periods of PA0010 and PA0011 through Week 16 were included in this analysis.

Pool SP2

Pool SP2 summarises the safety of bimekizumab 160mg Q4W over extended dosing, including during open-label periods, in 2 Phase 2 and 3 Phase 3 studies (including 2 ongoing studies) conducted in the PsA population. This includes combined data from PA0010, and PA0011 and OLE study PA0012 from Initial Treatment Period, Maintenance Treatment Period, and OLE Treatment Period available at the time of the clinical data. In the initial application the interim analysis for Study PA0010 included all safety data available at the time of the Week 24 data cut (25 October 2021). At the Week 24 data cut, 75% of study participants in PA0010 had reached Week 52. Data from PA0012 through the cut-off date of 04 January 2022 were included.

Upon CHMP's request, the MAH has provided a Safety Update including all safety data from completed Phase 3 studies PA0010 (database lock 27 July 2022), and PA0011 (database lock 04 March 2022), along with all safety data entered into the OLE study PA0012 database as of the designated clinical cut-off date (20 May 2022). This Safety Update combined these Phase 3 data with the data from Phase 2 studies PA0008 and PA0009.

Pool S3

A safety Pool S3 consisted of combined data through Week 16 (i.e., the Initial Treatment Period) across indications in development for Phase 3 placebo-controlled studies in rheumatology (PsA [PA0010 and PA0011] and axial spondylarthritis [axSpA; AS0010 and AS0011]) and dermatology (psoriasis [PSO; PS0009 and PS0013]) to support the detection of adverse drug reactions (ADRs) to bimekizumab.

Table 67: Overview of safety pools

Pool name/ description	Studies included in pool	Treatment groups included in pool	Treatment periods included in pool	Purpose of pool
SP1	PA0010[a] PA0011	Study participants exposed to: • PBO • BKZ 160mg Q4W	Initial Treatment Period (Weeks 0-16)	Primary study pool to summarize safety of BKZ compared to PBO through Week 16 in the PsA population
SP2	PA0008 PA0009 PA0010[b] PA0011 PA0012	Participants exposed to: • Phase 3 BKZ 160mg Q4W[c] • Phase 2/3 BKZ 160mg Q4W[c] • BKZ total[d]	Initial Treatment Period Maintenance Treatment Period OLE Treatment Period	Provide the most comprehensive overview of safety data on BKZ in PsA population
S3	AS0010 AS0011 PA0010 PA0011 PS0009 PS0013	Study participants exposed to: Rheumatology[e] • PBO • BKZ 160mg Q4W Dermatology[f] • PBO • BKZ 320mg Q4W Overall • PBO • BKZ total[d]	Initial Treatment Period (Weeks 0-16)	Summarize safety of BKZ compared to PBO through Week 16 across BKZ development program for Phase 3 PBO-controlled studies in rheumatology (PsA, axSpA), and dermatology (PSO)

axSpA=axial spondyloarthritis, BKZ=bimekizumab; OLE=open-label extension; PBO=placebo, PsA=psoriatic arthritis, PSO=psoriasis, Q4W=every 4 weeks
[a] Study participants from the PA0010 adalimumab treatment group are not included in Pool SP1
[b] Data from study participants while receiving adalimumab in PA0010 are not included in Pool SP2 but their data from the PA0012 study were included if applicable
[c] BKZ 160mg Q4W treatment groups includes study participants with or without a 320mg loading dose at Baseline or participants who switched to bimekizumab 160mg Q4W at any point in the study
[d] Study participant exposure to other bimekizumab treatment groups will only be displayed in the BKZ total column
[e] Rheumatology includes studies PA0010, PA0011, AS0010, and AS0011
[f] Dermatology includes studies PS0009 and PS0013

The bimekizumab PsA program also included 1 device presentation study (DV0004). This compared the safe and effective use of the bimekizumab-SS-1mL (safety syringe) or the bimekizumab-AI (autoinjector)-1mL for the SC self-injection of bimekizumab solution by adult study participants with PsA and was conducted as a sub study (in North America and Europe) of the ongoing OLE study PA0012.

Demographic and other characteristics of study population

Demographics and disease characteristics

Reference is made to the efficacy section for a summary of demographics and disease characteristics of the studied PsA population.

Previous or ongoing medical history and concomitant medications

In Pool SP1, the majority of study participants (88.4% in the bimekizumab 160mg Q4W group and 88.1% in the placebo group) reported a previous or ongoing medical condition at Baseline. The most frequently reported conditions/diseases at Baseline in the 'all study' participants group were in the SOCs of Metabolism and nutrition disorders (54.3%), Vascular disorders (41.9%), and Musculoskeletal and connective tissue disorders (38.0%). Overall, the most frequently reported medical history conditions at Baseline were hypertension (37.9%), obesity (35.9%), and osteoarthritis (14.2%). The incidences of previous or ongoing medical history conditions at Baseline by PT were generally similar across groups apart from Blood and lymphatic system disorders (7.5% vs 4.9%) which were slightly higher in the placebo group compared with the bimekizumab 160mg Q4W group and Metabolism and nutrition

disorders (51.8% vs 55.7%) and Psychiatric disorders (15.0% vs 18.2%) which were slightly lower in the placebo group compared with the bimekizumab 160mg Q4W group.

Extra-articular medical history: Dactylitis (47.2% vs 43.6%) was slightly higher in the placebo group compared with the bimekizumab 160mg Q4W group. A total of 12 study participants had prior or ongoing IBD; the incidence was similar in the 2 treatment groups (1.0% in the bimekizumab 160mg Q4W group and 1.2% in the placebo group).

In Pool SP2 89.6% in the bimekizumab Total group reported a previous or ongoing medical condition at Baseline. The most frequently reported conditions/diseases at Baseline in the bimekizumab Total group were in the SOCs of Metabolism and nutrition disorders (52.3%), Vascular disorders (42.1%), and Musculoskeletal and connective tissue disorders (38.8%).

The most frequently reported medical history conditions at Baseline in the bimekizumab Total group were hypertension (38.1%), obesity (32.1%), and osteoarthritis (14.2%).

Extra-articular medical history: Dactylitis was reported by 45.5% of study participants in the bimekizumab Total group as a prior or ongoing condition. A total of 14 study participants (1.0%) had prior or ongoing IBD; however, for 1 of these participants, IBD was reported in error.

In Pool SP1 (98.3% in the bimekizumab 160mg Q4W group and 97.6% in the placebo group) reported use of concomitant medications. 59.7% of patients in the bimekizumab 160mg Q4W and 58.1% in the placebo group had used antineoplastic and immunomodulating agents including methotrexate and immunosuppressants for PsA.

In Pool SP2 98.8% reported use of prior medications. Antineoplastic and immunomodulating agents were used by 61.9% of the BKZ total population.

The demographic and Baseline characteristics of Pool SP2 in the Safety Update were similar to those in the original submission.

Patient exposure

Overall, in the PsA clinical development program, 698 study participants in the primary safety Pool SP1 and 1413 study participants in the more comprehensive updated Pool SP2 were exposed to bimekizumab with total times at risk accounting for 218.7 and 2664.0 participant-years, respectively. As of the updated clinical cut-off date, study medication exposures of at least 12 months were achieved by 968, 1143, and 1147 study participants in the Phase 3 bimekizumab 160mg Q4W, Phase 2/3 bimekizumab 160mg Q4W, and bimekizumab Total groups, respectively.

Table 68: Study medication duration and participant-years of time at risk during the Initial Treatment Period (Pool SP1)

	Placebo N=413	BKZ 160mg Q4W N=698
Study medication duration (days)		
n	413	698
Mean (SD)	109.1 (13.94)	110.4 (9.68)
Median	112.0	112.0
Min, Max	14, 121	26, 133
Total time at risk (participant-years)	128.5	218.7

BKZ=bimekizumab; ISS=Integrated Summary of Safety; Max=maximum; Min=minimum; Q4W=every 4 weeks; SD=standard deviation

Table 69: Study medication duration and participant-years of time at risk during the combined Initial, Maintenance, and OLE Treatment Period (Pool SP2)

	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=1197	Phase 2/3 BKZ 160mg Q4W N=1395	BKZ Total N=1401	Phase 3 BKZ 160mg Q4W N=1209	Phase 2/3 BKZ 160mg Q4W N=1407	BKZ Total N=1413
Study drug duration (days)						
n	1197	1395	1401	1209	1407	1413
Mean (SD)	490.7 (247.56)	535.8 (275.45)	552.2 (295.34)	618.3 (272.30)	645.0 (281.04)	660.8 (294.52)
Median	505.0	602.0	607.0	617.0	721.0	727.0
Min, Max	1, 955	1, 1092	1, 1107	12, 1087	12, 1092	12, 1107
Duration of exposure (months), n (%)						
>0	1197 (100)	1395 (100)	1401 (100)	1209 (100)	1407 (100)	1413 (100)
≥4	1094 (91.4)	1285 (92.1)	1289 (92.0)	1152 (95.3)	1343 (95.5)	1347 (95.3)
≥8	933 (77.9)	1117 (80.1)	1124 (80.2)	1085 (89.7)	1269 (90.2)	1276 (90.3)
≥12	811 (67.8)	986 (70.7)	990 (70.7)	968 (80.1)	1143 (81.2)	1147 (81.2)
≥16	619 (51.7)	790 (56.6)	793 (56.6)	812 (67.2)	983 (69.9)	986 (69.8)
≥20	537 (44.9)	702 (50.3)	707 (50.5)	647 (53.5)	812 (57.7)	817 (57.8)
≥24	294 (24.6)	457 (32.8)	462 (33.0)	541 (44.7)	704 (50.0)	709 (50.2)
≥36	0	2 (0.1)	5 (0.4)	1 (<0.1)	3 (0.2)	6 (0.4)
Total time at risk (participant-years)	1647.9	2144.4	2217.5	2094.4	2590.8	2664.0

BKZ=bimekizumab; DBL=database lock; ISS=Integrated Summary of Safety; Max=maximum; Min=minimum; OLE=Open-Label Extension; Q4W=every 4 weeks; SD=standard deviation; SFU=Safety Follow-Up

Note: For duration of exposure, 1 month is defined as 30 days.

Note: Treatment groups are defined as follows:

- Phase 3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during PA0010, PA0011, and PA0012
- Phase 2/3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during the Phase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (including study participants in PA0008 with a bimekizumab 320mg loading dose at Baseline)
- The BKZ Total treatment group includes data from all study participants while treated with any bimekizumab regimen during PA0008, PA0009, PA0010, PA0011, and PA0012 (including the limited exposures to bimekizumab 16mg Q4W and 320mg Q4W in Phase 2 PA0008).

[a] The original submission is based on the following data cut off date: 04 Jan 2022.

[b] The Safety Update is based on the following data cut off dates: PA0010 27 Jul 2022 (SFU Period DBL), PA0011 04 Mar 2022 (SFU Period DBL), and PA0012 20 May 2022 (last Week 52 Visit of PA0010).

Adverse events

Safety results are presented for two separate time periods: the initial placebo-controlled period up to Week 16 (Pool SP1) and Pool SP2 up to the data cut-off dates for Studies PA0010 and PA0012.

Table 70: Overview of TEAEs during the Initial Treatment Period (Pool SP1)

	Placebo N=413 100 participant-yrs=1.28 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=698 100 participant-yrs=2.19 n (%) [#] EAIR (95% CI)
Any TEAEs	183 (44.3) [353] 198.0 (170.4, 228.9)	365 (52.3) [801] 245.9 (221.3, 272.5)
Serious TEAEs	3 (0.7) [3] 2.3 (0.5, 6.9)	12 (1.7) [13] 5.5 (2.9, 9.7)
Study participant discontinuations due to TEAEs	3 (0.7) [3] 2.3 (0.5, 6.9)	10 (1.4) [14] 4.6 (2.2, 8.5)
Permanent withdrawal of study medication due to TEAEs	3 (0.7) [3] 2.3 (0.5, 6.9)	10 (1.4) [14] 4.6 (2.2, 8.5)
Drug-related TEAEs	39 (9.4) [47] 32.2 (22.9, 44.0)	136 (19.5) [221] 70.1 (58.8, 82.9)
Severe TEAEs	0	9 (1.3) [10] 4.1 (1.9, 7.9)
All deaths (AEs leading to death)	0	0
Deaths (TEAEs leading to death)	0	0

AE=adverse event; BKZ=bimekizumab; 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.

Table 71: Overview of TEAEs during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SP2)

	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=1197 100 participant-yrs=16.48 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=1395 100 participant-yrs=21.44 n (%) [#] EAIR (95% CI)	BKZ Total N=1401 100 participant-yrs=22.18 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=1209 100 participant-yrs=20.94 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=1407 100 participant-yrs=25.91 n (%) [#] EAIR (95% CI)	BKZ Total N=1413 100 participant-yrs=26.64 n (%) [#] EAIR (95% CI)
Any TEAEs	896 (74.9) [3868] 147.2 (137.7, 157.2)	1067 (76.5) [4722] 141.3 (133.0, 150.1)	1081 (77.2) [4940] 143.5 (135.1, 152.3)	999 (82.6) [4825] 144.4 (135.6, 153.6)	1170 (83.2) [5679] 139.6 (131.7, 147.8)	1184 (83.8) [5897] 141.5 (133.6, 149.8)
Serious TEAEs	105 (8.8) [149] 6.7 (5.5, 8.1)	127 (9.1) [175] 6.2 (5.2, 7.4)	127 (9.1) [175] 6.0 (5.0, 7.2)	126 (10.4) [174] 6.4 (5.3, 7.6)	148 (10.5) [200] 6.1 (5.1, 7.1)	148 (10.5) [200] 5.9 (5.0, 6.9)
Study participant discontinuations due to TEAEs	51 (4.3) [66] 3.1 (2.3, 4.1)	66 (4.7) [81] 3.1 (2.4, 4.0)	67 (4.8) [82] 3.1 (2.4, 3.9)	64 (5.3) [79] 3.1 (2.4, 3.9)	79 (5.6) [94] 3.1 (2.4, 3.8)	80 (5.7) [95] 3.0 (2.4, 3.8)
Permanent withdrawal of study drug due to TEAEs	50 (4.2) [61] 3.1 (2.3, 4.0)	65 (4.7) [77] 3.1 (2.4, 3.9)	67 (4.8) [80] 3.1 (2.4, 3.9)	67 (5.5) [75] 3.2 (2.5, 4.1)	82 (5.8) [91] 3.2 (2.5, 4.0)	84 (5.9) [94] 3.2 (2.5, 3.9)
Drug-related TEAEs	380 (31.7) [927] 30.5 (27.5, 33.7)	459 (32.9) [1172] 28.9 (26.3, 31.6)	477 (34.0) [1233] 29.6 (27.0, 32.4)	425 (35.2) [1099] 27.5 (25.0, 30.3)	504 (35.8) [1344] 26.7 (24.4, 29.1)	522 (36.9) [1405] 27.3 (25.0, 29.8)
Severe TEAEs	70 (5.8) [86] 4.4 (3.4, 5.5)	82 (5.9) [101] 3.9 (3.1, 4.9)	84 (6.0) [105] 3.9 (3.1, 4.8)	78 (6.5) [100] 3.8 (3.0, 4.8)	90 (6.4) [115] 3.6 (2.9, 4.4)	92 (6.5) [119] 3.6 (2.9, 4.4)
All deaths (AEs leading to death)[c]	3 (0.3) [3] 0.2 (0.0, 0.5)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)
Deaths (TEAEs leading to death)	3 (0.3) [3] 0.2 (0.0, 0.5)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)

AE=adverse event; BKZ=bimekizumab; CI=confidence interval; DBL=database lock; EAIR=exposure-adjusted incidence rate; ISS=Integrated Summary of Safety; OLE=open-label extension; Q4W=every 4 weeks; serious TEAE=serious treatment-emergent adverse event; SFU=Safety Follow-Up; 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.
Note: Treatment groups are defined as follows:
• Phase 3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during PA0010,PA0011, and PA0012
• Phase 2/3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during thePhase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (including study participants in PA0008 with a bimekizumab 160mg loading dose at Baseline)
• The BKZ Total treatment group includes data from all study participants while treated with any bimekizumab regimen during PA0008, PA0009,PA0010, PA0011, and PA0012 (including the limited exposures to bimekizumab 16mg Q4W and 160mg Q4W in Phase 2 PA0008).
a The original submission is based on the following data cut off date: 04 Jan 2022.
b The Safety Update is based on the following data cut off dates: PA0010 27 Jul 2022 (SFU Period DBL), PA0011 04 Mar 2022 (SFU Period DBL), andPA0012 20 May 2022 (last Week 52 Visit of PA0010).
c Note that EAIRs from the "All deaths (AEs leading to death)" line were not calculated and were replicated from the "Deaths (TEAEs leading to death)" row.

Common TEAEs

Initial Treatment Period (Pool SP1)

TEAEs were most often reported in the Infections and infestations SOC, followed by the Gastrointestinal disorders SOC, Musculoskeletal SOC, Nervous System Disorders SOC and Vascular Disorders SOC. The most frequently reported TEAEs by PT in the bimekizumab 160mg Q4W group were nasopharyngitis (7.2%), upper respiratory tract infection (3.9%), headache (3.6%), diarrhoea (2.7%), and oral candidiasis (2.3%). Results (common TEAEs reported in ≥2% of study participants) are shown for the primary PsA Set up to week 16:

Table 72: Incidence of TEAEs per 100 participant-years in ≥2% of participants by PT in any treatment group during the Initial Treatment Period (Pool SP1)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=413 100 participant-yrs=1.28 n (%) [#] EAIR (95% CI)	BKZ 160mg Q4W N=698 100 participant-yrs=2.19 n (%) [#] EAIR (95% CI)
Any TEAE	183 (44.3) [353] 198.0 (170.4, 228.9)	365 (52.3) [801] 245.9 (221.3, 272.5)
Gastrointestinal disorders	24 (5.8) [31] 19.3 (12.4, 28.8)	76 (10.9) [101] 37.0 (29.2, 46.3)
Diarrhoea	8 (1.9) [9] 6.3 (2.7, 12.4)	19 (2.7) [20] 8.8 (5.3, 13.8)
Infections and infestations	73 (17.7) [89] 62.8 (49.3, 79.0)	189 (27.1) [267] 100.7 (86.8, 116.1)
Oral candidiasis	0	16 (2.3) [19] 7.4 (4.2, 12.0)
Nasopharyngitis	14 (3.4) [15] 11.1 (6.1, 18.6)	50 (7.2) [55] 23.8 (17.7, 31.4)
Upper respiratory tract infection	20 (4.8) [20] 15.9 (9.7, 24.6)	27 (3.9) [30] 12.6 (8.3, 18.3)
Urinary tract infection	7 (1.7) [8] 5.5 (2.2, 11.3)	14 (2.0) [15] 6.5 (3.5, 10.8)
Musculoskeletal and connective tissue disorders	40 (9.7) [50] 33.0 (23.6, 44.9)	39 (5.6) [51] 18.5 (13.1, 25.3)
Arthralgia	9 (2.2) [10] 7.1 (3.2, 13.4)	8 (1.1) [8] 3.7 (1.6, 7.3)
Psoriatic arthropathy	9 (2.2) [9] 7.1 (3.2, 13.5)	4 (0.6) [4] 1.8 (0.5, 4.7)
Nervous system disorders	15 (3.6) [16] 12.0 (6.7, 19.8)	32 (4.6) [38] 15.0 (10.3, 21.2)
Headache	7 (1.7) [7] 5.5 (2.2, 11.4)	25 (3.6) [27] 11.7 (7.5, 17.2)
Vascular disorders	16 (3.9) [17] 12.7 (7.3, 20.7)	18 (2.6) [19] 8.3 (4.9, 13.2)
Hypertension	14 (3.4) [15] 11.1 (6.1, 18.7)	15 (2.1) [16] 6.9 (3.9, 11.4)

Pool SP2

In Pool SP2, during the combined Initial, Maintenance, and OLE Treatment Period, TEAEs were reported in 77.2% (EAIR: 143.5/100 participant-years) study participants. Treatment-emergent AEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (52.5%), Gastrointestinal disorders (20.8%), Musculoskeletal and connective tissue disorders (17.8%), and Skin and subcutaneous tissue disorders (16.8%). Of the commonly reported TEAEs in Pool SP2, the most frequently reported TEAEs by PT were nasopharyngitis (11.4%), upper respiratory tract infection (8.9%), corona virus infection (7.0%), and oral candidiasis and urinary tract infection (6.7% each).

Pool SP2 Safety Update

TEAEs were reported for 83.8% (EAIR: 141.5/100 participant-years) of study participants. Treatment-emergent AEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (60.4%), Gastrointestinal disorders (22.9%), Musculoskeletal and connective tissue disorders (20.7%), and Skin and subcutaneous tissue disorders (19.5%). Of the commonly reported TEAEs in Pool SP2, the most frequently reported TEAEs by PT were corona virus infection (14.2%),

nasopharyngitis (13.4%), upper respiratory tract infection (10.0%), urinary tract infection (7.9%), and oral candidiasis (7.5%)

Table 73: Incidence of TEAEs in at least 2% of participants by PT in any treatment group during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SP2)

	Data in original submission[a]			Data in Safety Update[b]		
MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=1197 100 participant-yrs=16.48 n (%) [#]	Phase 2/3 BKZ 160mg Q4W N=1395 100 participant-yrs=21.44 n (%) [#]	BKZ Total N=1401 100 participant-yrs=22.18 n (%) [#]	Phase 3 BKZ 160mg Q4W N=1209 100 participant-yrs=20.94 n (%) [#]	Phase 2/3 BKZ 160mg Q4W N=1407 100 participant-yrs=25.91 n (%) [#]	BKZ Total N=1413 100 participant-yrs=26.64 n (%) [#]
Any TEAE	896 (74.9) [3868]	1067 (76.5) [4722]	1081 (77.2) [4940]	999 (82.6) [4825]	1170 (83.2) [5679]	1184 (83.8) [5897]
Blood and lymphatic system disorders	64 (5.3) [98]	82 (5.9) [123]	86 (6.1) [128]	72 (6.0) [111]	90 (6.4) [136]	94 (6.7) [141]
Neutropenia	22 (1.8) [27]	27 (1.9) [33]	28 (2.0) [34]	24 (2.0) [32]	29 (2.1) [38]	30 (2.1) [39]
Gastrointestinal disorders	242 (20.2) [384]	281 (20.1) [456]	291 (20.8) [472]	275 (22.7) [445]	314 (22.3) [517]	324 (22.9) [533]
Diarrhoea	63 (5.3) [71]	67 (4.8) [76]	70 (5.0) [79]	71 (5.9) [81]	75 (5.3) [86]	78 (5.5) [89]
Nausea	33 (2.8) [36]	35 (2.5) [38]	35 (2.5) [38]	39 (3.2) [42]	41 (2.9) [44]	41 (2.9) [44]
Stomatitis	22 (1.8) [23]	30 (2.2) [35]	32 (2.3) [38]	23 (1.9) [24]	31 (2.2) [36]	33 (2.3) [39]
General disorders and administration site conditions	112 (9.4) [186]	122 (8.7) [196]	129 (9.2) [204]	121 (10.0) [204]	131 (9.3) [214]	138 (9.8) [222]
Fatigue	25 (2.1) [27]	27 (1.9) [29]	28 (2.0) [31]	27 (2.2) [29]	29 (2.1) [31]	30 (2.1) [33]
Infections and infestations	588 (49.1) [1277]	718 (51.5) [1651]	735 (52.5) [1746]	707 (58.5) [1665]	837 (59.5) [2039]	854 (60.4) [2134]
Oral candidiasis	75 (6.3) [118]	91 (6.5) [154]	94 (6.7) [158]	87 (7.2) [140]	103 (7.3) [176]	106 (7.5) [180]
Conjunctivitis	23 (1.9) [25]	31 (2.2) [34]	33 (2.4) [36]	30 (2.5) [35]	38 (2.7) [44]	40 (2.8) [46]
Oral fungal infection	24 (2.0) [33]	35 (2.5) [49]	38 (2.7) [52]	25 (2.1) [34]	36 (2.6) [50]	39 (2.8) [53]
Bronchitis	31 (2.6) [34]	48 (3.4) [57]	50 (3.6) [60]	37 (3.1) [40]	54 (3.8) [63]	56 (4.0) [66]
Nasopharyngitis	123 (10.3) [155]	151 (10.8) [194]	160 (11.4) [208]	152 (12.6) [196]	180 (12.8) [235]	189 (13.4) [249]
Upper respiratory tract infection	90 (7.5) [108]	119 (8.5) [149]	124 (8.9) [160]	107 (8.9) [135]	136 (9.7) [176]	141 (10.0) [187]
Pharyngitis	39 (3.3) [54]	52 (3.7) [69]	56 (4.0) [76]	49 (4.1) [65]	62 (4.4) [80]	66 (4.7) [87]
Sinusitis	42 (3.5) [52]	57 (4.1) [69]	59 (4.2) [75]	48 (4.0) [59]	63 (4.5) [76]	65 (4.6) [82]
Tonsillitis	13 (1.1) [15]	25 (1.8) [27]	27 (1.9) [29]	18 (1.5) [22]	30 (2.1) [34]	32 (2.3) [36]
Rhinitis	19 (1.6) [19]	24 (1.7) [24]	26 (1.9) [26]	23 (1.9) [23]	28 (2.0) [28]	30 (2.1) [30]
Urinary tract infection	84 (7.0) [116]	93 (6.7) [129]	94 (6.7) [130]	101 (8.4) [142]	110 (7.8) [155]	111 (7.9) [156]
Corona virus infection	100 (8.4) [104]	100 (7.2) [104]	100 (7.1) [104]	201 (16.6) [214]	201 (14.3) [214]	201 (14.2) [214]
Investigations	160 (13.4) [283]	187 (13.4) [345]	196 (14.0) [364]	198 (16.4) [361]	225 (16.0) [423]	234 (16.6) [442]
Alanine aminotransferase increased	29 (2.4) [34]	40 (2.9) [49]	42 (3.0) [52]	34 (2.8) [41]	45 (3.2) [56]	47 (3.3) [59]
Aspartate aminotransferase increased	22 (1.8) [23]	31 (2.2 [34]	32 (2.3) [37]	32 (2.6) [35]	41 (2.9) [46]	42 (3.0) [49]
Gamma-glutamyltransferase increased	24 (2.0) [30]	31 (2.2) [40]	32 (2.3) [42]	28 (2.3) [34]	35 (2.5) [44]	36 (2.5) [46]
Metabolism and nutrition disorders	92 (7.7) [120]	109 (7.8) [143]	111 (7.9) [145]	117 (9.7) [152]	134 (9.5) [175]	136 (9.6) [177]
Hypercholesterolaemia	17 (1.4) [17]	23 (1.6) [23]	25 (1.8) [25]	28 (2.3) [28]	34 (2.4) [34]	36 (2.5) [36]
Musculoskeletal and connective tissue disorders	200 (16.7) [334]	244 (17.5) [400]	249 (17.8) [413]	243 (20.1) [422]	287 (20.4) [488]	292 (20.7) [501]
Arthralgia	34 (2.8) [45]	38 (2.7) [52]	40 (2.9) [54]	42 (3.5) [57]	46 (3.3) [64]	48 (3.4) [66]
Back pain	44 (3.7) [52]	46 (3.3) [54]	48 (3.4) [56]	53 (4.4) [62]	55 (3.9) [64]	57 (4.0) [66]
Psoriatic arthropathy	33 (2.8) [39]	47 (3.4) [54]	49 (3.5) [57]	40 (3.3) [48]	54 (3.8) [63]	56 (4.0) [66]
Nervous system disorders	124 (10.4) [164]	145 (10.4) [187]	146 (10.6) [194]	144 (11.9) [192]	165 (11.7) [215]	169 (12.0) [222]
Headache	55 (4.6) [64]	59 (4.2) [68]	60 (4.3) [69]	68 (5.6) [80]	72 (5.1) [84]	73 (5.2) [85]
Respiratory, thoracic and mediastinal disorders	84 (7.0) [105]	94 (6.7) [116]	101 (7.2) [125]	111 (9.2) [139]	121 (8.6) [150]	128 (9.1) [159]
Cough	12 (1.0) [13]	16 (1.1) [17]	18 (1.3) [19]	25 (2.1) [26]	29 (2.1) [30]	31 (2.2) [32]
Skin and subcutaneous tissue disorders	177 (14.8) [262]	228 (16.3) [338]	235 (16.8) [348]	217 (17.9) [327]	268 (19.0) [403]	275 (19.5) [413]
Psoriasis	23 (1.9) [27]	38 (2.7) [44]	39 (2.8) [46]	35 (2.9) [41]	50 (3.6) [58]	51 (3.6) [60]
Rash	21 (1.8) [23]	27 (1.9) [29]	28 (2.0) [30]	26 (2.2) [29]	32 (2.3) [35]	33 (2.3) [36]
Vascular disorders	62 (5.2) [71]	72 (5.2) [83]	75 (5.4) [86]	81 (6.7) [94]	91 (6.5) [106]	94 (6.7) [109]
Hypertension	43 (3.6) [47]	48 (3.4) [53]	50 (3.6) [55]	56 (4.6) [61]	61 (4.3) [67]	63 (4.5) [69]

Table 74: Treatment-emergent AEs by time of onset relative to start of bimekizumab treatment for the combined Initial and Maintenance Treatment Periods (Pool SP2)

Treatment group	Treatment duration		
	>0 to 16 weeks n (%) [#]	>16 to ≤32 weeks n (%) [#]	>32 to ≤48 weeks n (%) [#]
Phase 3 BKZ 160mg Q4W (N)	1197	1132	989
Any TEAE	587 (49.0) [1211]	468 (41.3) [909]	333 (33.7) [600]
Phase 2/3 BKZ 160mg Q4W (N)	1395	1329	1180
Any TEAE	670 (48.0) [1365]	546 (41.1) [1067]	408 (34.6) [722]
BKZ Total (N)	1401	1335	1185
Any TEAE	681 (48.6) [1406]	556 (41.6) [1095]	427 (36.0) [754]

BKZ=bimekizumab; ISS=Integrated Summary of Safety; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event

Note: n=number of study participants reporting at least 1 TEAE.

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

Note: The exposure duration categories represent duration of exposure to BKZ, not time in study.

Note: Treatment groups are defined as follows:

- Phase 3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during PA0010, PA0011, and PA0012
- Phase 2/3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during the Phase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (including study participants in PA0008 with a bimekizumab 320mg loading dose at Baseline)
- The BKZ Total treatment group includes data from all study participants while treated with any bimekizumab regimen during PA0008, PA0009, PA0010, PA0011, and PA0012 (including the limited exposures to bimekizumab 16mg Q4W and 320mg Q4W in Phase 2 PA0008).

Pool SP2 Safety Update

Longer exposure to bimekizumab was associated with an increase incidence of TEAEs and SAEs from week 52. The incidence of TEAEs and SAEs during 16-week intervals over the duration of the studies up to week 52 were similar to the original safety analysis. From week 52 there is an increase in incidence of TEAEs and SAEs. For the Total BZK population TEAE Onset by time period was as follows: >0-<=16 weeks n= 693 (**49.0**%); >16-<=32 weeks n=607 (**43.7**%) vs >32-<=48 weeks n= 521 (**39.4%**) >48 weeks n=748 (**62.7**%). Similar pattern was seen for Any Serious TEAE n= 27 (**1.9**%) vs n= 34 (**2.4**%) vs n=27 (**2.0**%) vs n= 78 vs (**6.5**%) for the same 16 week time intervals.

TEAEs by timing of onset relative to the COVID-19 pandemic

Pooled analyses of TEAEs by timing of onset relative to the COVID-19 pandemic (defined as having started on 11 March 2020 and continuing until the official declared end of the pandemic) were performed to evaluate the eventual impact of the pandemic on the reported safety profile.

In Pool SP1, for the bimekizumab 160mg Q4W group, the EAIRs were higher for TEAEs with onset prior to (274.3/100 participant-years) than during (219.4/100 participant-years) the pandemic. For the placebo group, the EAIRs were lower for TEAEs with onset prior to (189.5/100 participant-years) than during (217.1/100 participant-years) the pandemic.

In Pool SP2, EAIRs were higher for TEAEs with onset prior to (193.1/100 participant-years) than during (121.2/100 participant-years) the pandemic.

In Pool SP1, the EAIRs for the SOC Infections and infestations were lower during the pandemic (45.7/100 participant-years in the placebo group and 73.4/100 participant/years in the bimekizumab 160mg Q4W group) than prior to it (80.9/100 participant-years in the placebo group and EAIR 129.9/100 participant/years in the bimekizumab 160mg Q4W group).

– The highest imbalance at the HLT level was in the HLT Upper respiratory tract infections, with an EAIR of 73.5 prior to the pandemic compared with 27.2 during the pandemic in the bimekizumab 160mg Q4W group.

– For the majority of PTs within this SOC, with the exception of oral candidiasis, the incidences and EAIRs rates tend to be lower during the pandemic than prior to it in both treatment groups.

For Pool SP2, for the SOC Infections and infestations, in the bimekizumab Total group the EAIRs were lower during the pandemic (49.9/100 participant-years) than prior to the pandemic (86.7/100 participant-years).

– The highest imbalance at the HLT level was in the HLT Upper respiratory tract infections, with an EAIR of 41.0 prior to the pandemic compared with 15.4 during the pandemic in the bimekizumab Total group.

– For the majority of PTs within this SOC, with the exception of oral candidiasis, the incidences and EAIRs rates tend to be lower during the pandemic then prior to it.

Overview of TEAEs by COVID-19 period SP2 safety update

The EAIR was higher for TEAEs with onset prior to (272.8/100 participant-years) than during (125.0/100 participant-years) the pandemic. On a SOC level, the most notable difference occurred within the SOC of Infections and infestations, with the highest imbalances for the HLT of Upper respiratory tract infections.

For Pool SP2 in the Phase 3 bimekizumab 160mg Q4W group, for the SOC of Infections and infestations, the EAIRs were lower during the pandemic (53.5/100 participant-years) than prior to the pandemic (129.8/100 participant-years).

– The highest imbalance at the HLT level was in the HLT of Upper respiratory tract infections, with an EAIR of 67.7/100 participant-years prior to the pandemic compared with 16.2/100 participant-years during the pandemic in the Phase 3 bimekizumab 160mg Q4W group.

– For the majority of PTs within this SOC, the incidences and EAIRs tended to be lower during the pandemic than prior to it.

COVID-19 infections

The incidence of TEAEs with the PT of corona virus infection were similar in the placebo (1.5% EAIR: 4.7/100 participant-years) and bimekizumab 160mg Q4W (0.7% EAIR: 2.3/100 participant-years) groups in Pool SP1.

In Pool SP2 the incidence of TEAEs with the PT of corona virus infection was 7.5% (EAIR: 4.9/100 participant-years) in the bimekizumab Total group reflecting the increased prevalence of COVID-19 infection over time during the conduct of these studies.

There were no serious TEAEs with the PT of corona virus infection in Pool SP1.

The incidence of serious TEAEs with the PT of corona virus infection in the bimekizumab Total group in Pool SP2 was 0.4% (EAIR: 0.3/100 participant-years). None of the serious TEAEs were considered to be related to study medication. Two other serious TEAEs attributed to COVID-19 were identified following manual review of COVID terms. In Pool SP1, 1 study participant reported a serious TEAE of pneumonia (verbatim term: COVID-pneumonia confirmed); this participant was also included in Pool SP2. In Pool SP2, 1 participant had a serious TEAE that was uncoded at the time of data cut (verbatim term: acute

respiratory failure due to severe acute respiratory syndrome COVID-19 infection). None of the serious TEAEs were fatal or considered to be related to study medication. All but 1 were reported as recovered/resolved at the time of data cut; 1 was reported as recovering.

Of the 8 serious TEAEs of corona virus infection and those attributed to COVID-19 but having a different PT, all occurred in study participants who were unvaccinated (data on file). No COVID-19 infections resulted in study discontinuation.

In addition, during the course of the PsA studies, vaccinations for COVID-19 became available. The incidence of COVID-19 vaccinations was higher in Pool SP2 than in Pool SP1; this reflects the increased availability of COVID-19 vaccinations over time during the conduct of these studies.

Pool SP2 safety update

The incidence of TEAEs with the PT of corona virus infection was 14.2% (EAIR: 8.0/100 participant-years) in the bimekizumab Total group in Pool SP2. One additional serious TEAE with the PT of corona virus infection was reported; the event was resolved and did not lead to discontinuation. The incidence of serious TEAEs with the PT of corona virus infection in the bimekizumab Total group in Pool SP2 was 0.5% (EAIR: 0.3/100 participant-years).

Severity

The majority of TEAEs were mild or moderate in intensity in Pool SP1 and Pool SP2.

In Pool SP1, the incidence of severe TEAEs was 1.3%; (EAIR 4.1/100 participant-years) in the bimekizumab 160mg Q4W group and 0% in the placebo group. No severe TEAEs, by PT, were reported by >1 study participant (0.1%). The severe TEAEs reported for the bimekizumab 160mg Q4W group were neutropenia, stomatitis, bronchitis, pneumonia, limb injury, back pain, toxic encephalopathy, headache, renal pain, and pruritus. None of the severe TEAEs led to discontinuation.

In Pool SP2, the incidence of severe TEAEs was 6.0% (EAIR 3.9/100 participant-years) in the bimekizumab Total group. Severe TEAEs in the bimekizumab Total group were most frequently reported in the SOC of infections and infestations (1.1%). A total of 10 severe TEAEs were reported by more than 1 study participant in the bimekizumab Total group. These TEAEs include corona virus infection (0.2%), osteoarthritis (0.2%), acute myocardial infarction and ischemic stroke (2 cases, 0.1% each), and neutropenia, herpes zoster, pneumonia, aspartate aminotransferase increased, alanine aminotransferase increased, and arthralgia (2 cases, 0.1% each); twelve of the severe TEAEs led to discontinuation.

Pool SP2 Safety Update

The majority of TEAEs in Pool SP2 were mild or moderate in intensity. The incidence of severe TEAEs in this Safety Update Pool SP2 was 6.5% (EAIR 3.6/100 participant-years) in the bimekizumab Total group. Severe TEAEs in the bimekizumab Total group were most frequently reported in the SOC of infections and infestations (1.1%).

Relatedness

In Pool SP1 the incidence of drug related TEAEs (as assessed by the Investigator) was higher in the bimekizumab 160mg Q4W group (19.5%) compared with the placebo group (9.4%). The most commonly reported drug related TEAE was oral candidiasis which was only reported in the bimekizumab 160mg Q4W group (2.0%). The other frequently reported drug related TEAEs reported in the bimekizumab 160mg Q4W group were upper respiratory tract infection (1.6%) and nasopharyngitis (1.4%); the incidences of these events were similar in the bimekizumab 160mg Q4W group and the placebo groups.

In Pool SP2, 34.0% in the Phase 3 bimekizumab Total group reported at least 1 TEAE which was considered drug-related by the Investigator. A total of 14 drug-related TEAEs by PT were reported in at

least 1% of study participants in the bimekizumab Total group; the most commonly reported drug-related TEAEs in this group were oral candidiasis (5.4%), nasopharyngitis (2.6%), upper respiratory tract infection (2.5%), and oral fungal infection (2.4%).

Pool SP2 Safety Update

The Safety Update data showed similar trends to the original submission data; the EAIR for any related TEAE in the bimekizumab Total group was 27.3/100 participant-years compared with 29.6/100 participant-years in the original submission. In Safety Update Pool SP2, approximately one-third of the study participants (36.9%) in the bimekizumab Total group reported at least 1 TEAE which was considered drug related by the Investigator. The most commonly reported drug-related TEAE in this group was oral candidiasis (6.1%)

Adverse events for labelling

Determination of ADRs for labelling

A medical review of TEAEs from Pool S3 (Overall - Phase 3 16-week placebo-controlled period in PsA, axSpA, and PSO) and Pool SP1 (Phase 3 placebo-controlled studies in PsA) was performed in accordance with the strategy described below:

• TEAEs from Pool S3 with a reported incidence ≥1% higher in the bimekizumab Total group compared with placebo.

• TEAEs from Pool S3, which do not meet the threshold of ≥1% over placebo at PT level but at HLT level show a ≥1% higher incidence over placebo (considering synonyms and related group terms).

• TEAEs that are >1% higher than placebo in Pool SP1 that are biologically plausible based on mechanism of action and upon medical review are considered causally related (i.e., ADRs to bimekizumab).

Table 75: TEAEs with an incidence in the bimekizumab Total group of at least 1% higher than the placebo group during the Initial Treatment Period overall (Pool S3)

MedDRA v19.0 System Organ Class Preferred Term	Placebo N=819 n (%)	BKZ Total N=1717 n (%)
Infections and infestations		
Nasopharyngitis	35 (4.3) [37]	132 (7.7) [150]
Oral candidiasis	0	78 (4.5) [87]
Pharyngitis	6 (0.7) [8]	32 (1.9) [39]
Nervous system disorders		
Headache	14 (1.7) [17]	59 (3.4) [64]

BKZ=bimekizumab; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the TEAE.

The AEs that occurred at least 1% more frequently in the bimekizumab Total group than in the placebo group, based on Pool S3, which included the 16-week, placebo-controlled data across the indications of PSO, PsA and axSpA have been previously identified as ADRs to bimekizumab based on 16-week, placebo-controlled data for the indication of moderate to severe PSO.

Treatment-emergent AEs identified for medical review as possible ADRs from Pool SP1

Leukopenia, stomatitis, bronchitis, oropharyngeal pain and pruritus all occurred with an incidence in the bimekizumab group of at least 1% higher than in the placebo group during the Initial Treatment Period. These were not added as ADRs due to overlap with terms already considered ADRs or evidence for lack of a reasonable causal association with bimekizumab. Based on medical review of the Safety Update data, there are no additional events considered as adverse drug reactions by UCB in addition to those presented in the original submission.

Serious adverse event/deaths/other significant events

Three study participants, all treated with bimekizumab, experienced a TEAE with fatal outcome in the bimekizumab development program for PsA. All TEAEs with a fatal outcome were reviewed for adjudication by the CV-CAC and the Neuropsychiatric Adjudication Committee. None of these events were considered related to bimekizumab per the investigator.

Table 76: PsA study participants with fatal TEAEs

Study[a]	Age range (years)/ gender	Treatment at the time of death	Days since 1st inj./ Days since 1st BKZ inj./ Days since most recent BKZ inj.	Preferred Term/ Reported term	Included in Pool	Comment
PA0010	50-60/M	Bimekizumab 160mg Q4W	285/173/5	Traumatic shock/ Traumatic shock	SP2	Severe traumatic shock from a motorcycle accident.
PA0012	40-50/F	Bimekizumab 160mg Q4W	632/269/22	Acute myocardial infarction/ Acute transmural myocardial infarction	SP2	The study participant had a prior medical history of obesity and hypertension and also had high cholesterol levels at study entry. Also had a family history of angina pectoris. She died at work due to a severe acute transmural myocardial infarction.
PA0012	50-60/M	Bimekizumab 160mg Q4W	181/69/13	Sudden death/ Sudden death	SP2	Had prior medical history of hypertension, aortic regurgitation, dilated ascending aorta and smoking. Sudden death while repairing his car; no symptoms were reported on the day of his death.

BKZ=bimekizumab; F=female; IMP=investigational medicinal product; inj.=injection; ISS=Integrated Summary of Safety; M=male; PsA=psoriatic arthritis; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event
Note: data from narratives for information in the comment column.
[a] Note that this column indicates the study when the death occurred.

There were no additional deaths in the Safety Update data.

Serious Adverse events

Pool SP1

In Pool SP1, incidences of serious TEAEs were 1.7% (n=12) (EAIR: 5.5/100 participant-years) in the bimekizumab 160mg Q4W group and 0.7% (n=3) in the placebo group during the Initial Treatment Period. By PT, 2 serious TEAEs were reported by >1 study participant in the bimekizumab Total group: pneumonia and joint injury (0.3%; EAIR 0.9/100 participant-years each) and no participants in the placebo group. All other serious TEAEs by PT were reported by 1 study participant in any treatment group.

Pool SP2

In Pool SP2, the incidence of serious TEAEs was 9.1% (EAIR 6.0/100 participant-years) in the bimekizumab Total group. Serious TEAEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (1.9%), Gastrointestinal disorders and Musculoskeletal and connective tissue disorders (1.1% each), and Injury, poisoning and procedural complications (1.0%).

The most common serious TEAEs by PT in the bimekizumab Total group were corona virus infection (6 study participants [0.4%]; EAIR 0.3/100 participant- years) and cholelithiasis and osteoarthritis (5 study participants [0.4%] each; EAIR 0.2/100 participant-years). Acute myocardial infarction was reported by 2 participants (0.1%; EAIR 0.1/100 participant years). In addition, myocardial infarction and myocardial ischaemia were reported by 1 participant (<0.1%; EAIR 0.0/100 participant-years) each. Drug-induced liver injury was reported by 2 participants (0.1%; EAIR 0.1/100 participant-years).

Pool SP2 Safety update

For Pool SP2, the incidence of serious TEAEs was 10.5% in the bimekizumab Total group. There was no notable increase in EAIRs with longer duration of exposure (EAIR: 5.9/100 participant-years in the Safety Update vs 6.0/100 participant-years in the original submission [bimekizumab Total group]).

Serious TEAEs in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (2.1%); Musculoskeletal and connective tissue disorders (1.3%); and Injury, poisoning and procedural complications (1.2%). The most common serious TEAEs by PT in the bimekizumab Total group were cholelithiasis (8 study participants [0.6%]; EAIR 0.3/100 participant-years), corona virus infection (7 study participants [0.5%]; EAIR 0.3/100 participant-years), and osteoarthritis (5 study participants [0.4%]; EAIR 0.2/100 participant-years).

Table 77: Incidence of serious TEAEs per 100 participant-years in at least 3 study participants by PT in the bimekizumab Total group during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SP2)

	Data in original submission[a]			Data in Safety Update[b]		
MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W N=1197 100 participant-yrs=16.48 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=1395 100 participant-yrs=21.44 n (%) [#] EAIR (95% CI)	BKZ Total N=1401 100 participant-yrs=22.18 n (%) [#] EAIR (95% CI)	Phase 3 BKZ 160mg Q4W N=1209 100 participant-yrs=20.94 n (%) [#] EAIR (95% CI)	Phase 2/3 BKZ 160mg Q4W N=1407 100 participant-yrs=25.91 n (%) [#] EAIR (95% CI)	BKZ Total N=1413 100 participant-yrs=26.64 n (%) [#] EAIR (95% CI)
Any serious TEAE	105 (8.8) [149] 6.7 (5.5, 8.1)	127 (9.1) [175] 6.2 (5.2, 7.4)	127 (9.1) [175] 6.0 (5.0, 7.2)	126 (10.4) [174] 6.4 (5.3, 7.6)	148 (10.5) [200] 6.1 (5.1, 7.1)	148 (10.5) [200] 5.9 (5.0, 6.9)
Hepatobiliary disorders	5 (0.4) [6] 0.3 (0.1, 0.7)	8 (0.6) [9] 0.4 (0.2, 0.7)	8 (0.6) [9] 0.4 (0.2, 0.7)	8 (0.7) [9] 0.4 (0.2, 0.8)	11 (0.8) [12] 0.4 (0.2, 0.8)	11 (0.8) [12] 0.4 (0.2, 0.7)
Cholelithiasis	3 (0.3) [4] 0.2 (0.0, 0.5)	5 (0.4) [6] 0.2 (0.1, 0.5)	5 (0.4) [6] 0.2 (0.1, 0.5)	6 (0.5) [7] 0.3 (0.1, 0.6)	8 (0.6) [9] 0.3 (0.1, 0.6)	8 (0.6) [9] 0.3 (0.1, 0.6)
Infections and infestations	22 (1.8) [24] 1.3 (0.8, 2.0)	26 (1.9) [28] 1.2 (0.8, 1.8)	26 (1.9) [28] 1.2 (0.8, 1.7)	26 (2.2) [28] 1.3 (0.8, 1.8)	30 (2.1) [32] 1.2 (0.8, 1.7)	30 (2.1) [32] 1.1 (0.8, 1.6)
Pneumonia	3 (0.3) [3] 0.2 (0.0, 0.5)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)
Corona virus infection	6 (0.5) [7] 0.4 (0.1, 0.8)	6 (0.4) [7] 0.3 (0.1, 0.6)	6 (0.4) [7] 0.3 (0.1, 0.6)	7 (0.6) [8] 0.3 (0.1, 0.7)	7 (0.5) [8] 0.3 (0.1, 0.6)	7 (0.5) [8] 0.3 (0.1, 0.5)
Cellulitis	1 (<0.1) [1] 0.1 (0.0, 0.3)	2 (0.1) [2] 0.1 (0.0, 0.3)	2 (0.1) [2] 0.1 (0.0, 0.3)	2 (0.2) [2] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)
Injury, poisoning and procedural complications	12 (1.0) [15] 0.7 (0.4, 1.3)	14 (1.0) [17] 0.7 (0.4, 1.1)	14 (1.0) [17] 0.6 (0.3, 1.1)	15 (1.2) [18] 0.7 (0.4, 1.2)	17 (1.2) [20] 0.7 (0.4, 1.1)	17 (1.2) [20] 0.6 (0.4, 1.0)
Meniscus injury	2 (0.2) [2] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	4 (0.3) [4] 0.2 (0.0, 0.4)	4 (0.3) [4] 0.2 (0.0, 0.4)
Musculoskeletal and connective tissue disorders	12 (1.0) [15] 0.7 (0.4, 1.3)	16 (1.1) [19] 0.8 (0.4, 1.2)	16 (1.1) [19] 0.7 (0.4, 1.2)	15 (1.2) [18] 0.7 (0.4, 1.2)	19 (1.4) [22] 0.7 (0.4, 1.2)	19 (1.3) [22] 0.7 (0.4, 1.1)
Foot deformity	1 (<0.1) [1] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	1 (<0.1) [1] 0.0 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)
Osteoarthritis	4 (0.3) [6] 0.2 (0.1, 0.6)	5 (0.4) [7] 0.2 (0.1, 0.5)	5 (0.4) [7] 0.2 (0.1, 0.5)	4 (0.3) [6] 0.2 (0.1, 0.5)	5 (0.4) [7] 0.2 (0.1, 0.5)	5 (0.4) [7] 0.2 (0.1, 0.4)
Nervous system disorders	9 (0.8) [10] 0.5 (0.3, 1.0)	10 (0.7) [11] 0.5 (0.2, 0.9)	10 (0.7) [11] 0.5 (0.2, 0.8)	9 (0.7) [10] 0.4 (0.2, 0.8)	10 (0.7) [11] 0.4 (0.2, 0.7)	10 (0.7) [11] 0.4 (0.2, 0.7)
Ischemic stroke	3 (0.3) [3] 0.2 (0.0, 0.5)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.4)	3 (0.2) [3] 0.1 (0.0, 0.3)	3 (0.2) [3] 0.1 (0.0, 0.3)

BKZ=bimekizumab; CI=confidence interval; DBL=database lock; EAIR=exposure-adjusted incidence rate; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PT=Preferred Term; Q4W=every 4 weeks; SFU=Safety Follow-Up; SOC=System Organ Class; TEAE=treatment-emergent adverse event; yrs=years

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

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

Note: EAIR=incidence of new cases per 100 participant-years and associated 95% CI.

Note: Treatment groups are defined as follows:

- Phase 3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during PA0010, PA0011, and PA0012
- Phase 2/3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during the Phase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (including study participants in PA0008 with a bimekizumab 320mg loading dose at Baseline)
- The BKZ Total treatment group includes data from all study participants while treated with any bimekizumab regimen during PA0008, PA0009, PA0010, PA0011, and PA0012 (including the limited exposures to bimekizumab 16mg Q4W and 320mg Q4W in Phase 2 PA0008).

[a] The original submission is based on the following data cut off date: 04 Jan 2022.

[b] The Safety Update is based on the following data cut off dates: PA0010 27 Jul 2022 (SFU Period DBL), PA0011 04 Mar 2022 (SFU Period DBL), and PA0012 20 May 2022 (last Week 52 Visit of PA0010).

Safety topics of interest

Analyses focusing on Pool SP1 and Pool SP2 and Pool SP2 updated are provided for infections, malignancies, MACE, neutropenia, SIB, IBD, anaphylaxis, hypersensitivity, and injection-site reactions, and hepatic TEAEs and LFT elevations.

Table 78: Summary of safety topics of interest for Pool SP1 And SP2

	Pool SP1[a]				Pool SP2[b]	
	Placebo N=413 100 participant-yrs=1.28		BKZ 160mg Q4W N=698 100 participant-yrs=2.19		BKZ Total N=1401 100 participant-yrs=22.18	
Parameter	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR
Any TEAE	183 (44.3)	198.0	365 (52.3)	245.9	1081 (77.2)	143.5
Any SAE	3 (0.7)	2.3	12 (1.7)	5.5	127 (9.1)	6.0
Any TEAE leading to discontinuation	3 (0.7)	2.3	10 (1.4)	4.6	67 (4.8)	3.1
Deaths	0	NA	0	NA	3 (0.2)	0.1
Safety topics of interest						
Serious infections	0	NA	3 (0.4)	1.4	26 (1.9)	1.2
Fungal infections (HLGT)	4 (1.0)	3.1	32 (4.6)	15.0	199 (14.2)	10.0
Candida infections (HLT)	2 (0.5)	1.6	18 (2.6)	8.3	118 (8.4)	5.6
Fungal infections NEC (HLT)	2 (0.5)	1.6	13 (1.9)	6.0	86 (6.1)	4.1
Tinea infections (HLT)	0	NA	1 (0.1)	0.5	5 (0.4)	0.2
Opportunistic infections defined by UCB convention	0	NA	0	NA	17 (1.2)	0.8
Malignancies per malignant tumours SMQ	2 (0.5)	1.6	1 (0.1)	0.5	14 (1.0)	0.6
Adjudicated MACE[c]	0	NA	0	NA	9 (0.6)	0.4
TEMA neutrophil count low	1 (0.2)	NA	5 (0.7)	NA	30 (2.1)	NA
SIB-adjudicated neuropsychiatric events	0	NA	0	NA	1 (<0.1)	0.1
Adjudicated IBD (definite and probable)	0	NA	0	NA	7 (0.5)	0.3
Hypersensitivity reactions (SMQ)	7 (1.7)	5.5	25 (3.6)	11.7	132 (9.4)	6.4
Anaphylactic reactions	0	NA	0	NA	0	NA
Injection site reactions (HLT)	3 (0.7)	2.3	8 (1.1)	3.7	32 (2.3)	1.5
Hepatic events[d]	11 (2.7)	8.7	28 (4.0)	13.1	130 (9.3)	6.3
Liver function analyses (HLT)	11 (2.7)	8.7	22 (3.2)	10.2	103 (7.4)	4.9
ALT or AST >5xULN	0 (0)	NA	4 (0.6)	NA	16 (1.1)	NA

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BKZ=bimekizumab; EAIR=exposure-adjusted incidence rate; HLGT=High Level Group Term; HLT=High Level Term; incl=including; IBD=inflammatory bowel disease; MACE=major adverse cardiac event; MedDRA=Medical Dictionary of Regulatory Activities; MI=myocardial infarction; NA=not applicable; NEC=not elsewhere classified; OLE=open-label extension; PsA=psoriatic arthritis; PSO=psoriasis; Q4W=every 4 weeks; SAE=serious adverse event; SIB=suicidal ideation and behavior; SMQ=standardized MedDRA query; TEAE=treatment-emergent adverse event; TEMA=treatment-emergent markedly abnormal; ULN=upper limit of normal; yrs=years

[a] Pool SP1: data to assess safety of bimekizumab vs placebo through Week 16 in Phase 3 placebo-controlled studies (PA0010, PA0011)

[b] Pool SP2: data from all blinded PsA studies and their respective OLE studies (PA0008, PA0009, PA0010, PA0011, and PA0012) for investigation of long-term exposure and safety data in all bimekizumab-treated study participants with active PsA.

[c] A MACE was defined as cardiovascular death, non-fatal MI, and stroke.

[d] By SMQ Drug related hepatic disorders (excluding sub-SMQs Liver neoplasms, benign (incl cysts and polyps) and Liver neoplasms, malignant and unspecified).

Infections

In the PsA development program, the vast majority of reported infections were nonserious, mild to moderate, rarely led to drug discontinuation, and were consistent with the type of infections observed in the Phase 3 PSO studies. The most frequently reported infections in the PsA development program were upper respiratory tract infection and oral candidiasis. There were no study discontinuations due to COVID-19 infections.

Serious Infections

Pool SP1

In Pool SP1, the incidence of serious infections was 0.4% EAIR: 1.4/100 participant-years in the bimekizumab 160mg Q4W group. Three serious infections were reported: pneumonia (2 study participants [0.3%]) and bronchitis (1 study participant [0.1%]). Both TEAEs of pneumonia were resolved and the TEAE of bronchitis was reported as resolving. No study participant reported serious infections while receiving placebo.

Pool SP2

In Pool SP2, the incidence of serious infections was 1.9%; EAIR: 1.2/100 participant-years in the bimekizumab Total group. The majority of serious infections by HLT in the bimekizumab Total group were reported by 1 study participant each, except for Viral infections not elsewhere classified (NEC) (all Corona virus infection) in 6 study participants (0.4%), Lower respiratory tract infections and Urinary tract infections in 4 study participants (0.3%) each, Bacterial infections NEC and Upper respiratory tract infections in 3 study participants (0.2%) each, and Ear infections in 2 study participants (0.1%).

A total of 26 study participants in the bimekizumab Total group had serious infections; subsequently, the following actions were taken with the study drug. Study drug was withdrawn in 5 study participants with TEAEs of cellulitis (2 study participants) and hepatitis E, otitis media acute, and postoperative wound infection (1 study participant each). Study drug was temporarily interrupted in 15 study participants and was re-introduced in 14 study participants after TEAEs of otitis media chronic, chronic sinusitis, renal cyst infection, pneumonia (2 study participants), gangrene, corona virus infection (5 study participants), upper respiratory tract infection (2 study participants), and oropharyngeal candidiasis, with no recurrence of serious infections.

Pool SP2 Safety Update

The incidence of serious infections in the combined Initial, Maintenance, and OLE Treatment Period was 2.1% EAIR 1.1/100 participant-years in the bimekizumab Total group. A total of 4 additional serious infections (cellulitis, pyelonephritis, pyelonephritis acute, and corona virus infection) were reported; 1 TEAE (pyelonephritis) was considered related to study drug, 1 TEAE (cellulitis) led to discontinuation, and all 4 TEAEs were resolved.

In the Adalimumab group in PA0010, one study participant reported two serious infections herpes zoster and atypical pneumonia. The EAIR for serious infection in the adalimumab active reference population in PA0010 was 1.44/100PYs.

Opportunistic infections (including TB)

Opportunistic infections

Pool SP1

In Pool SP1, no opportunistic infection was reported in the bimekizumab 160mg Q4W group or placebo group. No systemic opportunistic infections were reported and no study participant in Pool SP1 developed active TB.

Pool SP2

In Pool SP2, the incidence of any opportunistic infection in the combined Initial, Maintenance, and OLE Treatment Period was low overall (1.2%; EAIR: 0.8/100 participant-years in the bimekizumab Total group). Opportunistic infections reported in Pool SP2 in the bimekizumab Total group were a total of 10 cases of oesophageal candidiasis and fungal oesophagitis (0.4% (5 cases) each), and oropharyngeal candidiasis (4 cases 0.3%). All other opportunistic infections were reported by <0.1% of the study

participants. No systemic opportunistic infections were reported. The incidence of opportunistic infections was similar for the active reference drug (0.7%; EAIR: 0.72/100 participant-years in the adalimumab group) in PA0010.

Updated Pool SP2

In the updated Pool SP2, the incidence of any opportunistic infection in the combined Initial, Maintenance, and OLE Treatment Period was low overall (1.3%; EAIR: 0.7/100 participant-years in the bimekizumab Total group).

Fungal infections

Incidences of fungal infections were higher in the bimekizumab-treated study participants compared with placebo, mainly driven by oral candidiasis infections. No systemic Candida infections were observed in the PsA program.

Pool SP1

The incidence of any fungal infection was higher in the bimekizumab 160mg Q4W group (4.6%; EAIR 15/100PY) compared with the placebo group (1.0%; EAIR 3.1/100PY). By HLT, Candida infections were reported by 2.6% of participants in the bimekizumab 160mg Q4W group and 0.5% of participants in the placebo group. The HLT Fungal infections NEC was reported by 1.9% of study participants in the bimekizumab 160mg Q4W group and 0.5% of study participants in the placebo group. By PT, the only fungal infection TEAE reported with an incidence of ≥1% in the bimekizumab 160mg Q4W group was oral candidiasis (2.3%).

Pool SP2

In Pool SP2, the incidence of any fungal infection in the bimekizumab Total group (which includes participants on higher doses of bimekizumab) was 14.2% (EAIR: 10.0/100 participant-years). Oral candidiasis (6.7%) and oral fungal infection (2.7%) were reported with an incidence ≥2% in the bimekizumab Total group. 12/199 subjects with any fungal infection discontinued the study due to fungal infections, including oral candidiasis (7 study participants), oral fungal infection (2 study participants), and skin candida, tongue fungal infection, and gastrointestinal fungal infection (1 study participant each). One study participant had a serious fungal infection (oropharyngeal candidiasis). The incidence of any fungal infection was lower for the active reference drug (1.4%; EAIR: 1.49/100 participant-years in the adalimumab group) in PA0010.

Updated Pool SP2

The incidence of any fungal infection in the bimekizumab Total group was 15.7%. The EAIR (9.4/100 participant-years) did not increase compared to the original submission (10.0/100 participant-years). By PT, oral candidiasis (7.5%) and oral fungal infection (2.8%) were reported with an incidence ≥2% in the bimekizumab Total group.

Two additional study participants discontinued the study due to fungal infections (PTs: oral candidiasis and fungal skin infection. No additional serious fungal infections were reported.

Malignancies

Pool SP1

Pool SP1, incidences of malignant tumor TEAEs were 0.1%; EAIR: 0.5/100 participant-years in the bimekizumab 160mg Q4W group and 0.5%; EAIR: 1.6/100 participant-years in the placebo group. None of the reports of malignancy were assessed as related.

Pool SP2

In Pool SP2 the incidence for the bimekizumab Total group was (1.0%; EAIR: 0.6/100 participant-years). A total of 14 malignancies (malignant melanoma in situ, chronic lymphocytic leukaemia stage 0, colon cancer, basal cell carcinoma (4 cases), breast cancer, ovarian neoplasm, uterine cancer, papillary thyroid cancer (2 events in 1 study participant were reported due to 2 hospitalisations), endometrial cancer stage I) were reported by 12 study participants. All malignant tumor TEAEs were reported by 1 study participant each (<0.1%; EAIR: 0.0/100 participant-years) except for basal cell carcinoma (4 study participants [0.3%]; EAIR: 0.2/100 participant-years). Two were judged as related to study treatment by the Investigator: malignant melanoma in situ and chronic lymphocytic leukaemia stage 0. No malignancies were reported for the active reference drug (adalimumab) in PA0010.

Pool SP2 Updated

The incidence of malignant tumor TEAEs in the bimekizumab Total group was 1.5%; EAIR: 0.8/100 participant-years). This is higher than the EAIR in the original submission (0.6/100 participant-years). A total of 6 additional malignancy TEAEs (gastric cancer recurrent, chronic lymphocytic leukaemia, ovarian cancer, prostate cancer, bone giant cell tumour, and renal neoplasm) were reported; 1 TEAE (ovarian cancer) was considered related to study drug, all 6 TEAEs were considered serious, and all TEAEs led to study discontinuation with the exception of bone giant cell tumour.

MACE

Pool SP1

In Pool SP1, no adjudicated MACE was reported in the bimekizumab 160mg Q4W or placebo groups. The incidence of any extended MACE in the bimekizumab 160mg Q4W group was 0.1% (1 study participant with a serious event of cardiac failure congestive). No extended MACE was reported in the placebo group.

The incidence of any adjudicated cardiovascular event was similar in the bimekizumab 160mg Q4W (0.6%) and placebo (0.7%) groups. The majority of these events were resolved at the time of data cut.

Pool SP2

In Pool SP2, adjudicated MACE were reported for 9 (0.6%) study participants EAIR 0.4/100PYs (Acute myocardial infarction 2 cases (1 with fatal outcome), myocardial infarction 1 case, sudden death, ischaemic stroke 2 cases, cerebral haemorrhage 1 case, cerebrovascular accident, and thrombotic cerebral infarction). One additional event of ischemic stroke was adjudicated as MACE only after the data cut due to a change in the reported term by the study site. Extended MACE occurred in 13 study participants EAIR 0.6/100PYs in the bimekizumab group. All events were serious and 9 were severe.

Pool SP2 updated

The incidence of adjudicated MACE was 0.7% in the SP2 updated safety analysis. The EAIR was the same as the original submission (0.4/100 participant-years). One additional participant experienced an adjudicated MACE (PT: ischemic stroke). This event was reported in a study participant with a significant medical history, including hypertension, hypercholesterolemia, coronary artery disease, recurrent transient ischemic attacks, and critical symptomatic carotid artery stenosis. The event was serious, severe, assessed as not drug related by the Investigator, did not lead to study discontinuation, and resolved at time of data cut.

One additional participant experienced extended MACE (PTs: cardiac failure congestive and hypoxia) adjudicated as hospitalisation for heart failure. This event was reported in a 72-year-old female with past medical history of hypertension (data on file). The PT of cardiac failure congestive was serious, severe, assessed as not drug-related by the Investigator, did not lead to study discontinuation, and had not

resolved at the time of the data cut. The PT of hypoxia was not serious, mild, assessed as not drug related by the Investigator, and the outcome was unknown at the time of reporting.

Neutropenia

Pool SP1

In Pool SP1, the incidence of neutropenia TEAEs reported was 1.3% and 0.2% in the bimekizumab 160mg Q4W group and placebo group, respectively. None of the reported neutropenia TEAEs were serious. One TEAE of neutropenia was severe, considered related to study drug by the Investigator, led to interruption of study drug, and recovered/resolved at the time of data cut. Four TEAEs of neutropenia were mild or moderate in intensity and considered related to study drug (by the Investigator). The majority of the neutropenia TEAEs (90.0%) were resolved at the time of data cut. Five study participants (0.7%) in the bimekizumab 160mg Q4W group and 1 study participant (0.2%) in the placebo group had a TEMA neutrophils low count (<1.0x10^9/L). No study participant had Grade 4 neutrophil reduction. All Gr3 values returned to normal.

Pool SP2

In Pool SP2, the incidence of neutropenia TEAEs in the bimekizumab Total group was low (2.4%; EAIR: 1.5/100 PYs). The majority of the neutropenia cases were transient. None were associated with serious infections. No neutropenia event was serious. The majority were mild or moderate in intensity except for 2 TEAEs of neutropenia (by PT) that were considered severe. One resolved, the other resulted in study discontinuation. The majority of cases were assessed as drug related. The majority of the neutropenia TEAEs (86 %) were resolved at the time of data cut.

Thirty study participants (2.1%) in the bimekizumab Total group had a TEMA neutrophils low count (< 1 x10^9/L). Twenty-three of these 30 study participants had Grade 3 or Grade 4 neutrophil values which were transient and had resolved at the data cut. Seven were ongoing. No TEMA neutrophil counts were associated with serious infections. PTs of upper respiratory tract infection (3 total events; 2 events in the same study participant), laryngitis, nasopharyngitis (4 events), oral herpes, and pneumonia were reported within 30 days of a Gr3 or 4 neutrophil value.

Pool SP2 updated

In Pool SP2, the incidence of neutropenia was 2.5%; EAIR: 1.4/100 participant-years compared with the original submission (2.4%; EAIR: 1.5/100 participant-years). In Pool SP2, 6 additional study participants in the bimekizumab Total group had a TEMA neutrophils low count. All 6 of these study participants had Grade 3 or Grade 4 neutrophil values which were transient, and values returned to normal at subsequent visits. None of the neutropenia events were associated with serious infections or led to discontinuation

SIB

Pool SP1

In Pool SP1, no TEAEs were adjudicated as SIB by the Neuropsychiatric Adjudication Committee.

Pool SP2

In Pool SP2, one TEAE in the bimekizumab Total group was adjudicated as SIB by the Neuropsychiatric Adjudication Committee. The event of suicidal behaviour in the bimekizumab-treated study participant was reported as serious, moderate in intensity, considered not drug-related (as assessed by the Investigator), resolved at the time of data cut, and led to study discontinuation. The participant had prior history of depression and anxiety and was reportedly noncompliant with her anxiety/depression medications prior to the event. No completed suicides were observed in the PsA program. No adjudicated SIB was reported for the active reference drug (adalimumab) in PA0010.

Pool SP2 updated

The incidence of adjudicated SIB in Pool SP2 was 0.1%; EAIR: 0.1/100 participant-years) compared with the original submission (<0.1%; EAIR: 0.0/100 participant-years). One additional TEAE in the bimekizumab Total group was adjudicated as SIB by the Neuropsychiatric Adjudication Committee. The event of psychiatric evaluation abnormal in the bimekizumab-treated study participant was reported as severe in intensity, considered not drug related (as assessed by the Investigator), not resolved at the time of data cut off, and led to withdrawal of study drug. This event was reported in a study participant with past medical history of anxiety and depression with noncompliance to medications. No completed suicides were observed in the PsA program.

Inflammatory bowel disease

Pool SP1

In Pool SP1, no study participants in the bimekizumab 160mg Q4W group or placebo group reported a TEAE that was adjudicated as IBD.

Pool SP2

In Pool SP2, definite or probably adjudicated IBD TEAEs occurred in 7 study participants (0.5%; EAIR 0.3/100 participant-years). Definite adjudicated IBD events occurred in 3 study participants (0.2%; EAIR: 0.1/100 participant-years). Three study participants (4 events) reported TEAEs of colitis ulcerative, enteritis, IBD, and colitis microscopic. The TEAE of colitis ulcerative was mild in intensity, considered related to study drug (as assessed by the Investigator), and recovered/resolved at the time of data cut. All other TEAEs were mild or moderate in intensity and not considered as related to study drug with the exception of enteritis, which was severe and considered as not related to study drug.

Probable adjudicated IBD events occurred in 4 study participants (0.3%; EAIR: 0.2/100 participant-years). Three study participants reported TEAEs of diarrhoea and 1 study participant reported a TEAE of colitis. All TEAEs were mild or moderate in intensity, did not lead to study discontinuation, and recovered/resolved at the time of data cut. All TEAEs were considered not related to study drug (as assessed by the Investigator), except for 1 event of diarrhoea.

Possible adjudicated IBD events occurred in 10 study participants (0.7%; EAIR: 0.5/100 participant-years). Seven participants reported diarrhoea and 1 participant reported each of the following: anal fistula, enteritis, colitis, and abdominal pain. Three participants (0.2%) had symptoms not consistent with IBD and 1 participant (<0.1%) had an event with not enough information to adjudicate.

Of the 14 study participants with a history of prior or ongoing IBD, only 1 participant had an event during the study which was adjudicated as definite or probable IBD (one participant TEAE of colitis ulcerative).

The remaining 6 definite or probable cases (UC [1 participant], Crohn’s disease [1 participant], microscopic colitis [1 participant], IBD no further differentiation [3 participants]) represent instances of new onset/de novo IBD cases. In only 1 of the 7 cases was study drug withdrawn due to the event; in the remaining 6 cases, the study drug was continued, and the participants all completed their respective studies with no subsequent flares.

The event outcome for all events except 1 were reported as recovered; the event of inflammatory bowel disease in one participant was considered ongoing at the time of the report.

Pool SP2 updated

No additional definite or probable IBD cases were reported.

Hypersensitivity

Anaphylactic reactions

No anaphylactic reactions were reported in Pool SP1 or Pool SP2 (original submission and Safety Update).

Other hypersensitivity reactions

Pool SP1

In Pool SP1, any hypersensitivity reaction was reported in 3.6% (EAIR 11.7/100PYs) of bimekizumab treated study participants compared to 1.7% of placebo treated participants (EAIR 5.5/100PYs). The most frequently reported PT terms identified by the MedDRA SMQ narrow search for hypersensitivity belonged to the HLT Dermatitis and eczema (and included eczema (0.6%), dermatitis (0.4%) and dermatitis allergic (0.3%). None were considered serious. 12 TEAEs were considered drug-related (injection site rash, toxic skin eruption, dermatitis [2 study participants], urticarias, gingival swelling [2 study participants], rash, swelling face, rash macular, dermatitis allergic, and dermatitis acneiform). One study participant in the bimekizumab 160mg Q4W group discontinued due to toxic skin eruption, which was moderate in intensity, considered related by the Investigator, and resolved on treatment with antihistaminic medication. The majority of these potential hypersensitivity reactions (75.9%) were resolved at the time of this analysis.

Pool SP2

In Pool SP2, the incidence of hypersensitivity (PT terms identified as potential hypersensitivity reactions by MedDRA SMQ narrow search for hypersensitivity) in the combined Initial, Maintenance, and OLE Treatment Period was 9.4% (EAIR: 6.4/100 participant-years). The most frequently reported hypersensitivity reactions by PT were eczema (1.4%), dermatitis allergic (1.3%), and dermatitis and dermatitis contact (0.7% each).

Hypersensitivity reactions (5.0%; EAIR: 5.17/100 participant-years) were reported for the active reference drug (adalimumab) in PA0010.

Of the 132 study participants in the bimekizumab Total group with potential hypersensitivity reactions, one study participant had a potential hypersensitivity reaction reported as a serious event. The event (PT dermatitis) was moderate in intensity, not considered drug-related and did not lead to study discontinuation.

Five study participants had potential hypersensitivity reactions that led to study discontinuation. Thirty-one study participants had potential hypersensitivity reactions considered drug related, and 1 study participant had severe hypersensitivity reactions. The majority of the hypersensitivity reactions (79.4%) were resolved.

Pool SP2 Update

In Pool SP2, the incidence of hypersensitivity was 10.8% (EAIR: 6.2/100 participant-years). The most frequently reported hypersensitivity reactions by PT were eczema (1.8%), dermatitis allergic (1.3%), and dermatitis and dermatitis contact (0.8% each). One potential hypersensitivity reaction reported as severe in intensity in the bimekizumab group (PT: dermatitis allergic) was considered drug related and led to study discontinuation

Administration and injection site reactions

In Pool SP1, the incidence of injection site reactions by HLT during the Initial Treatment Period was low and reported by 1.1% of study participants in the bimekizumab 160mg Q4W group and by 0.7% of study participants in the placebo group.

In Pool SP2, the incidence of injection site reactions was 2.3% in the bimekizumab Total group. The most frequently reported injection site reactions by PT were injection site erythema (1.1%) and injection site reaction (0.6%). The incidence of injection site reactions was 9.3% for adalimumab in PA0010.

Overall, Safety Update results were comparable with those in the original submission.

Hepatic TEAEs and LFT elevations

Pool SP1

Hepatic TEAEs

The incidence of hepatic TEAEs was 4.0% (EAIR: 13.1/100 participant-years) in the bimekizumab 160mg Q4W group compared to 2.7% (EAIR: 8.7 /100 participant-years) in the placebo group.

All hepatic TEAEs in the bimekizumab 160mg Q4W group and all in the placebo group occurred in 1 study participant each apart from gamma-glutamyl transferase and liver function test increased (0.9% each), hepatic steatosis and alanine aminotransferase (ALT) increased (0.7% each), blood bilirubin increased, and hepatic enzyme increased (0.6%), aspartate aminotransferase (AST) increase (0.4%), and transaminases increased (0.3%).

Four study participants in the bimekizumab 160mg Q4W group discontinued the study due to drug induced liver injury, blood bilirubin increased, alanine aminotransferase increased, and hepatic enzyme increased.

One study participant in the bimekizumab 160mg Q4W group met the laboratory criteria for potential Hy's Law (ALT or AST ≥3xULN and total bilirubin ≥2xULN in the absence of ALP ≥2xULN). Due to the alternative explanations for the LFT elevations (alcohol abuse, obesity, concomitant treatment with methotrexate) this event was not considered a Hy's Law case.

Pool SP2

In Pool SP2, the incidence of any hepatic TEAEs in the bimekizumab Total group was 9.3% (EAIR: 6.3/100 participant-years). The most frequently reported hepatic TEAEs by PT in the bimekizumab Total group were ALT increased (3.0%), and gamma glutamyltransferase (GGT) increased and AST increased (2.3% each).

2 serious hepatic TEAEs (both drug-induced liver injury) were reported. Two participants in the bimekizumab Total group met laboratory criteria for PDILI. Both cases resulted in withdrawal from study and were considered possibly related to study medication. Both cases were confounded by concomitant medication Nimesulide and methotrexate for one case and methotrexate and sertraline for the other case. In total, five participants reported 6 hepatic TEAEs that led to study discontinuation: hepatic enzyme increased and drug-induced liver injury (2 participants [0.1%] each) and ALT increased, and blood bilirubin increased (1 participant [<0.1%] each).

The incidence of hepatic TEAEs reported for the active reference drug (adalimumab) in PA0010 was 9.3% (EAIR: 10.2/100 participant-years).

Pool SP2 update

In Pool SP2, the incidence of any hepatic TEAEs was 10.5% (EAIR: 6.0/100 participant-years). No new serious or severe hepatic TEAEs were reported in this Safety Update. No new participants met the laboratory criteria for Hy's Law

Treatment-emergent markedly abnormal liver function

Pool SP1

1.3% of bimekizumab exposed study participants had an AST or ALT elevation >3×ULN. Four study participants (0.6%) in the bimekizumab 160mg Q4W group had at least one incidence of ALT or AST >5×ULN. One study participant had an ALT >8xULN. No subjects in placebo group had an AST or ALT elevation >3×ULN

Table 79: Treatment-emergent abnormal liver function during the Initial Treatment Period (Pool SP1)

	Placebo N=413 n/Nsub (%)	BKZ 160mg Q4W N=698 n/Nsub (%)
AST		
>3xULN	0/411	5/698 (0.7)
>5xULN	0/411	3/698 (0.4)
>8xULN	0/411	1/698 (0.1)
>10xULN	0/411	0/698
>20xULN	0/411	0/698
ALT		
>3xULN	0/411	7/698 (1.0)
>5xULN	0/411	1/698 (0.1)
>8xULN	0/411	0/698
>10xULN	0/411	0/698
>20xULN	0/411	0/698
Either AST or ALT		
>3xULN	0/411	9/698 (1.3)
>5xULN	0/411	4/698 (0.6)
>8xULN	0/411	1/698 (0.1)
>10xULN	0/411	0/698
>20xULN	0/411	0/698
Total bilirubin		
>1.5xULN	4/411 (1.0)	11/698 (1.6)
>2xULN	0/411	1/698 (0.1)
ALP		
>1.5xULN	2/411 (0.5)	1/698 (0.1)
>2xULN	0/411	0/698

Pool SP2

Sixteen study participants (1.1%) in the bimekizumab Total group had at least one incidence of ALT or AST >5×ULN. Ten participants had multiple peaks/persistent LFT elevations and in each case an alternate aetiology (including LFT elevation due to hepatitis E or alcohol abuse), risk factor including concomitant medications (such as MTX, meloxicam, diclofenac, valsartan), and/or underlying medical conditions (as cholelithiasis, hepatic steatosis, fatty liver disease, obesity) could have led to the LFT elevations. The remaining 6 participants all had isolated spikes or transient increases and either had an alternative aetiology, one or more strong confounders or were temporally not considered due to bimekizumab

treatment. Five of the 16 participants with at least one incidence of ALT or AST >5×ULN were withdrawn due to the elevated liver enzymes.

One case met Hy's law laboratory criteria but was not considered a confirmed Hy's law case as the LFT elevations were attributed to excessive alcohol consumption prior to testing.

16 cases of liver enzyme TEMA (ALT or AST >5×ULN) were independently and blindly adjudicated by an external Hepatology Adjudication Committee (HAC) using the drug-induced liver injury network scoring system (Fontana et al,2009): 12 were adjudicated as unlikely to be related to study medication whereas 4 were considered as possibly related. None of the TEMA cases of liver enzyme elevations across the PsA development program were adjudicated as definitely, highly likely, or probably related to the investigational medicinal product (IMP).

Pool SP2 update

Twenty study participants (1.4%) in the bimekizumab Total group had at least 1 incidence of ALT or AST >5×ULN.

The majority of the ALT/AST CTCAE Grade 3 or above findings were transient. Four new cases of AST >5xULN were reported in addition to the previous cases. There were no new >5xULN elevations of ALT. In all study participants, abnormal liver function values were transient and reduced from the peak within a few days and all cases had other more likely causes of the events.

These 4 cases were independently and blindly adjudicated by the HAC, and 3 cases were adjudicated as unlikely because of either clear alternative explanations (progressive fatty liver disease with increase in obesity in one study participant and elevated CK suggesting muscle injury in another study participant) or incompatible chronology of the events (negative dechallenge with LFT values suggestive of alcohol use in one study participant).

One case was considered possibly related given lack of clear alternative explanations; however, the long latency and the ratio of AST>ALT makes acute drug-induced liver injury from the study drug unlikely.

The external, independent HAC also reviewed all TEMA transaminase elevations (ALT or AST >5x ULN) data from the development programs of axial spondyloarthritis and psoriatic arthritis and did not detect a significant liver safety concern with bimekizumab in any development program to date.

Table 80: Treatment-emergent markedly abnormal liver function during the combined Initial, Maintenance, and OLE Treatment Periods (Pool SP2)

	Data in original submission[a]			Data in Safety Update[b]		
	Phase 3 BKZ 160mg Q4W N=1197 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=1395 n/Nsub (%)	BKZ Total N=1401 n/Nsub (%)	Phase 3 BKZ 160mg Q4W N=1209 n/Nsub (%)	Phase 2/3 BKZ 160mg Q4W N=1407 n/Nsub (%)	BKZ Total N=1413 n/Nsub (%)
AST						
>3xULN	32/1195 (2.7)	39/1392 (2.8)	40/1399 (2.9)	40/1208 (3.3)	47/1405 (3.3)	48/1412 (3.4)
>5xULN	7/1195 (0.6)	11/1392 (0.8	12/1399 (0.9)	11/1208 (0.9)	15/1405 (1.1)	16/1412 (1.1)
>8xULN	4/1195 (0.3)	6/1392 (0.4)	7/1399 (0.5)	6/1208 (0.5)	8/1405 (0.6)	9/1412 (0.6)
>10xULN	3/1195 (0.3)	5/1392 (0.4)	6/1399 (0.4)	5/1208 (0.4)	7/1405 (0.5)	8/1412 (0.6)
>20xULN	1/1195 (<0.1)	1/1392 (<0.1)	1/1399 (<0.1)	1/1208 (<0.1)	1/1405 (<0.1)	1/1412 (<0.1)
ALT						
>3xULN	27/1195 (2.3)	36/1392 (2.6)	38/1399 (2.7)	29/1208 (2.4)	38/1405 (2.7)	40/1412 (2.8)
>5xULN	5/1195 (0.4)	8/1392 (0.6)	10/1399 (0.7)	5/1208 (0.4)	8/1405 (0.6)	10/1412 (0.7)
>8xULN	1/1195 (<0.1)	4/1392 (0.3)	4/1399 (0.3)	1/1208 (<0.1)	4/1405 (0.3)	4/1412 (0.3)
>10xULN	0/1195	2/1392 (0.1)	2/1399 (0.1)	0/1208	2/1405 (0.1)	2/1412 (0.1)
>20xULN	0/1195	1/1392 (<0.1)	1/1399 (<0.1)	0/1208	1/1405 (<0.1)	1/1412 (<0.1)
Either AST or ALT						
>3xULN	41/1195 (3.4)	51/1392 (3.7)	53/1399 (3.8)	49/1208 (4.1)	59/1405 (4.2)	61/1412 (4.3)
>5xULN	10/1195 (0.8)	14/1392 (1.0)	16/1399 (1.1)	14/1208 (1.2)	18/1405 (1.3)	20/1412 (1.4)
>8xULN	5/1195 (0.4)	9/1392 (0.6)	10/1399 (0.7)	7/1208 (0.6)	11/1405 (0.8)	12/1412 (0.8)
>10xULN	3/1195 (0.3)	6/1392 (0.4)	7/1399 (0.5)	5/1208 (0.4)	8/1405 (0.6)	9/1412 (0.6)
>20xULN	1/1195 (<0.1)	2/1392 (0.1)	2/1399 (0.1)	1/1208 (<0.1)	2/1405 (0.1)	2/1412 (0.1)
>1.5xULN	41/1195 (3.4)	47/1392 (3.4)	48/1399 (3.4)	46/1208 (3.8)	52/1405 (3.7)	53/1412 (3.8)
>2xULN	5/1195 (0.4)	6/1392 (0.4)	6/1399 (0.4)	8/1208 (0.7)	9/1405 (0.6)	9/1412 (0.6)
ALP						
>1.5xULN	2/1195 (0.2)	4/1392 (0.3)	6/1399 (0.4)	3/1208 (0.2)	5/1405 (0.4)	7/1412 (0.5)
>2xULN	1/1195 (<0.1)	2/1392 (0.1)	3/1399 (0.2)	2/1208 (0.2)	3/1405 (0.2)	4/1412 (0.3)

ALP=alkaline phosphatase; ALT=alanine aminotransferase; AST=aspartate aminotransferase; BKZ=bimekizumab; DBL=database lock; ISS=Integrated Summary of Safety; OLE=open-label extension; Q4W=every 4 weeks; SFU=Safety Follow-Up; TEMA=treatment-emergent markedly abnormal; ULN=upper limit of normal

Note: n=number of study participants meeting each criterion at any time through Week 16; Nsub=number of study participants with available data post Baseline. Percentages are based on Nsub.

Note: Study participants are summarized according to the treatment randomized/assigned to receive at start of the period during which the TEMA laboratory value occurred.

Note: This table may include local laboratory data.

Note: Treatment groups are defined as follows:

- Phase 3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during PA0010, PA0011, and PA0012
- Phase 2/3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during the Phase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (including study participants in PA0008 with a bimekizumab 320mg loading dose at Baseline)
- The BKZ Total treatment group includes data from all study participants while treated with any bimekizumab regimen during PA0008, PA0009, PA0010, PA0011, and PA0012 (including the limited exposures to bimekizumab 16mg Q4W and 320mg Q4W in Phase 2 PA0008).

[a] The original submission is based on the following data cut-off date: 04 Jan 2022.

[b] The Safety Update is based on the following data cut off dates: PA0010 27 Jul 2022 (SFU Period DBL), PA0011 04 Mar 2022 (SFU Period DBL), and PA0012 20 May 2022 (last Week 52 Visit of PA0010).

Immunogenicity

Formation of ADAb and NAb was monitored in all studies in the bimekizumab PsA development program for potential association with an increase in the occurrence of TEAEs.

ADAb assessment up to Week 16 (Pool SP1)

In Pool SP1, the incidence of study participants who were ADAb positive at Baseline was low (4.0% [28/698]). Overall, by Week 16, 31.2% (218/698) of study participants had at least 1 ADAb-positive sample. Approximately half of these (15.3% [107/698]) had at least 2 ADAb-positive samples by Week 16. The incidence of NAb-positive study participants was 10.3% (72/698 participants).

Table 81: ADAb and NAb status up to Week 16 (Pool SP1)

Parameter Status	BKZ 160mg Q4W N=698 n (%)
ADAb status by Week 16	
ADAb Positive	218 (31.2)
NAb status by Week16	
NAb Positive	72 (10.3)
IL-17AA NAb Positive Only	7 (1.0)
IL-17FF NAb Positive Only	7 (1.0)
Both IL-17AA and IL-17FF Positive	58 (8.3)
ADAb Positive/NAb Negative	143 (20.5)
NAb Missing	19 (2.7)

ADAb=anti-drug antibody; BKZ=bimekizumab; IL=interleukin; ISS=Integrated Summary of Safety; NAb=neutralizing antibody; PsA=psoriatic arthritis; Q4W=every 4 weeks

Relationship between ADAb and bimekizumab safety in PsA (Pool SP2)

51.7% of TEAEs started before the first ADAb-positive result, 65.1% of TEAEs started on or after the first ADAb-positive result, and 72.1% of TEAEs for participants who were always ADAb negative.

Incidences of serious TEAEs by time of onset relative to ADAb status in Pool SP2 were 2.2% for TEAEs starting before the first ADAb positive result, 7.9% for TEAEs starting on or after the first ADAb-positive result, and 9.5% 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 remained higher than for TEAEs starting before the first ADAb-positive result (7.7/100 participant-years [95% CI: 5.6, 10.2] vs 4.5/100 participant-years [95% CI: 2.3, 7.9]) but was comparable to the EAIR in participants who were always ADAb negative (7.8/100 participant-years [95% CI: 5.8, 10.4]).

Incidences of TEAEs leading to study medication discontinuation by time of onset relative to ADAb status in Pool SP2 were 0.5% for TEAEs starting before the first ADAb-positive result, 4.0% for TEAEs starting on or after the first ADAb-positive result, and 4.5% for TEAEs in participants who were always ADAb negative. The exposure-adjusted incidence for TEAEs starting on or after the first ADAb-positive result remained higher than for TEAEs starting before the first ADAb-positive result (3.7/100 participant-years [95% CI: 2.3, 5.5] vs 1.1/100 participant-years [95% CI: 0.2, 3.3]) but was comparable to the EAIR in participants who were always ADAb negative (3.4/100 participant-years [95% CI: 2.2, 5.2]). There was no trend observed for the types of TEAE leading to discontinuation in the study participants who were ADAb positive.

Table 82: 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 and on/after the first ADAb-positive result) (Pool SP2)

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=551 100 participant-yrs=2.70 n (%) [#] Incidence (95% CI)	AEs starting on or after 1st anti-BKZ antibody positive result N=582 100 participant-yrs=6.32 n (%) [#] Incidence (95% CI)	AEs for participants who are always anti-BKZ antibody negative N=494 100 participant-yrs=6.46 n (%) [#] Incidence (95% CI)
Any TEAE	285 (51.7) [779] 205.8 (182.6, 231.2)	379 (65.1) [1360] 130.8 (117.9, 144.6)	356 (72.1) [1534] 140.9 (126.7, 156.4)
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			
Infections and infestations	155 (28.1) [261] 78.9 (66.9, 92.3)	240 (41.2) [463] 56.5 (49.6, 64.2)	227 (46.0) [481] 55.2 (48.3, 62.9)
Nasopharyngitis	31 (5.6) [39] 12.2 (8.3, 17.3)	47 (8.1) [55] 8.0 (5.9, 10.6)	46 (9.3) [56] 7.7 (5.6, 10.3)
Corona virus infection	9 (1.6) [9] 3.4 (1.5, 6.4)	45 (7.7) [48] 7.5 (5.5, 10.0)	32 (6.5) [33] 5.2 (3.5, 7.3)
Additional PTs reported in ≥5% of study participants in any group			
Oral candidiasis	15 (2.7) [16] 5.7 (3.2, 9.4)	31 (5.3) [51] 5.1 (3.5, 7.2)	29 (5.9) [47] 4.7 (3.1, 6.7)
Upper respiratory tract infection	17 (3.1) [17] 6.5 (3.8, 10.4)	30 (5.2) [35] 5.0 (3.4, 7.1)	39 (7.9) [48] 6.4 (4.5, 8.7)
Urinary tract infection	17 (3.1) [24] 6.5 (3.8, 10.4)	29 (5.0) [38] 4.7 (3.2, 6.8)	36 (7.3) [48] 5.9 (4.1, 8.2)

ADAb=anti-drug antibody; AE=adverse event; BKZ=bimekizumab; CI=confidence interval; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; n=number of study participants reporting at least 1 TEAE within System Organ Class/High Level Term/Preferred Term; PsA=psoriatic arthritis; PT=preferred term; Q4W=every 4 weeks; TEAE=treatment-emergent adverse event; yrs=years

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

Note: AEs starting before the first ADAb-positive result includes ADAb Categories 2 and 5; AEs starting on the same date or after the first ADAb-positive result includes ADAb Categories 2, 3, 4, 5, and 6.

Note: All available ADAb data from PA0010, PA0011, and PA0012 at the time of the clinical cut-off were included in the classification of ADAb status for study participants initially randomized to placebo or BKZ.

Relationship between NAb and bimekizumab safety in PsA (Pool SP2)

The overall exposure-adjusted TEAE incidence was slightly higher in NAb-positive participants (EAIR: 156.3/100 participant-years [95% CI: 134.0, 181.2]) compared with ADAb-negative participants (140.9/100 participant-years [95% CI: 126.7, 156.4]. The TEAEs with the largest incidence difference (≥2.5%) between the groups of NAb-positive and ADAb-negative participants by PT were corona virus infection, nasopharyngitis, back pain, rash, and hypertension.

Table 83: Incidence of TEAEs per 100 participant-years during the combined Initial, Maintenance, and OLE Treatment Period by NAb status reported by PT in ≥5% of study participants in any group, and/or with an incidence difference of ≥2.5% between NAb-positive and ADAb-negative groups) (Pool SP2)

MedDRA v19.0 System Organ Class Preferred Term	Phase 3 BKZ 160mg Q4W ADAb Negative N=494 100 participant-yrs=6.46 n (%) [#] Incidence (95% CI)	Phase 3 BKZ 160mg Q4W ADAb-positive participants by NAb status	
		NAb Negative N=365 100 participant-yrs=5.60 n (%) [#] Incidence (95% CI)	NAb Positive N=216 100 participant-yrs=3.42 n (%) [#] Incidence (95% CI)
Any TEAE	356 (72.1) [1534] 140.9 (126.7, 156.4)	292 (79.8) [1342] 150.8 (134.0, 169.1)	176 (81.5) [797] 156.3 (134.0, 181.2)
PTs reported with an incidence difference of ≥2.5% between NAb-positive and ADAb-negative			
Nasopharyngitis	46 (9.3) [56] 7.7 (5.6, 10.2)	46 (12.6) [65] 9.2 (6.7, 12.3)	26 (12.0) [29] 8.4 (5.5, 12.3)
Corona virus infection	32 (6.5) [33] 5.2 (3.5, 7.3)	31 (8.5) [32] 5.8 (3.9, 8.2)	23 (10.6) [25] 7.0 (4.5, 10.6)
Back pain	15 (3.0) [19] 2.4 (1.3, 3.9)	15 (4.1) [17] 2.7 (1.5, 4.5)	12 (5.6) [14] 3.6 (1.9, 6.4)
Rash	5 (1.0) [5] 0.8 (0.3, 1.8)	5 (1.4) [5] 0.9 (0.3, 2.1)	9 (4.2) [11] 2.7 (1.2, 5.1)
Hypertension	15 (3.0) [16] 2.4 (1.3, 3.9)	12 (3.3) [12] 2.2 (1.1, 3.9)	14 (6.5) [16] 4.3 (2.4, 7.3)
Additional PTs reported in ≥5% of study participants in any group, but without an incidence difference of ≥2.5% between NAb-positive and ADAb-negative groups			
Oral candidiasis	29 (5.9) [47] 4.7 (3.1, 6.7)	27 (7.4) [41] 5.0 (3.3, 7.3)	16 (7.4) [26] 4.9 (2.8, 7.9)
Urinary tract infection	36 (7.3) [48] 5.9 (4.1, 8.2)	27 (7.4) [38] 5.0 (3.3, 7.3)	17 (7.9) [24] 5.2 (3.1, 8.4)

General safety related to hypersensitivity and immunogenicity in the pooled PsA studies

There were increased reports of rash (4.2%) in the Nab +ve group compared with 1.4% in the Nab –ve group and 1% in the ADAb-ve group. Hypersensitivity reaction TEAEs were reported before and on/after the first ADAb-positive result in ADAb-positive participants (4.2% and 6.5%, respectively) and also in ADAb-negative study participants (7.7%).

When adjusted for exposure, the incidence of hypersensitivity reaction TEAEs was slightly lower for TEAEs that started on/after the first ADAb-positive result (6.3/100 participant-years [95% CI: 4.5, 8.7]) compared with TEAEs starting before the first ADAb-positive result (8.8/100 participant-years [95% CI: 5.6, 13.2]) and was comparable to the group that was always ADAb negative (6.4/100 participant-years [95% CI: 4.5, 8.7]). One study participant experienced a TEAE of drug hypersensitivity that started on/after the first ADAb-positive result.

No anaphylactic reactions were observed in the PsA Phase 3 studies.

The rate of injection site reactions was low overall and no association between ADAb and NAb status and the occurrence of injection site reactions was observed. In the HLT of Injection site reactions, EAIRs were similar in NAb-positive and ADAb-negative participants with EAIRs of 2.1/100 participant-years (95% CI: 0.8, 4.3) and 2.1/100 participant years (95% CI: 1.1, 3.5), respectively.

SP2 update

Pool SP2 was updated with final immunogenicity and safety data from both PA0010 (52 weeks and SFU) and PA0011 (16 weeks and SFU) and available data from PA0012 at the cut-off date of 20 May 2022).

No events were reported for anaphylactic reactions in the Phase 3 studies in PsA.

The incidence of TEAEs by time of onset relative to ADAb status was comparable to the original SP2 analysis with 52.4% (TEAEs starting before the first ADAb-positive result), 72.0% (TEAEs starting on or after the first and 82.4% (TEAEs for participants who were always ADAb negative). Exposure-adjusted incidence rates (EAIRs) were 205.0/100 PYs (95% CI: 182.6, 229.4), 123.7/100 PYs (95% CI: 112.4, 135.8), and 141.7/100 PYs (95% CI: 128.0, 156.4), respectively. The TEAEs with the largest incidence difference (≥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 (6.1% vs 2.9%), nasopharyngitis (9.7% vs 5.7%), upper respiratory tract infection (6.2% vs 3.4%), urinary tract infection (6.1% vs 3.1%), corona virus infection (15.5% vs 1.9%) and arthralgia (3.6% vs 0.7%). The incidence of injection site reaction TEAEs was 1.6% for TEAEs starting before the first ADAb-positive result and 1.3% for TEAEs starting on/after the first ADAb-positive result.

The overall TEAE EAIR was 139.2/100 PYs (95% CI: 117.6, 163.6) in the highest ADAb titer category of ≥ 180 compared with 141.7/100 PYs (95% CI: 128.0, 156.4) in ADAb-negative study participants.

The overall exposure-adjusted TEAE incidence was slightly higher in NAb-positive participants (EAIR: 155.6/100 PYs [95% CI: 135.1, 178.3]) compared with ADAb-negative participants (141.7/100 participant-years [95% CI: 128.0, 156.4]);

The HLT of Injection site reactions, EAIRs were similar in NAb-positive and ADAb-negative participants with EAIRs of 1.8/100 PYs (95% CI:0.8, 3.6) and 1.4/100 PYs (95% CI: 0.7, 2.5), respectively. The rate of injection site reactions was low overall and no association between ADAb and NAb status and the occurrence of injection site reactions was observed.

Laboratory findings

Haematology

Pool SP1

During the Initial Treatment Period, the incidence of TEMA haematology values was 1.3% in the bimekizumab 160mg Q4W group and 0.2% in the placebo group. Neutrophils low were reported for 5 participants in the bimekizumab 160mg Q4W group (0.7%). Lymphocytes low were reported for 4 participants in the bimekizumab 160mg Q4W group (0.6%). Two of these participants had low lymphocyte count since Baseline. None of the 4 participants with TEMA lymphocytes low values had any concurrent infections and all recovered without treatment interruption.

Pool SP2

The incidence of markedly abnormal haematology data was 2.6% in the bimekizumab Total group. Haemoglobin low (<8.0g/dL) was reported for two study participants (0.1%). Lymphocytes low (<0.5x10^9/L) was reported for 4 study participants (0.3%). Neutrophils low, reported in 30 study participants (2.1%) in the bimekizumab Total group. None of these CTCAE Grade 3 or Grade 4 neutrophil count values were associated with a serious infection and majority of them were transient. All other markedly abnormal haematology values were reported in <0.1% of subjects.

Pool SP2 update

The incidence of markedly abnormal hematology data was 3.0% in the bimekizumab Total group. The most frequent markedly abnormal hematology value was neutrophils low, reported in 36 study participants (2.5%) in the bimekizumab Total group. None of these CTCAE Grade 3 or Grade 4 neutrophil count values were associated with a serious infection and the majority of them were transient.

Biochemistry

Individual study participant changes in laboratory values

Pool SP1 and SP2 (Original analysis and update)

There were no clinically meaningful shifts from Baseline to maximum/minimum post-Baseline values in any biochemistry parameter.

Markedly abnormal values (excluding LFTs)

Pool SP1

The incidence of TEMA biochemistry laboratory values was 2.6% in the bimekizumab 160mg Q4W group and 2.2% the placebo group. The most frequently reported TEMA biochemistry value was high glucose >13.9mmol/L; bimekizumab 160mg Q4W group [1.9%] and the placebo group [1.5%], respectively. The proportion of study participants who experienced other TEMA biochemistry laboratory values was low (<1.0%).

Pool SP2

The incidence of markedly abnormal biochemistry data was 3.9% in the bimekizumab Total group. The most frequent markedly abnormal biochemistry value was glucose high, reported in 36 study participants (2.6%) in the bimekizumab Total group. All other markedly abnormal biochemistry values occurred in <0.5% of study participants.

Pool SP2 update

The incidence of markedly abnormal biochemistry values was 4.3% in the bimekizumab Total group. The most frequent markedly abnormal biochemistry value was glucose high, reported in 38 study participants (2.7%) in the bimekizumab Total group. All other markedly abnormal biochemistry values occurred in <0.5% of study participants.

Vitals signs, physical findings, and other observations related to safety

Vital signs

In Pool SP1, no clinically meaningful changes in SBP and DBP measurements were noted across treatment groups. During the Initial Treatment Period, the incidence of shifts in SBP or DBP from Baseline at any visit during the Initial Treatment Period was low and similar in the bimekizumab 160mg Q4W and placebo groups. For Pool SP1, the proportion of study participants with normal or elevated BP at Baseline who shifted to a maximum post-Baseline Stage 2 category in the bimekizumab 160mg Q4W group was low (<5.0%), and no meaningful imbalance was noted compared with placebo.

In both safety pools, the proportion of study participants who experienced post-Baseline markedly abnormal SBP or DBP values in the bimekizumab group was low (<1% [Pool SP1] and <2% [Pool SP2]).

Pool SP2 Update

Safety Update results for Pool SP2 were similar to what was observed in the original submission. In Pool SP2, the proportion of study participants who experienced post-Baseline markedly abnormal SBP or DBP values in the bimekizumab Total group was low (≤2.1%)

Physical examination findings

No safety concern was identified from physical examination findings including body weight over time.

Electrocardiograms

Standard 12-lead ECGs that included QTcF, RR, PR, QRS, and QT variables were performed as outlined in the study protocols. All ECGs in the Phase 3 program were read by a central cardiologist. No notable trends were observed in the 12-lead ECG results across all treatment groups in Pool SP1. No notable trends were observed in the 12-lead ECG central interpretation results during the combined Initial, Maintenance, and OLE Treatment Period for Pool SP2.

QTcF increases

For Pool SP1, no study participant had QTcF>500ms. No notable trends were observed in the 12-lead ECG central interpretation results for Pool SP1.

For Pool SP2, one study participant had QTcF >500ms with no associated cardiac TEAE.

Safety Update results for Pool SP2 were similar to what was observed in the original submission.

Adverse events related to ECG findings

In Pool SP2, 1 study participant was identified as experiencing any Torsade de pointes/QT prolongation. The PT for the event was sudden death and it was serious, severe in intensity, and not considered related to study medication.

One study participant had QTcF >500ms with no associated cardiac TEAE. Overall, taking into account both the duration of exposure and frequency of assessments, there is no increase of abnormal findings over time.

Safety in special populations

Age

In both Pool SP1 and Pool SP2, similar proportions of participants were <40 years of age (23.9% and 23.8%, respectively), 40 to <65 years of age (64.1% and 64.2%, respectively), and ≥65 years of age (12.1% and 12.1%, respectively).

Pool SP1

In Pool SP1, the incidences of TEAEs in the bimekizumab 160mg Q4W group were higher in the 40 to <65 year age group (54.6%) compared with the <40 years and ≥65 years groups (49.1% and 46.5%, respectively), while in the placebo group the incidences were higher in the ≥65 years group (50.0%) compared with the <40 and 40 to <65 years age groups (40.6%, and 44.6%, respectively) Treatment-emergent AEs were most frequently reported in the SOC of Infections and infestations in the <40, 40 to <65, and ≥65 year groups (26.6%, 26.9%, 29.1%, respectively, in the bimekizumab 160mg Q4W group and 16.7%, 17.8%, and 18.8%, respectively, in the placebo group). The incidence of infections was similar in different age groups. Higher incidences by HLT in the ≥65 years group were noted for Candida infections in the bimekizumab 160mg Q4W group (0.6%, 2.3%, and 8.1%, respectively). Higher incidences by PT in the ≥65 years group were noted for oral candidiasis in the bimekizumab 160mg Q4W group (0%, 2.3%, and 7.0%, respectively).

Pool SP2

In Pool SP2, in the bimekizumab Total group, the overall incidence of TEAEs was similar across the age groups (80.2%, 75.8%, and 78.7%, respectively, for the <40, 40 to <65, and ≥65 year groups). Treatment-emergent AEs were most frequently reported in the SOC of Infections and infestations (54.1%, 51.5%, and 54.4%, respectively). Within the HLT Candida infections, the PT of oral candidiasis in

the ≥65 years group (10.1%) was slightly higher than that in the 40 to <65 years age group (7.2%) and higher than that in the<40 years age group (3.6%).

Pool SP2 update

Table 84: Incidence of TEAEs by age during the combined Initial, Maintenance, and OLE Treatment Period – overview (analysis set: Pool SP2)

Category	BKZ Total group n (%)			
	<65 years N=1232	65-74 years N=152	75-84 years N=16	≥85 years N=1
Any TEAEs	948 (76.9)	118 (77.6)	14 (87.5)	1 (100)
Serious TEAEs - Total	101 (8.2)	22 (14.5)	4 (25.0)	0
TEAEs leading to death	3 (0.2)	0	0	0
Permanent withdrawal of study medication due to TEAEs	51 (4.1)	15 (9.9)	1 (6.3)	0
Any TEAEs coding into Psychiatric disorders SOC	42 (3.4)	4 (2.6)	0	0
Any TEAEs coding into Nervous system disorders SOC	130 (10.6)	15 (9.9)	3 (18.8)	1 (100)
Any TEAEs coding into Accidents and injuries SMQ	113 (9.2)	20 (13.2)	2 (12.5)	0
Any TEAEs coding into Cardiac disorders SOC	22 (1.8)	8 (5.3)	0	0
Any TEAEs coding into Vascular disorders SOC	60 (4.9)	13 (8.6)	2 (12.5)	0
Any TEAEs coding into Cerebrovascular disorders SOC	0	0	0	0
Any TEAEs coding into Infections and infestations SOC	643 (52.2)	81 (53.3)	11 (68.8)	0
Any TEAEs coding into Anticholinergic syndrome SMQ	0	0	0	0
Any TEAEs coding to Quality of life decreased PT	0	0	0	0
Any TEAEs coding to Postural hypotension, Fall, Blackout, Syncope, Dizziness, Ataxia, or Fracture[a] PTs	62 (5.0)	8 (5.3)	2 (12.5)	1 (100)
Other TEAEs appearing more frequently in older patients:				
Any TEAEs coding into Gastrointestinal disorders SOC	246 (20.0)	41 (27.0)	4 (25.0)	0
Any TEAEs coding into Musculoskeletal and connective tissue disorders SOC	215 (17.5)	29 (19.1)	5 (31.3)	0
Any TEAEs coding into Skin and subcutaneous tissue disorders SOC	203 (16.5)	29 (19.1)	3 (18.8)	0
Any TEAEs coding into Oral candidiasis PT	77 (6.3)	15 (9.9)	2 (12.5)	0
Any TEAEs coding into Urinary tract infection PT	74 (6.0)	17 (11.2)	3 (18.8)	0

BKZ=bimekizumab; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PT=Preferred Term; SMQ=Standardized MedDRA Query; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Note: N=number of study participants in Pool SP2 within the respective age group.
Note: n=number of study participants reporting at least 1 TEAE within the category being summarized.
Note: Pool SP2 includes data from PA0008, PA0009, PA0010, PA0011, and PA0012.
[a] Fracture events include all PTs containing the term "fracture."

Table 85: Incidence of serious TEAEs by age during the combined Initial, Maintenance, and OLE Treatment Period – overview (analysis set: Pool SP2 – Phase 3 studies)

Category	BKZ Phase 3 160mg Q4W group n (%)			
	<65 years N=1049	65-74 years N=133	75-84 years N=14	≥85 years N=1
Serious TEAEs – Phase 3 Total	80 (7.6)	21 (15.8)	4 (28.6)	0
Criteria for seriousness[a]				
Fatal	3 (0.3)	0	0	0
Hospitalization/prolong existing hospitalization	74 (7.1)	19 (14.3)	4 (28.6)	0
Life-threatening	1 (<0.1)	2 (1.5)	0	0
Disability/incapacity	2 (0.2)	0	0	0
Other (medically significant)	4 (0.4)	4 (3.0)	0	0

Body Weight

In Pool SP2, in the bimekizumab Total group incidence of TEAEs was higher in the>100kg weight group compared with the ≤100kg weight group for any TEAEs (81.8% and 76.1%, respectively) and for serious TEAEs (11.5% and 8.5%, respectively), discontinuations due to TEAEs (6.5% vs 3.7%), and severe TEAEs (7.8% vs 5.4%). Of the 3 deaths that occurred in the bimekizumab PsA program, 2 occurred in study participants with a body weight of ≤100kg, and 1 occurred in a study participant with a body weight >100kg.

Study participants in the >100kg weight group had a higher incidence of TEAEs compared with the ≤100kg weight group in the following SOCs: Hepatobiliary disorders (5.6% and 3.1%, respectively), Investigations (16.4% and 13.4%, respectively), Metabolism and nutrition disorders (13.0% and 6.7%, respectively), HLT Diabetes mellitus (incl subtypes): 5.6% and 0.8%, respectively, Musculoskeletal and connective tissue disorders (21.6% and 16.9%, respectively), Respiratory, thoracic and mediastinal disorders (9.7% and 6.6%, respectively), Skin and subcutaneous tissue disorders (19.0% and 16.3%, respectively), Cardiac disorders SOC (3.9% and 1.9% respectively).

Many of the reported TEAEs were considered not related to bimekizumab but are expected comorbidities of being overweight.

By TEAE PT, an inverse relationship between body weight and oral candidiasis was observed with a higher incidence in the ≤100kg weight group (7.2%) than in the >100kg weight group (4.8%). The HLT Candida infections was reported in 8.9% of participants ≤100kg and 6.3% of participants >100kg.

Pool SP2 update

Safety Update results for Pool SP2 were similar to what was observed in the original submission.

Gender

Pool SP1

In Pool SP1, the incidences of TEAEs were higher in female study participants compared with male study participants regardless of treatment (55.0% vs 49.2%, respectively in bimekizumab 160mg Q4W group and 51.8% vs 35.3%, respectively in the placebo group). Treatment-emergent AEs were most frequently reported and at a higher incidence (≥5%) in female compared with male bimekizumab-treated study participants in the SOC Infections and infestations.

Pool SP2

In Pool SP2, 666 study participants (47.5%) were male and 735 (52.5%) were female. The same trend with higher incidences of TEAEs in female compared with male study participants was observed in Pool SP2 in the bimekizumab Total group (77.4% in female study participants and 71.9% in male study participants). Treatment-emergent AEs were most frequently reported at a higher incidence (≥5%) in female study participants compared with male study participants in the Infections and Infestation (female 56.3% and male 48.2%, respectively) and Musculoskeletal SOCs ((female 20.5% and male 14.7% respectively). Differences by HLT were noted for Upper respiratory tract infections (40.8% vs 34.3%) and Urinary tract infections (11.4% vs 2%), and Candida infections (19.2% vs 16.1%) respectively.

Pool SP2 update

In Pool SP2, 675 study participants (47.8%) were male and 738 (52.2%) were female. The same trend of higher incidence of TEAEs in female compared with male study participants was observed in Pool SP2 in the bimekizumab Total group (86.3% in female study participants and 81.0% in male study participants). Additional treatment emergent AEs were most frequently reported at a higher incidence (≥5%) in female study participants compared with male study participants in the SOC of Infections and infestations (65.2% for females and 55.3% for males).

Race

In Pool SP2, there were a total of 1341 White (95.7%), 7 Black (0.5%), 41 Asian (2.9%), and 12 other (0.9%) study participants. Based on these data, the low numbers of Black, Asian, and other study participants do not allow for meaningful interpretation of the safety in race subgroups.

Safety Update results for Pool SP2 were similar to what was observed in the original submission

Extrinsic Factors

Two subgroups for extrinsic factors were analysed geographic region and Baseline cDMARD type.

Geographic region

The incidence of TEAEs in bimekizumab 160mg Q4W group was highest in Asia (75.9%) and lowest in Eastern Europe (45.5%) A similar picture was observed for Pool SP2; the incidence of TEAEs was higher in Asia (88.3%) compared with the other regions (74.9% [Eastern Europe], 79.1% [North America], and 80.6% [Western Europe]). The incidences of TEAEs were comparable for the geographic regions for the SOC of Infections and Infestations (range 49.4% to 54.4%). No trends of specific TEAEs have been observed by geographic region.

Pool SP2 update

In Pool SP2, in the Phase 2/3 bimekizumab group, the incidence of TEAEs was 93.9% in Asia, 80.4% in Eastern Europe, 84.5% in North America, and 90.2% in Western Europe. The incidences of TEAEs were comparable for the geographic regions for the SOC of Infections and Infestations (range: 55.6% to 63.8%).

Baseline DMARD type

Treatment-emergent AEs were summarised for study participants in the following subgroups: MTX (alone or with other cDMARDs), Other cDMARDs (any cDMARD other than MTX) and No MTX or other DMARD.

Methotrexate was being used by 55.2% of study participants, while other cDMARDs were used by 9.3% of study participants. A total of 35.5% of study participants were not receiving any cDMARDs and 30.4% had prior anti-TNF therapy. The majority of study participants (62.4%) had used 1 prior cDMARD, while 25.8% used no prior cDMARDs and 11.8% used at least 2 prior cDMARDs.

Pool SP1

In Pool SP1 in the placebo group, the incidence of TEAEs was higher in the other cDMARDs group (52.4%) compared with the MTX and no MTX or other cDMARDs groups (42.7% and 44.3%, respectively). The inverse relationship was observed in the bimekizumab 160mg Q4 group: the incidence of TEAEs was lower in the other cDMARDs (42.0%) group than in the MTX and no MTX or other cDMARDs groups (53.6% and 53.1%, respectively). In the bimekizumab 160mg Q4W group, the incidences of TEAEs were comparable for the Baseline cDMARD subgroups for the SOC of Infections and Infestations (range 26.7% to 27.5%). No trends of specific TEAEs have been observed by baseline DMARD type.

Pool SP2

In Pool SP2 in the bimekizumab Total group, the incidence of TEAEs was higher in the MTX and other cDMARDs groups (79.2% each) compared with the no MTX or other cDMARDs group (73.5%). The incidences of TEAEs by SOCs were generally comparable for the Baseline cDMARDs subgroups.

Study participants in the no MTX or other cDMARDs subgroup reported fewer TEAEs compared with the other Baseline cDMARDs subgroups in the SOC of Infections and infestations.

Pool SP2 update

In Pool SP2 in the bimekizumab Total group, the incidence of TEAEs was similar in the MTX (84.5% each) and other cDMARDS groups (84.8%) compared with the no MTX or other cDMARDs group (82.4%).

Although the proportion of study participants receiving other cDMARDs was smaller, overall, safety profile of bimekizumab in combination with MTX was similar to that observed when given in combination with other cDMARDs or as a monotherapy. Study participants in the no MTX or other cDMARDs subgroup reported fewer TEAEs compared with the other MTX and baseline cDMARDs subgroups in the SOC of Infections and infestations. (62.1% vs 61.4% vs 57.7% respectively (BKZ Total population)).

Use in pregnancy and lactation

There is a limited amount of data from the use of bimekizumab in pregnant women since female study participants of childbearing potential were required to use a highly effective method of birth control and study drug was discontinued as per pre-specified withdrawal criteria if they became pregnant. No clinical study has been specifically designed to evaluate the safety of bimekizumab in pregnant or lactating women; in the UCB Global Safety Database as of the clinical cut-off date (04 January 2022), 1 maternal bimekizumab exposure pregnancy was reported in the studies included in Pool SP2. In PA0010, there was 1 pregnancy in the partner of a male study participant. The pregnancy resulted in delivery at full term infant by vaginal delivery. No abnormalities were reported. In PA0011, one study participant had an unintended pregnancy (nonserious adverse event) that occurred 116 days after the first, and 22 days after the most recent, bimekizumab injections. Per the Investigator, the pregnancy was due to contraceptive failure. The study participant experienced a post-treatment serious adverse event of severe nephrolithiasis 152 days after the final dose was given. Following cystoscopy and ureteral stent insertion, a serious infection (septic shock) was reported. Rapid deterioration in the participant's condition was noted and she experienced post-treatment severe SAEs of septic shock; premature separation of placenta; and haemolytic uremic syndrome (HUS), elevated liver enzymes and low platelets (HELLP syndrome). She underwent an emergency caesarean section secondary to coagulation disorder and partial placental abruption. She delivered a premature baby girl at 25 weeks and 5 days of gestational age, (weight of 740g and height 31cm) with failure to thrive but no developmental delay or congenital abnormality was detected; the baby did not survive. The action taken with study drug was reported as not applicable for the unintended pregnancy. The unintended pregnancy resolved on 21 June 2020, 133 days after onset. The nephrolithiasis was reported as resolving at the time of this report. The premature separation of placenta resolved on 21 June 2020, same day as the onset. The HELLP syndrome resolved

on 22 June 2020. The septic shock resolved on 28 June 2020. No congenital anomaly or maternal complications were reported that had a reasonable likelihood of being associated with bimekizumab exposure at the time of conception.

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction study with bimekizumab has been performed.

Population pharmacokinetic (PK) data analysis indicated that the apparent clearance of bimekizumab was not impacted by concomitant administration of methotrexate, corticosteroids or cDMARDs. In addition, bimekizumab concentrations were found to be generally comparable between bDMARD naive and TNF-IR patients with PsA in studies PA0010 and PA0011, respectively. These results were confirmed by population PK analysis suggesting no clinically relevant impact for prior biologic use on bimekizumab apparent clearance or steady-state exposure.

Discontinuation due to adverse events

Pool SP1

During the Initial Treatment Period, the incidence of TEAEs leading to discontinuation in Pool SP1 was 1.4% in the bimekizumab 160mg Q4W group and 0.7% in the placebo group. No obvious trend in TEAEs leading to discontinuation was identified.

Pool SP2

During the combined Initial, Maintenance, and OLE Treatment Period, the incidence of TEAEs leading to discontinuation was 4.8%. Treatment-emergent AEs leading to discontinuation in the Phase 3 bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (1.5%), Gastrointestinal disorders (0.9%), and Skin and subcutaneous tissue disorders (0.7%).

Pool SP2 updated

The incidence of TEAEs leading to discontinuation was 5.7% of study participants in the bimekizumab Total group. The EAIR for TEAEs leading to discontinuation in the Safety Update (3.0/100 participant-years) was similar compared with the original submission (3.1/100 participant-years).

Treatment-emergent AEs leading to discontinuation in the bimekizumab Total group were most frequently reported in the SOCs of Infections and infestations (1.7%), and Gastrointestinal disorders and Skin and subcutaneous tissue disorders (0.8% each).

Table 86: Incidence of TEAEs leading to discontinuation in >1 study participant by PT (Pool SP2)

	Data in original submission[a]			Data in Safety Update[b]		
MedDRA v19.0 Preferred Term	Phase 3 BKZ 160mg Q4W N=1197 100 participant-yrs=16.48 n (%) [#]	Phase 2/3 BKZ 160mg Q4W N=1395 100 participant-yrs=21.44 n (%) [#]	BKZ total N=1401 100 participant-yrs=22.18 n (%) [#]	Phase 3 BKZ 160mg Q4W N=1209 100 participant-yrs=20.94 n (%) [#]	Phase 2/3 BKZ 160mg Q4W N=1407 100 participant-yrs=25.91 n (%) [#]	BKZ Total N=1413 100 participant-yrs=26.64 n (%) [#]
Any TEAE leading to discontinuation	51 (4.3) [66]	66 (4.7) [81]	67 (4.8) [82]	64 (5.3) [79]	79 (5.6) [94]	80 (5.7) [95]
Oral candidiasis	6 (0.5) [6]	6 (0.4) [6]	6 (0.4) [6]	7 (0.6) [7]	7 (0.5) [7]	7 (0.5) [7]
Abdominal pain	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]
Aphthous ulcer	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]
Stomatitis	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]
Tongue discolouration	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]
Drug-induced liver injury	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]
Cellulitis	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]
Oral fungal infection	0	2 (0.1) [2]	2 (0.1) [2]	0	2 (0.1) [2]	2 (0.1) [2]
Hepatic enzyme increased	1 (<0.1) [1]	1 (<0.1) [1]	2 (0.1) [2]	1 (<0.1) [1]	1 (<0.1) [1]	2 (0.1) [2]
Psychiatric evaluation abnormal	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]
Psoriatic arthropathy	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	1 (<0.1) [1]	1 (<0.1) [1]	1 (<0.1) [1]
Skin fissures	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]
Dermatitis atopic	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]	2 (0.2) [2]	2 (0.1) [2]	2 (0.1) [2]
Psoriasis	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]	3 (0.2) [3]	4 (0.3) [4]	4 (0.3) [4]

BKZ=bimekizumab; DBL=database lock; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; OLE=open-label extension; PT=Preferred Term; SFU=Safety Follow-Up; TEAE=treatment-emergent adverse event; yrs=years

Note: n=number of study participants reporting at least 1 TEAE within the PT.

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

Note: Treatment groups are defined as follows:

- Phase 3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during PA0010, PA0011, and PA0012
- Phase 2/3 BKZ 160mg Q4W treatment group includes data from all study participants while treated with bimekizumab 160mg Q4W during the Phase 2 and Phase 3 studies PA0008, PA0009, PA0010, PA0011, and PA0012 (including study participants in PA0008 with a bimekizumab 320mg loading dose at Baseline)
- The BKZ total treatment group includes data from all study participants while treated with any bimekizumab regimen during PA0008, PA0009, PA0010, PA0011, and PA0012 (including the limited exposures to bimekizumab 16mg Q4W and 320mg Q4W in Phase 2 PA0008).

[a] The original submission is based on the following data cut off date: 04 Jan 2022.

[b] The Safety Update is based on the following data cut off dates: PA0010 27 Jul 2022 (SFU Period DBL), PA0011 04 Mar 2022 (SFU Period DBL), and PA0012 20 May 2022 (last Week 52 Visit of PA0010).

Clinical-use study (DV0004)

No adverse device effects (ADEs) were reported in this sub-study. There were no TEADEs, no SADEs, no study participant discontinuations due to TEADEs, and no deaths reported for either device presentation. There were 11 injection site reaction AEs reported during the study; however, none were assessed to be related to the device presentation (based on the Investigator's judgement) and all were reported to be mild in intensity.

Post marketing experience

Cumulatively since approval on 20 August 2021 up to 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 safety of bimekizumab has been evaluated in Phase 2 (PA008 and PA009) and Phase 3 (PA0010, PA001 and PA0012) clinical studies in patients with active PsA. Pooled data are presented to assess short-term (16 week – SP1) and longer-term safety (SP2) up to the data cut-off dates (25 October 2021 for Study PA0010; 22 December 2021 for Study PA0011; and 04 January 2022 for PA0012). In the initial submission, pooled safety data were available for at least 16 weeks of treatment for all subjects. At the Week 24 data cut, 75% of study participants in PA0010 had reached Week 52. Upon CHMP request's, the MAH has provided an updated safety analysis for safety pool SP2. The update consisted of long-term safety data from the 52-week Phase 3 study PA0010 that was ongoing at the time of the original submission data cut off. PA0010 is now completed and the Pool SP2 update included all data up through the completion of the Safety Follow-Up (SFU) Period (database lock 27 July 2022). In addition, all SFU data from the completed Phase 3 study PA0011 (database lock 04 March 2022) and all safety data entered into the open-label extension (OLE) study PA0012 database as of the designated clinical cut-off date (20 May 2022 [the last Week 52 Visit in PA0010]) were included. The open-label follow-up study PA0012 is ongoing; final CSR will be submitted post-approval (see RMP).

Safety outcomes of interest include MACE, malignancy, IBD, serious infection, SIB, neutropenia, hepatic events and serious hypersensitivity.

Exposure

A total of 1413 subjects have been exposed with 1143 subjects exposed to bimekizumab 160 mg Q4W across the phase 2/3 studies for PsA for ≥ 1 year. This builds on the 1789 study participants exposed to bimekizumab in the PSO development plan. The ICH E1 drug exposure requirements have thus been met.

Pooled placebo-controlled safety data are available for at least 16 weeks of treatment for all subjects in the two pivotal trial PA0010 and PA0011. The Pool SP2 update includes 12 additional study participants (study participants in the adalimumab group in the feeder studies who enrolled in PA0012) in comparison to the original submission. A total of 1413 study participants with PsA with a total time at risk of 2664.0 participant-years in the bimekizumab Total group are represented compared with 1401 study participants with a total time at risk of 2217.5 participant-years in the original submission. Safety Pool S3 included combined data through Week 16 from the psoriatic arthritis, axial spondylarthritis and psoriasis development programs and was used to identify adverse drug reactions for bimekizumab.

Overall, the pooling strategy is rational and supports comparisons against placebo during the initial 16 weeks of PsA studies, and longer-term safety tolerability in the PsA indication. Determinations of ADRs based on evaluation of bimekizumab across all exposed patients is endorsed. Different posology for the dermatology and rheumatology indications should be kept in mind. Different background rates of comorbidities for PSO, PsA and axSpA were taken into account.

As this is a chronic condition, Study PA0012 open-label extension of up to 140 weeks (~2.7 years) will assess the long-term safety, tolerability, and efficacy of bimekizumab however this may not be adequate to capture some rarer risks or risks with longer latency, i.e. malignancy. A study protocol for a cohort study on the safety of bimekizumab in patients with plaque psoriasis was concluded at PRAC. This is a 10-year, non-interventional, post-authorisation study to evaluate any potential increase in the risk of safety outcomes of interest (MACE, malignancy, serious infections, inflammatory bowel disease and serious hypersensitivity reactions) in bimekizumab-exposed plaque psoriasis (PSO) patients compared to PSO patients exposed to other biologics indicated for moderate to severe PSO. Upon CHMP's request, PsA indication was added to the planned PASS (see RMP). A revised protocol will be submitted within 3 months.

Demographic and Baseline characteristics

Overall, demographic and Baseline characteristics were well balanced between the treatment groups and are reflective of a population with active PsA patients who are candidates for treatment with bDMARDs. There were no notable differences in demographic and Baseline characteristics between Pool SP1 and Pool SP2. The majority of study participants were White (95,7% in pool S1), inclusion of other racial groups was very low. The reported comorbidities were expected for the PsA population. Exclusion criteria were selected to recruit a study population close to the real-world patients with active PsA, while ensuring the safety of the study participants. The prevalence of some co-morbidities could be higher in real-world patients.

Treatment emergent adverse events (TEAEs)

In the initial 16-week placebo-controlled period, TEAEs were reported at a higher incidence in the bimekizumab 160mg Q4W group compared with the placebo group (52.3% vs 44.3%). AEs were mostly non-serious (> 98%), mild to moderate in severity (> 98%), and did not require drug discontinuation (> 98 %). Drug related TEAEs were more commonly reported in the bimekizumab 160mg Q4W group (19.5%) compared with of the placebo arm (9.5%).

TEAEs were most commonly reported in the Infections and infestations SOC, in the high-level terms (HLTs) Upper respiratory tract infections and Candida infections. The most commonly reported TEAEs were, nasopharyngitis (7.2%), upper respiratory tract infection (3.9%), headache (3.6%), diarrhoea (2.7%), and oral candidiasis (2.3%). The majority of TEAEs were mild or moderate in intensity in Pool SP1 with low rates of discontinuation of study drug.

The AE profile in placebo-controlled study periods resembles the AE profile observed in the initial submission for the psoriasis indication, apart from oral candidiasis (7.3%) which was reported more frequently in the PSO MAA.

In Pool SP2 (updated), the most frequently reported TEAEs by PT by PT were corona virus infection (14.2%), nasopharyngitis (13.4%), upper respiratory tract infection (10.0%), urinary tract infection (7.9%), and oral candidiasis (7.5%).

The majority of TEAEs were mild or moderate in intensity in Pool SP2 (updated). The incidence of severe TEAEs was 6.5% (EAIR 3.6/100 participant-years). The most frequently reported severe TEAEs occurred in the SOC of Infections and infestations 1.1% (EAIR 0.6/100PYs). The exposure-adjusted incidence rate (EAIR) for TEAEs was similar to that in the original submission. There was no evidence of increase in risk with longer exposure to bimekizumab.

In the updated safety analysis, the data for time to onset of TEAEs were similar to the original submission up to week 52. The incidence of TEAEs and SAEs increases noticeably after week 52. The MAH has clarified that the increase in reports of TEAEs and serious TEAEs after week 52 is due to the increased exposure in this time period.

Adverse drug reactions

All ADRs were in line with the previously established safety profile of bimekizumab in the approved PSO indication. All of the identified ADRs are adequately reflected in the PI. No new or changes in frequency category of existing ADRs are proposed based on the analyses of the updated Pool SP2 safety data. This is agreed.

COVID-19 pandemic

The incidence of TEAEs with the PT of corona virus infection were slightly higher in the placebo (1.5% EAIR: 4.7/100 participant-years) compared to the bimekizumab 160mg Q4W (0.7% EAIR: 2.3/100 participant-years) groups in Pool SP1.

The incidence of TEAEs with the PT of corona virus infection was 7.5% (EAIR: 4.9/100 participant-years) in the bimekizumab Total group in Pool SP2 in the original submission and 14.2% (EAIR: 8.0/100 participant-years) in Pool SP2 (updated) reflecting the increased prevalence of COVID-19 infection over time during the conduct of these studies. In Pool SP2 there were 9 serious TEAEs of corona virus infection /COVID-19 related. The incidence of serious TEAEs with the PT of corona virus infection in the bimekizumab Total group in Pool SP2 was 0.5% (EAIR: 0.3/100 participant-years). All occurred in study participants who were unvaccinated and had underlying risk factors. No COVID-19 infections resulted in study discontinuation.

SAEs and Deaths

Three deaths were reported in patients receiving bimekizumab. Two of these deaths were associated with significant cardiovascular risks and co-morbidity and it is agreed they are unlikely to be related to the study medications in the PsA studies. No exact cause was identified for the event of sudden death as no autopsy was conducted and no death cert was available. The third death was related to a road traffic accident (RTA) and was not related to study medication.

Twelve SAEs were reported in the bimekizumab (1.7% EAIR 5.5/100PYS) treated group in Pool SP1.There were 2 reports each of pneumonia and joint injury. All other reports were reported in one subject each. There is no obvious clustering or pattern in the type of event reported.

In Pool SP2 (updated), the incidence of serious TEAEs was 10.5% (EAIR 5.9/100 participant-years) in the bimekizumab Total group. There was no increase in EAIRs with longer duration of exposure (EAIR: 5.9/100 participant-years in the Safety Update vs 6.0/100 participant-years in the original submission.

The most common serious TEAEs by PT in the bimekizumab Total group were cholelithiasis (0.6%; EAIR 0.3/100 PYs), corona virus infection (0.5%; EAIR 0.3/100 PYs), and osteoarthritis (0.4%; EAIR 0.2/100 PYs).

The incidence rates of SAEs for the PsA safety pools were broadly comparable, albeit slightly lower than those observed in the PSO S1 and S2 safety pools.

Safety Topics of Interest

Analyses focusing on Pool SP1 and Pool SP2 (update) are provided for infections, malignancies, MACE, neutropenia, SIB, IBD, anaphylactic, hypersensitivity, and injection-site reactions, and hepatic TEAEs and LFT elevations. Overall, the frequency of AEs categorised as adverse events of special interest including important potential and identified risks was generally similar in both Pool SP1, SP2 and SP2 (updated), except for small increases in the adjudicated MACE (EAIR SP1 0/100PYs vs SP2 (updated) 0.4/100PYs), SIB adjudicated neuropsychiatric events (EAIR SP1 0/100PYs vs SP2(updated) 0.1/100PYs), hypersensitivity reactions (EAIR SP1 5.5/100PYs vs SP2(updated) 6.2/100/PYs) and adjudicated IBD (EAIR SP1 0/100PYs vs SP2(updated) 0.3/100PYs), all of which recorded a slightly higher EAIR in Pool SP2 (updated) compared to SP1.

Serious Infection

The overall rate of serious infections in PsA patients treated with bimekizumab is similar albeit slightly lower than the rates of infection in the psoriasis indication (Pool SP2 PSA EAIR 1.2/100PYs vs Pool S2 PSO EAIR 1.4/100PYS respectively).

The EAIR for updated SP2 safety pool was 1.1 /100PYs showing no increase compared with the original submission (1.2/100 participant-years). An additional 4 additional serious infections (cellulitis, pyelonephritis, pyelonephritis acute, and corona virus infection) were reported along with the 26 serious infections observed in the original submission, Corona Virus infection in 7 study participants, Lower respiratory tract infections and Urinary tract infections in 4 study participants each, Bacterial infections

NEC and Upper respiratory tract infections in 3 study participants each, and Ear infections in 2 study participants were the only PTs reported in more than 1 study participant.

In pool SP2, the outcome of most serious infections, including the 4 serious events reported in the SP2 safety update, was resolved. The outcomes of the remaining infections were resolved with sequelae (postoperative wound infection), resolving (gangrene), at the time of data cut-off.

In the original submission the incidence of Fungal infections was lower for the PSA Study population (SP2 EAIR 10/100PYs) compared to the PSO population (Pool S2 EAIR: 26.0/100 PYs). A similar pattern was seen for HLTs Candida infections, Fungal infections NEC and Tinea infections. In Pool SP2 (updated) the incidence of any fungal infection was 15.7%. The EAIR (9.4/100 participant-years) did not increase compared to the original submission (10.0/100 participant-years).

The reports of fungal infections were localised, mucocutaneous with low rate of discontinuation. There were no reports of systemic fungal infection. The lower rate of fungal infections in the PsA population compared to the PSO population is likely to be related to the lower dose of bimekizumab used in the PSO studies.

There were no cases of active TB among bimekizumab-treated study participants. No reactivation of TB in study participants with a history of latent TB was observed in the PsA development program and no study participant developed active TB.

Currently serious infections are included as an important identified risk in the RMP. In the SmPC, clinically important active infections (e.g. active tuberculosis) are included as a contraindication (SmPC Section 4.3) and information is also included in SmPC Section 4.4 and SmPC Section 4.8 to minimise the risk of serious infections. Wording regarding a recommendation to discontinue treatment in patients who develop infections that become serious or are not responding to standard therapy has been included in SmPC section 4.4. In addition, the section 4.8 of the SmPC was updated to reflect that Infection rates observed in PsA Phase 3 clinical studies were similar to those observed in plaque psoriasis apart from oral and oropharyngeal candidiasis rates in patients treated with bimekizumab, which were lower at 2.3% and 0% respectively in PsA compared to 0% with placebo.

Inflammatory Bowel Disease

There were 6 new onset cases and one case of exacerbation of IBD with bimekizumab (EAIR 0.3/100 participant-years) in Pool SP2 in the PsA development program. The incidence was somewhat higher than that observed during the PSO development program (the EAIR for IBD events was 0.055/100 PYs in the Phase 2/3 bimekizumab Total group in Pool S2 in the PSO MAA). No additional definite or probable IBD cases were reported in the SP2 pool safety update.

The MAH has indicated that a different strategy was used to identify IBD events in the PSO MAA submission compared to the PSA submission. Gastrointestinal events of interest (broad inclusive terms) were adjudicated by an expert committee as 'Definite' and 'probable' cases whereas TEAEs coding to HLT of "Colitis (excl infective)," were identified in the PSO program surmising that the cases of IBD in the PSO program are more likely to be definite cases of IBD. The incidence of definite IBD is still higher in the PsA program compared to the PSO program (EAIR 0.113 vs EAIR of 0.055/100 participant-years in the PSO program). The mechanism for identifying cases of IBD in the PSA program is more robust. The incidence of IBD in the PSO program may have been underreported. Of note, no new definite or probable IBD events were reported in the PsA Safety Update and the overall IBD incidence rate in the PsA development program has decreased slightly. The difficulties outlined by the MAH, associated with comparisons between clinical trial data and observational data, are acknowledged. The MAH's statement that the observed incidence rate in the PsA development program is in line with the published incidence rates of other marketed interleukin-17 inhibitors is not further substantiated. Overall, some uncertainty remains regarding the risk of developing IBD when treated for PsA with BKZ. The absolute IBD incidence rate in

the PsA development program is low. Information related to IBD is described in SmPC Section 4.4 (Special warnings and precautions for use) and SmPC Section 4.8 (Undesirable effects) and is included as an important identified risk in the EU Risk Management Plan. It will continue to be closely monitored via routine pharmacovigilance activities in Study PS0012 and the post-authorisation safety study (PS0038). No additional risk minimisation measures are considered needed at this point.

Hypersensitivity

The incidence of any hypersensitivity reactions in bimekizumab treated patients in Pool SP1 was 3.6% (EAIR 11/100PYs) compared to 9.4% (EAIR 6.4/100PYs) in Pool SP2. The incidence of hypersensitivity reactions was less than that recorded for Pool S2 of the PSO MAA (EAIR 10.9; the PSO development program). The incidence of any hypersensitivity reactions in bimekizumab treated patients in Pool SP2 (updated) was 10.8% (EAIR 6.2/100PYs)

Dermatitis and Eczema were the most frequently reported allergic reactions in the bimekizumab treated patients (Pool SP2) and were also reported more frequently in the bimekizumab treated population compared to the active reference drug (adalimumab) in PA0010. The majority of reactions were mild to moderate in severity and resolved on treatment. There was 1 serious hypersensitivity reaction (dermatitis) that was not considered to be related to study medication. In the SP2 safety update there was one potential hypersensitivity reaction reported as severe in intensity in the bimekizumab group (PT: dermatitis allergic). It was considered drug related and led to study discontinuation. There were no anaphylactic reactions reported.

Dermatitis and eczema are currently recorded as common side effects in section 4.8 of the SmPC. Hypersensitivity is further described under the subheading 'Description of selected adverse events' in section 4.8. Serious hypersensitivity reactions which will include serious forms of dermatitis are captured under the important potential risk of 'serious hypersensitivity reactions' in the RMP and will be further addressed post-approval. No additional risk minimisation measures are recommended at this time.

Injection site reactions

The incidence of injection site reactions was low in Pool SP2 (2.3%) All events were mild or moderate in intensity with none leading to discontinuation. The SP2 Safety Update results were comparable with those in the original submission.

MACE

The exposure-adjusted incidence rate of MACE (EAIR 0.4/100PYs) reported for the bimekizumab PsA program SP2 pool is slightly lower than the EAIR recorded for the S2 pool of the PSO MAA (EAIR 0.657/100PYs). No MACE were reported for pool SP1. In Pool SP2 (updated), the incidence of adjudicated MACE was low (0.7%) and EAIR was the same as the original submission (0.4/100 participant-years).

MACE with fatal outcome (acute myocardial infarction and sudden death) was reported for two study participants in the original submission. One additional participant experienced an adjudicated MACE (PT: ischemic stroke) during the safety update period. The event was serious, severe, assessed as not drug related by the Investigator, did not lead to study discontinuation, and resolved at time of data cut.

The majority of adjudicated MACE in the bimekizumab Total group were resolved. No trend was observed with respect to the time to onset of the MACE. There is no clear evidence of increased risk of MACE beyond that attributable to the potential underlying risk with PsA. MACE is included as an important potential risk in the RMP and will continue to be followed up post-marketing in study PA0012. Upon CHMP's request, The MAH has provided narratives of 6 cases of thromboembolic events (PE - 1 case, VTE - 5 cases) classified as 'Any adjudicated cardiovascular TEAES'. All six cases of thromboembolic disease identified in the clinical development plan for Bimzelx in PsA had confounding factors (obesity, neoplasm, knee injuries). These underlying comorbidities could plausibly have contributed to onset of these events.

None of these events were assessed as being related to study medication and treatment was continued in all cases. There is no clear suggestion of a signal here. Thromboembolic events will continue to be closely monitored in future PSURs as part of routine pharmacovigilance.

Malignancy

Malignancies were observed at low incidence rates (SP1 EAIR 0.5/100PYs and SP2 EAIR: 0.6/100 PYs) and with no trend in type or incidence in the bimekizumab treated study participants. This incidence rate was slightly lower than the PSO Pool S2 EAIR: 0.8/100 PYs. No case was fatal. In the Pool SP2 safety update incidences of malignant tumor TEAEs were slightly higher in the bimekizumab Total group (1.5%; EAIR: 0.8/100 participant-years) compared to the EAIR in the original submission (0.6/100 participant-years). Six additional malignancy TEAEs (gastric cancer recurrent, chronic lymphocytic leukaemia, ovarian cancer, prostate cancer, bone giant cell tumour, and renal neoplasm) were reported; 1 TEAE (ovarian cancer) was considered related to study drug. All TEAEs led to study discontinuation with the exception of bone giant cell tumour. There is no obvious clustering of tumour type. It is difficult to draw any conclusion on this small increase in incidence. Malignancy is included as an important potential risk in the RMP and malignancy will continue to be monitored post-approval over the remainder of Study 012 and in the planned PASS PS0038 in subjects with PSO.

Hepatic Events

In Pool SP1, the incidence of hepatic TEAEs was low (BKZ 4.0% EAIR 13.1 vs PBO 2.7% EAIR 8.7). The majority were nonserious and mild to moderate in severity. Four study participants discontinued due to hepatic TEAEs including one subject with drug induced liver injury. The proportion of subjects in the bimekizumab 160mg Q4W group with ALT or AST >5×ULN was low (0.6%). One study participant in the bimekizumab 160mg Q4W group met the laboratory criteria for potential Hy's Law. Due to the alternative explanations (alcohol abuse) for the LFT elevations and other confounding risk factors including obesity and concomitant MTX, this event was not considered a Hy's Law case.

In Pool SP2 the exposure adjusted incidence of hepatic events was lower than that seen in Pool SP1. 9.3% (EAIR: 6.3/100 participant-years) group. Two cases of pDILI were reported in Pool SP2. Both cases were considered to be possibly related to study medication but were confounded by concomitant medication and possible alternative aetiology. Both cases were reported as resolved, however GGT>2ULN remained in one case.

In Pool SP2 (updated), the incidence of any hepatic TEAEs was 10.5% (EAIR: 6.0/100 participant-years) compared with 9.3% (EAIR: 6.3/100 participant-years) in the original submission. No new serious or severe hepatic TEAEs were reported and the incidence of abnormal liver function values was low and comparable across all treatment groups. 1.4% in the bimekizumab Total group had at least 1 incidence of ALT or AST >5×ULN compared with 1.1% in the original analysis.

Sixteen cases of TEMA liver enzyme elevations (ALT or AST >5×ULN) were reviewed by a HAC, 12 were adjudicated as unlikely to be related to study medication whereas 4 were considered as possibly related. All cases had confounding factors, alternative aetiology, or did not have a temporal association with bimekizumab. Five participants were withdrawn due to elevated LFTs. In the Pool SP2 update four new cases of AST >5xULN were reported in addition to the previous cases. There were no new >5xULN elevations of ALT. In all study participants, abnormal liver function values were transient and reduced from the peak within a few days and all cases had other more likely causes of the events.

Overall, no new hepatic signal was identified in the PsA safety pools.

Neutropenia

The incidence of neutropenia was low in both safety pools (1.3% in the bimekizumab 160 mgQ4W group [Pool SP1] and 2.4% in the bimekizumab Total group [Pool SP2]). Cases were mostly transient and mild

to moderate in intensity with isolated severe cases. In Pool SP2, 30 study participants (2.1%) in the bimekizumab Total group had a TEMA neutrophils low count. No TEMA neutrophil counts were associated with serious infections.

In the Pool SP2 update, the incidence of neutropenia TEAEs was slightly lower compared with the original submission (EAIR: 1.4/100 PYs vs EAIR: 1.5/100 participant-years respectively). 6 additional study participants in the bimekizumab Total group had a TEMA neutrophils low count. All 6 of these study participants had Grade 3 or Grade 4 neutrophil values which were transient, and values returned to normal at subsequent visits. None of the neutropenia events were associated with serious infections or led to discontinuation.

The section 4.8 of the SmPC was updated to reflect that the frequency of neutropenia in PsA clinical studies was similar to that observed in plaque psoriasis studies.

SIB

No increased risk of suicide or suicidal behaviour was observed under bimekizumab treatment in the PsA development program. No completed suicides were observed in study participants treated with bimekizumab in the PsA program. In Pool SP2, 1 TEAE of suicidal behaviour was adjudicated as SIB but was not considered to be related to study medication. In the Pool SP2 update, there was a slight increase in the incidence of adjudicated SIB compared with the original submission (0.1%; EAIR: 0.1/100 participant-years vs <0.1%; EAIR: 0.0/100 PYs in the respectively). One additional TEAE 'psychiatric evaluation abnormal' was adjudicated as SIB by the Neuropsychiatric Adjudication Committee. The event was reported as severe in intensity, considered not drug related (as assessed by the Investigator), not resolved at the time of data cut off, and led to withdrawal of study drug. The study participant had a past medical history of anxiety and depression with noncompliance to medications. No new concerns have been identified here.

Clinical laboratory measurements, vital signs, and physical examination findings, and ECGs

No new safety signals were identified on analysis of the laboratory data. No safety signals were observed in haematology, biochemistry, vital signs, and physical examination findings. No notable trends were observed in the 12-lead ECG results across all treatment groups in Pool SP1 and Pool SP2.

There were no clinically relevant findings in the updated Pool SP2 analysis of vital signs, physical findings, and other observations related to safety. There were no clinically relevant increases in QTcF noted. One additional study participant was identified as experiencing ventricular tachycardia (reported term: non sustained ventricular tachycardia). It was reported as not serious, was mild in intensity, and was not considered related to study drug (as assessed by the Investigator).

Immunogenicity

Pool SP1

By Week 16, 31.2% of study participants had at least 1 ADAb-positive sample. By Week 16, the overall incidence of NAb-positive study participants in the overall pooled PsA Phase 3 population was 10.3%. The majority of participants were positive for both IL-17AA and IL-17FF.

Pool SP2

Available safety and immunogenicity (ADAb and NAb) data from PsA Phase 3 studies PA0010 (including data beyond Week 24 at the time of the Week 24 data cut-off), PA0011 and PA0012 (both at the time of the Week 16 data cut-off for PA0011) were considered. No notable trends were observed in ADAb or NAb positivity on the safety profile of bimekizumab in PsA

The MAH has clarified that they were unable to provide pooled immunogenicity data to week 52 based on Phase 3 studies in PsA studies due to the different timepoints for collecting ADAb and NAB values across the studies. Consequently, there was no cumulative collection timepoint for Study PA0012 for collecting 52-week data. Therefore, the MAH's proposal to present antibody data for 52-week results for Study PA0010 is acceptable. A further update will be provided on completion of Study 0012 post approval (see RMP).

In Study PA0010, by Week 52, 46.6% of study participants in the bimekizumab 160mg every 4 weeks (Q4W) group had ADAb and 17.9% had Nab. Study PA0010 only included treatment naïve subjects. This was reflected in for the section 4.8 of the SmPC, as requested.

The relationship between NAb and bimekizumab safety in PsA (Pool SP1 And Pool SP2) was further evaluated with a review of hypersensitivity reactions and administration site reactions. The majority of these reactions occurred in subjects who were always ADAb negative. In subjects who were ADAb positive the majority of cases started before the first ADAb positive result.

In the updated Pool SP2 the exposure-adjusted incidence of hypersensitivity and administration site reactions was highest in the Nab positive subjects (EAIR 13.4 /100PYs) compared with NAb negative but ADAb positive subjects (EAIR 11.4/100PYs). This is mainly down to an exposure-adjusted increase in reports of dermatitis and eczema in NAB positive compared to NAB negative subjects (EAIR 8.8/100PYs vs 4.4/100PYs). The absolute number of cases remain small. No new safety concerns have been identified in relation to ADAb status in this analysis of TEAEs, including injection site reactions and TEAEs of hypersensitivity reactions and anaphylactic reactions.

The section 4.8 of the SmPC was updated to reflect that across all indications, an association between immunogenicity and TEAEs has not been clearly established.

Safety in special populations

Overall, no new safety concerns were identified in an evaluation of TEAE profile, gender, race, and body weight. No safety trends were noted that would indicate a need to modify the dose regimen for any of these subgroups. Safety data by age, including older subjects >75 years has been provided for review. Serious TEAEs (<65yrs; 7.6% vs 65-74 yrs; 15.8% vs 75-84yrs; 28.4%) were reported more frequently in the age cohorts >65 years. Upon CHMP's request, the MAH has provided a tabulated summary and comment on SAEs by age group (<65yrs; 65-74 yrs; and 75-84yrs). The increase in SAEs is mainly attributed to disorders common in older people. Interpretation of this dataset is difficult due to the relatively small size of the dataset. The uncertainty around these findings is reflected in a new statement in Section 4.8 of the SmPC stating that exposure is limited in older patients. TEAEs leading to Permanent withdrawal of study medication due to TEAEs were also increased in the older age cohorts (<65yrs; 4.1% vs 65-74 yrs; 9.9% vs 75-84yrs; 6.3%). The commonest reason for withdrawal was oral candida. SmPC section 4.8 has also been updated to include warnings regarding increased reports of candida and dermatitis in older patients with PsA.

Baseline cDMARD type

The safety profile of bimekizumab in combination with MTX was generally similar to that observed when given in combination with other cDMARDs or as a monotherapy. There was some evidence of increased infections for bimekizumab in combination treatment with methotrexate or other cDMARDs in Pool SP2. These were attributed to URTIs (MTX 29.9% vs other cDMARDS 30.8% vs no cDMARDs 22.6%) and Viral infections NEC, mostly due to Corona Virus infections that were more commonly reported in the MTX (11.5%) and other cDMARDs groups (13%) than the no cDMARDS group (5%), suggesting a small increase in risk in viral for infections with combination therapy. There was no increase in risk for serious infections reported.

In the Pool SP2 (update), study participants in the no MTX or other cDMARDs subgroup (82.4%) reported slightly fewer TEAEs compared with the MTX group (84.4%) and other cDMARDs group (84.5%). [Pool SP2 updated, BKZ Total].

There was some evidence of increased infections for bimekizumab in combination treatment with methotrexate (62.1%) or other cDMARDs (61.4%) compared with no MTX or other cDMARDS (57.7%). There was no increase in risk for serious infections reported.

Overall, the proportion of study participants receiving other cDMARDs was small (8.9%). Although no new safety issues of concern were identified in this subgroup, knowledge of the comparative safety of bimekizumab in combination with cDMARDs other than MTX is insufficient to support the applied for indication: treatment with bimekizumab in 'combination with conventional DMARDs'. The MAH has revised this wording to remove reference to treatment in combination with conventional DMARDs and to restrict the indication to 'in combination with methotrexate'. This revised wording is acceptable.

2.5.2. Conclusions on clinical safety

The safety profile for bimekizumab in the SP1 and SP2 and updated SP2 safety pools for PsA is generally consistent with that identified in the PSO MAA submission although serious infections and fungal infections were reported less frequently than in the PSO population most likely due to the lower dose of bimekizumab used in the initial phase of PsA studies. There is no suggestion of an increase in risk with longer exposure to bimekizumab.

The number of rare and/or long latency events (such as MACE, malignancy, IBD) is typically low in this clinical development program. IBD is the only TEAE of special interest that was reported at a slightly higher incidence in the PsA studies compared to the PSO indication. The MAH has clarified that different methods of identification were used for cases of IBD in the PSO and PsA development programs that may contribute to the different reporting rates. The MAH will nevertheless continue to evaluate this safety topic post approval (see RMP).

2.5.3. PSUR cycle

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

2.6. Risk management plan

The MAH submitted an updated RMP version with this application.

The PRAC considered that the risk management plan version 1.7 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

Summary of safety concerns	
	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				
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.

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Annual recruitment report	01 Jun 2024 and annually thereafter until recruitment close
			Interim feasibility assessment	End of third year from start of recruitment
			Final study report	31 Dec 2034
PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy Planned	To monitor the safety of bimekizumab use in pregnancy.	Missing information: Use during pregnancy and lactation	Final protocol	Draft protocol submitted on 25 Nov 2021, endorsed 10 Nov 2022. 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 safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE,	Submission of interim clinical study report	31 May 2023

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO Ongoing		malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of final clinical study report	31 Dec 2024
PS0015 (EudraCT Number: 2017-003784-35) A multicenter, randomized, double-blind, secukinumab-controlled, parallel-group study to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque PSO Ongoing	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 Jan 2023
			Submission of final clinical study report	31 Jul 2024
PA0012 (EudraCT Number: 2018-004725-86) A multicenter, open label extension study to assess the long-term safety, tolerability, and efficacy of bimekizumab in the treatment of study participants with active PsA. Ongoing	Assess the safety and efficacy of long-term use of bimekizumab in PsA	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of clinical study report	Estimated clinical study report date 18 Sep 2026

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Important identified risks		

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindication) Risk of infections is discussed under SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.4 (Special warnings and precautions for use) SmPC Section 4.8 (Undesirable effects) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012
Important potential risks		
Serious hypersensitivity reactions	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.3 (Contraindication) SmPC Section 4.4 (Special warnings and Precautions) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012

Safety concern	Risk minimization measures	Pharmacovigilance activities
Major adverse cardiovascular events	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012
Malignancy	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0038: Bimekizumab real-world outcomes study PS0014; PS0015; PA0012
Missing Information		
Use during pregnancy and lactation	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). SmPC Section 4.6 (Fertility, Pregnancy, and Lactation) Further information is also provided in the PL **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0036: Bimekizumab pregnancy exposure and outcomes registry PS0037: An observational cohort study to evaluate bimekizumab exposure during pregnancy
Long-term safety	**Routine risk minimization measures:** Bimzelx is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of conditions for which Bimzelx is indicated (SmPC Section 4.2 Posology and method of administration). **Additional risk minimization measures:** None	**Routine PhV activities beyond adverse reactions reporting and signal detection:** None **Additional PhV activities:** PS0014; PS0015; PA0012

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 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

Psoriatic arthritis (PsA) is a chronic inflammatory arthropathy associated with psoriasis, which is classified within the group of the spondyloarthritis. Spondyloarthritis (SpA) is an umbrella term applied to a family of rheumatic diseases (including psoriatic arthritis [PsA], axial spondyloarthritis [axSpA], reactive arthritis, the arthritis of inflammatory bowel disease [IBD], and undifferentiated spondyloarthritis) that have features in common with each other and distinct from other inflammatory arthritides, particularly rheumatoid arthritis (RA).

PsA generally has, distal interphalangeal joint involvement, asymmetric distribution, dactylitis inflammation of the whole digit), enthesitis (inflammation at the site of tendon insertion into bone), spinal involvement, and an association with the human leukocyte antigen (HLA)-B27 allele.

There are many comorbidities that have an increased prevalence in patients with PsA compared to the general population such as cardiovascular disease, autoimmune-related conditions (ie, coeliac disease, uveitis, and autoimmune bowel disorders), Synovitis, acne, pustulosis, hyperstosis, and osteitis (SAPHO) syndrome, depression, and anxiety are also noted to co-occur with PsA.

3.1.2. Available therapies and unmet medical need

In the treatment of PsA, there are several options available including conventional disease modifying antirheumatic drugs (cDMARDs), biologic DMARDs (bDMARDs), and targeted synthetic DMARDs. Conventional DMARDs (eg, hydroxychloroquine, methotrexate [MTX], sulfasalazine [SSZ], and leflunomide [LEF]) are generally the first line of therapy. If the patient does not respond adequately to cDMARDs, a bDMARD or targeted-synthetic DMARD may be considered. Biologic DMARDs include tumour necrosis factor (TNF)α inhibitors (eg, infliximab, adalimumab, etanercept, golimumab, and certolizumab pegol), interleukin (IL)-17A inhibitors (eg, secukinumab and ixekizumab), IL-12/IL-23 inhibitors (eg, ustekinumab), and IL-23 inhibitors (eg, risankizumab and guselkumab). Targeted synthetic DMARDs include PDE4 inhibitors (eg, apremilast) and JAK inhibitors (eg, tofacitinib, upadacitinib).

Although the availability of treatment options has expanded over the years, there is still a significant unmet need, in particular in patients who are not responsive to these treatments or who do not maintain a clinical response. In addition, when patients do respond to treatment, many fail to achieve low disease activity or remission.

Patients with PsA symptoms who are not adequately treated or not well controlled are at risk of irreversible life-long joint damage that impacts the patient's quality of life including mobility, ability to

work, and control of pain. Hence, there remains a medical need for additional therapeutic options in PsA for patients with inadequate response to or intolerance to currently available therapies.

3.1.3. Main clinical studies

The development programme is based on two pivotal Phase 3 studies that evaluate the efficacy and safety of bimekizumab for the treatment of active PsA.

PA0010 and PA0011 are randomised, multicentre, double-blind, parallel-group, placebo-controlled studies to evaluate the efficacy and safety of bimekizumab in adult study participants with active PsA through 52 weeks and 16 weeks, respectively. PA0010 also included an active reference arm (adalimumab). PA0011 study participants had a history of inadequate response or intolerance to 1 or 2 TNFα inhibitors for either PsA or PSO and PA0010 study participants were bDMARD naïve and eligible to receive adalimumab.

In addition, both studies used the same dose, dosage form, and dosing schedule from Week 0 to Week 16. Both PsA Phase 3 clinical studies evaluated a dose regimen of bimekizumab 160mg Q4W.

After completion of the treatment period of PA0010 or PA0011, eligible study participants were allowed to enrol in an OLE study, PA0012, where long-term safety, tolerability, and efficacy of bimekizumab will be collected for up to 160 weeks.

3.2. Favourable effects

The primary objective was met in both pivotal studies (PA0010 and PA0011). In PA0010, Bimekizumab 160mg Q4W treatment demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.9% vs 10.0%, respectively). This difference is considered clinically meaningful, with a statistically significant odds ratio versus placebo of 7.082 ($p<0.001$). In PA0011, treatment with bimekizumab 160mg Q4W demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.4% vs 6.8%, respectively). This difference is also considered clinically meaningful, with a statistically significant odds ratio versus placebo of 11.086 ($p<0.001$). The results of all supportive analyses of the primary efficacy variable confirmed the primary efficacy results.

PA0010 and PA0011 also met all of the ranked secondary efficacy endpoints.

Change from Baseline HAQ-DI superior to Placebo

At Week 16 in PA0010, the bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in HAQ-DI compared with the placebo group (-0.2567 vs -0.0880, respectively; $p<0.001$).

At Week 16 in PA0011, the bimekizumab 160mg Q4W group had a greater mean decrease from Baseline (ie, improvement) in HAQ-DI compared with the placebo group (-0.3751 vs -0.0701, respectively; $p<0.001$).

PASI90 Response superior to Placebo

At Week 16 in PA0010, the bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group (61.3% vs 2.9%, respectively; $p<0.001$) in study participants with PSO involving at least 3% BSA at Baseline.

At Week 16 in PA0011, the bimekizumab 160mg Q4W group had a higher PASI90 responder rate compared with the placebo group (68.8% vs 6.8%, respectively; $p<0.001$) in study participants with PSO involving at least 3% BSA at Baseline.

Change from Baseline SF-36 PCS superior to Placebo

At Week 16 in PA0010, the bimekizumab 160mg Q4W group had a greater increase from Baseline (ie, improvement) in SF-36 PCS score compared with the placebo group (6.219 vs 2.326, respectively; p<0.001).

At Week 16 in PA0011, the bimekizumab 160mg Q4W group had a greater increase from Baseline (ie, improvement) in SF-36 PCS compared with the placebo group (7.258 vs 1.413, respectively; p<0.001).

MDA superior to Placebo

At Week 16 in PA0010, the bimekizumab 160mg Q4W group had a higher MDA responder rate compared with the placebo group (45.0% vs 13.2%, respectively; p<0.001).

At Week 16 in PA0010 the bimekizumab 160mg Q4W group had a higher MDA responder rate compared with the placebo group (44.2% vs 6.0%, respectively; p<0.001).

Change from Baseline vdHmTSS superior to Placebo on study participants with elevated hs- CRP and/or with at least one bone erosion (hs-CRP ≥6mg/L and/or erosion-positive) - PA0010 only

At Week 16 in PA0010, the bimekizumab 160mg Q4W group had a minimal change from Baseline in vdHmTSS, indicating inhibition of structural progression, whereas the placebo group worsened (0.04 vs 0.36, respectively; p<0.001) in study participants with elevated hs-CRP and/or at least 1 bone erosion at Baseline.

Enthesitis-free state superior to Placebo

The bimekizumab 160mg Q4W group had a higher proportion of study participants in the enthesitis-free state compared with placebo at Week 16 (49.8% vs 34.9%, respectively; p=0.008) in study participants with enthesitis at Baseline in the pooled PA0010/PA0011 population.

Dactylitis-free state superior to Placebo

The bimekizumab 160mg Q4W group had a higher proportion of study participants in the dactylitis-free state compared with placebo at Week 16 (75.6% vs 51.1%, respectively; p=0.002) in study participants with dactylitis at Baseline in the pooled PA0010/PA0011 population.

Change from Baseline vdHmTSS superior to Placebo – PA0010 only

In PA0010, the bimekizumab 160mg Q4W group had a minimal change from Baseline in vdHmTSS, whereas the placebo group worsened at Week 16 (0.04 vs 0.32, respectively; p=0.001) in all study participants.

Additionally, numerically greater improvements compared with placebo were observed for the non-ranked secondary efficacy endpoints following bimekizumab treatment. The results of all supportive analyses of the primary and secondary efficacy variables confirmed the results of the primary analyses, and subgroup analyses demonstrated consistent efficacy over placebo at Week 16 across multiple subgroups.

Across both studies, results demonstrated that bimekizumab 160mg Q4W treatment for 16 weeks resulted in improvements in multiple aspects of PsA disease, including improvement in joint and skin symptoms, improvement in multiple disease domains (e.g. physical function and peripheral disease manifestations), low disease activity, and improvement in patient-reported outcomes of fatigue (FACIT-Fatigue subscale scores), HRQoL (PsAID-12 response), and social life and work productivity (EQ 5D-3L and WPAI-SHP) Inhibition of structural damage in a bDMARD-naïve population was also shown (vdHmTSS assessment) in PA0010.

Updated PA0010 Week 52 efficacy data, provided upon CHMP's request during the review, demonstrated that efficacy outcomes achieved at Week 16 either continued to improve or were sustained up to 1 year

(Week 52). At Week 52, in both overall and in the subset of study participants with elevated hs-CRP and/or with at least 1 bone erosion at Baseline, the bimekizumab 160mg Q4W group and placebo/ bimekizumab 160mg Q4W group had a minimal mean change from Baseline in the vdHmTSS total score, indicating that the inhibition of structural progression observed with bimekizumab treatment was sustained.

In both pivotal Phase 3 studies, participants receiving bimekizumab 160mg Q4W showed significant improvement in signs and symptoms of PsA disease within 16 weeks of treatment regardless of whether they were bDMARD-naïve or TNFα-IR. The magnitude of improvement was consistent across both populations.

3.3. Uncertainties and limitations about favourable effects

There was insufficient representation of patients receiving concomitant treatment with "other csDMARD" in the pivotal studies to support B/R assessment in this patient group. Given that the majority of subjects enrolled were taking MTX as their cDMARD, the MAH agreed to restrict the indication for use of bimekizumab in PsA to monotherapy or in combination with methotrexate.

A largely PK focused rationale has been submitted in support of the proposed posology in patients with active PsA who have moderate to severe plaque PSO for bimekizumab 320mg Q4W for the first 16 weeks and Q8W thereafter. Nevertheless, further rationale was requested in support of this posology, in particular further justification for the efficacy (ACR response) of the proposed maintenance dose regimen in patients with PsA and concomitant moderate to severe PSO. In order to give the clinician flexibility in the treatment of patients with PsA and concomitant PSO who may not respond optimally to 320mg Q8W for joint symptoms in the maintenance phase, a switch to 160 mg Q4W in patients with PsA and concomitant PSO is proposed. It is agreed with the MAH that the risk of reduced ACR responses is small. The risk is acknowledged as more likely in patients with high body weight, however this risk is mitigated by additional posology available for patients with PsA and concomitant PSO and weighing ≥120kg to continue dosing with 320mg Q4W after Week 16. In addition, the newly proposed wording supports the general PsA treatment goals which aim to reflect patient preferences, with patients being provided with the best information concerning relevant options and consideration of all disease domains is available. The section 4.2 of the SmPC was thus updated to reflect that after 16 weeks, regular assessment of efficacy is recommended and if a sufficient clinical response in joints cannot be maintained, a switch to 160mg every 4 weeks can be considered.

3.4. Unfavourable effects

In Pool SP1 (up to 16 weeks; placebo control), the overall incidence of AEs was 52.3% in the bimekizumab treatment groups and 64.4% in the placebo groups, respectively. AEs were mostly non-serious, mild to moderate in severity, and did not require drug discontinuation. TEAEs were most commonly reported in the Infections and infestations SOC, in particular for events related to the high level terms (HLTs) Upper respiratory tract infections and Candida infections. The most commonly reported TEAEs were nasopharyngitis (7.2%), upper respiratory tract infection (3.9%), headache (3.6%), diarrhoea (2.7%), and oral candidiasis (2.3%).

In Pool SP2 over longer term, the most frequently reported TEAEs by PT were nasopharyngitis (11.4%), upper respiratory tract infection (8.9%), corona virus infection (7.0%), and oral candidiasis and urinary tract infection (6.7% each). In the Pool SP2 update the most frequently reported TEAEs by PT were corona virus infection (14.2%), nasopharyngitis (13.4%), upper respiratory tract infection (10.0%), urinary tract infection (7.9%), and oral candidiasis (7.5%). The majority of TEAEs were mild or moderate in intensity.

The incidence of severe TEAEs was 6.0% (EAIR 3.9/100 participant-years). The most frequently reported severe TEAEs occurred in the SOC of Infections and infestations: 1.1% (EAIR 0.7/100PYs). Herpes Zoster (2 cases), pneumonia (2 cases) and Coronavirus (3 cases) were the only TEAEs reported in more than one study participant. The incidence of severe TEAEs in the update Pool SP2 was 6.5% (EAIR 3.6/100 participant-years)

In Pool SP1, incidences of serious TEAEs were 1.7% (EAIR 5.5/100PYs) in the bimekizumab 160mg Q4W group and 0.7% (EAIR 2.3/100 PYs) in the placebo group during the Initial Treatment Period. In Pool SP2, the incidence of serious TEAEs was 9.1% (EAIR 6.0/100PYs) in the bimekizumab Total group. For Pool SP2(updated), the incidence of serious TEAEs was 10.5% (EAIR: 5.9/100 PYs).

A known risk for patients treated with bimekizumab is serious infection. The overall rate of serious infections was comparable between Pool SP1 and Pool SP2 (Pool SP1 EAIR 1.4/100PYs vs Pool SP2 EAIR 1.2/100PYs). The incidence of serious infections in updated Pool SP2 was 2.1% (EAIR 1.1/100 PYs). Incidences of fungal infections were higher in the bimekizumab-treated study participants (4.6% EAIR 15/100PYs)) compared with placebo (1.0% EAIR 3.1/100PYs), mainly driven by oral candidiasis infections (2.3% EAIR 7.4/100PYs). In Pool SP2, the incidence of any fungal infection in the bimekizumab Total group (which includes participants on higher doses of bimekizumab) was 14.2% (EAIR: 10.0/100 participant-years). Oral candidiasis (6.7%) and oral fungal infection (2.7%) were the most frequently reported fungal infections. In the Pool SP2 update, the incidence of any fungal infection was 15.7% (EAIR 9.4/100 PYs). No systemic Candida infections were observed in the PsA program.

Other Safety topics of interest selected by the MAH included malignancies, MACE, neutropenia, SIB, inflammatory bowel disease (IBD), hypersensitivity reactions, and injection site reactions. IBD was reported more frequently in the PsA compared to the PSO clinical development program. The Pool SP2 safety update results were similar to the original submission. No new safety concerns emerged from analyses of these safety topics of interest other than a small increase in reports of malignancy (1.5%; EAIR: 0.8/100 participant-years) in this updated analysis compared to the EAIR in the original submission (0.6/100 participant-years).

Serious TEAEs were reported more frequently in the age cohorts >65years. These were mainly attributed to age related conditions. TEAEs leading to Permanent withdrawal of study medication due to TEAEs were also increased in the older age cohorts. Oral candidiasis was the most commonly reported TEAE leading to withdrawal.

From a safety perspective the incidence of TEAEs in Pool S1 was lower in the other cDMARDs group (42%) compared with the MTX and no treatment groups (53.6% and 53.1%, respectively).

Over the longer term (Pool SP2) the incidence of TEAEs was higher in the MTX and other cDMARDs groups compared with the no MTX or other cDMARDs group mainly due to increased reports of URTI and coronavirus infections.

27.9% study participants were ADAb +ve and 10% were NAb +ve positive at week 16 in Pool SP1. In Study PA0010 (in treatment naïve patients) by Week 52, 46.6% of study participants had ADAb and 17.9% had Nab.

3.5. Uncertainties and limitations about unfavourable effects

In Pool SP2 in the PsA development program, the incidence of IBD was somewhat higher than that observed during the PSO development program; the EAIR for IBD events was 0.3/100 PYs in the PSA SP2 pool vs 0.055/100 PYs in the Pool S2 in the PSO MAA. The MAH has clarified that this may be due to differences in the methodology for identifying IBD in the PSO and PSA clinical trials. Nevertheless, this safety topic will be closely followed-up post approval (PASS, see RMP).

Immunogenicity data provided so far for bimekizumab was not associated with increases in injection site reactions or serious hypersensitivity reactions. Nevertheless, the absolute number of cases remain small to draw any firm conclusions. Hence, the section 4.8 of the SmPC was updated to reflect that across all indications, an association between immunogenicity and TEAEs has not been clearly established.

Study PA0012 open-label extension of up to 140 weeks (~2.7 years) which is still ongoing will assess the long-term safety, tolerability, and efficacy of bimekizumab; however, this may not be adequate to capture some rarer risks or risks with longer latency, i.e. malignancy. Longer term safety with BKZ will thus be assessed during the planned PASS PS0038 (see RMP).

Noticeable differences in the incidence of SAEs and TEAEs leading to discontinuation was noted when comparing between <65, and the >65 years age groups. There was wide variation in age subgroup sizes, with particularly low number of study participants in the over 75 to 84 years and ≥85 years age groups. The increase in SAEs is mainly attributed to disorders common in older people. Interpretation of this dataset is difficult due to the relatively small size of the dataset. The uncertainty around these findings is reflected in a new statement in Section 4.8 of the SmPC stating that exposure is limited in older patients. TEAEs leading to Permanent withdrawal of study medication due to TEAEs were also increased in the older age cohorts (<65yrs; 4.1% vs 65-74 yrs; 9.9% vs 75-84yrs; 6.3%). The commonest reason for withdrawal was oral candida. SmPC section 4.8 has also been updated to include warnings regarding increased reports of candida and dermatitis in older patients with PsA.

3.6. Effects Table

Effects Table for bimekizumab in PsA

Effect	Short description	Unit	Treatment BKZ 160mg Q4W vs Placebo	Uncertainties / Strength of evidence	References (Studies)
Favourable Effects					
ACR50 at Week 16 (Primary endpoint)	At least 50% improvement relative to baseline in joints and tenderness swelling as measured by ACR scale	%	PA0010: BKZ 43.9% (n=431) vs placebo 10.0% (n=281) PA0011: BKZ 43.4% (n=267) vs Placebo 6.8% (n=133) Pool E1: BKZ 43.7% (n=698) vs Placebo 8.9% (n=414)	p<0.001 for BKZ vs placebo (Pool E1, PA0010, and PA0011)	PA0010: Initial treatment period (placebo-controlled) in Phase 3 study PA0010 PA0011: Initial treatment period (placebo-controlled) in Phase 3 study PA0011 Pool E1: Pool of Initial treatment period (placebo-controlled) in Phase 3 studies PA0010 and PA0011
PASI 90 at Week 16	At least 90% improvement from baseline PASI in the subgroup of participants with PSO involving at least 3% BSA	%	PA0010: BKZ 61.3% (n=217) vs placebo 2.9% (n=140) PA0011: BKZ 68.8% (n=176) vs Placebo 6.8% (n=88) Pool E1: BKZ 64.6% (n=393) vs Placebo 4.4% (n=228)	p<0.001 for BKZ vs placebo (Pool E1, PA0010, and PA0011)	
MDA at Week 16	Participants achieving MDA at Week 16	%	PA0010: BKZ 45.0% (n=431) vs placebo 13.2% (n=281) PA0011: BKZ 44.2% (n=267) vs Placebo 6.0% (n=133)	p<0.001 for BKZ vs placebo (Pool E1, PA0010, and PA0011)	

			Pool EI: BKZ 44.7% (n=698) vs Placebo 10.9% (n=414)		
Enthesitis (LEI) free state at Week 16	Participants with enthesitis-free state at Week 16 based on the LEI in the subgroup of participants with enthesitis at Baseline	%	PA0010: BKZ 50.3% (n=143) vs Placebo 41.4% (n=70)	p=0.008 for BKZ vs placebo (Pool E1)	
			PA0011: BKZ 49.1% (n=106) vs Placebo 22.2% (n=36)		
			Pool E1: BKZ 49.8% (n=249) vs Placebo 34.9% (n=106)		
Enthesitis (SPARCC) Free state at Week 16	Participants with enthesitis-free state based on the SPARCC index in the subgroup of participants with enthesitis at Baseline	%	PA0010: BKZ 50.0% (n=166) vs Placebo 35.6% (n=90)	p<0.001 for BKZ vs placebo (Pool E1)	
			PA0011: BKZ 45.9% (n=122) vs Placebo 23.5% (n=51)		
			Pool E1: BKZ 48.3% (n=288) vs Placebo 31.2% (n=141)		
Dactylitis Free state at Week 16	Participants with dactylitis-free state based on the LDI in the subgroup of participants with dactylitis at Baseline	%	PA0010: BKZ 78.6% (n=56) vs Placebo 54.5% (n=33)	p=0.002 for BKZ vs placebo (Pool E1)	
			PA0011: BKZ 70.6% (n=34) vs Placebo 42.9% (n=14)		
			Pool E1: BKZ 75.6% (n=90) vs Placebo 51.1% (n=47)		
HAQ-DI (response)	Proportion of participants with a decrease of HAQ-DI from baseline of at least 0.35 in those with HAQ-DI>0.35 at Baseline	%	PA0010: BKZ 50.6% (n=318) vs placebo 32.1% (n=221)	Pool E1: BKZ 53.0% (n=549) vs Placebo 28.7% (n=331)	
			PA0011: BKZ 56.3% (n=231) vs Placebo 21.8% (n=110)		
			Pool E1: BKZ 53.0% (n=549) vs Placebo 28.7% (n=331)		
Inhibition of joint damage at Week 16	Assessed by LS mean of vdHmTSS that quantifies the extent of bone erosions and joint space narrowing (Radiographic Set)	Mean improve-ment	PA0010: BKZ 0.031 (n=420) vs placebo 0.312 (n=269)	Not measured in PA0011 p=0.001 for BKZ vs placebo in PA0010	
Unfavourable Effects					
Serious infections	Serious TEAEs under Infections and infestations SOC	%, EAIR	Pool SP1: BKZ 0.4% (n=698) vs Placebo 0.0% (n=413) Pool SP2: BKZ 1.9% (n=1401) EAIR 1.2 per 100PY (95% CI 0.8, 1.7)	Vast majority of infections seen with BKZ were nonserious, mild to moderate, and did not lead to study discontinuation. The incidence of serious infections was low overall.	Pool SP1 is pooled safety data of Initial treatment period (placebo-controlled) in Phase 3 studies PA0010 and PA0011. Pool SP2 consists pooled safety data for the combined Initial, Maintenance, and OLE Treatment Periods with the available data at the time of the 24-week data cut-off. Includes study participants who received at least 1 dose of bimekizumab in the Phase
Fungal infectious disorder	Events under HLGT Fungal infectious disorder	%, EAIR	Pool SP1: BKZ 4.6% (n=698) vs Placebo 1.0% (n=413) Pool SP2: BKZ 14.2% (n=1401) EAIR 10.0 per 100PY (95% CI: 8.7, 11.5)	Vast majority were mild-to-moderate, responded well to oral or local antifungals and did not lead to treatment discontinuation. None were systemic.	

MACE	Adjudicated MACE	%, EAIR	Pool SP1: BKZ 0.0% (n=698) vs Placebo 0.0% (n=413) Pool SP2: BKZ 0.6% (n=1401) EAIR 0.4 per 100PY (95% CI: 0.2, 0.8) Updated Pool SP2 BKZ 0.7% (n=1413) EAIR 0.4 per 100PY (95% CI: 0.2, 0.7)	Incidence low and similar to background. All MACE occurred in participants with multiple cardiovascular risk factors.	2 and Phase 3 PsA studies PA0008, PA0009, PA0010, PA0011, and PA0012 The SP2 Safety Update includes completed 52-week Phase 3 study PA0010 and the 16-week Phase 3 study PA0011, and all safety data entered into the OLE study PA0012 database as of the designated clinical cut off date 20 May 2022 (last Week 52 Visit of PA0010)
Malignancy	TEAEs in Malignant tumor SMQ	%, EAIR	Pool SP1: BKZ 0.1% (n=698) vs Placebo 0.5% (n=413) Pool SP2: BKZ 0.9% (n=1401) EAIR 0.5 per 100PY (95% CI: 0.3, 0.9) Updated Pool SP2 BKZ (n=1413) EAIR 0.8 per 100PY (95% CI: 0.5, 1.2)	Incidences of malignant tumor TEAEs in BKZ group were low and similar to placebo during the Initial treatment period. Overall low incidences with no trend in type of malignancies.	
Cutaneous hypersensitivity	TEAEs in Dermatitis and eczema HLT	%, EAIR	Pool SP1: BKZ 1.6% (n=698) vs Placebo 0.5% (n=413) Pool SP2: BKZ 4.4% (n=1401) EAIR 2.8 per 100PY (95% CI: 2.2, 3.6) Updated Pool SP2 BKZ 5.0% (n=1413) EAIR 2.7 per 100PY (95% CI: 2.1, 3.4)	No anaphylactic reactions observed. Potential cutaneous hypersensitivity observed, vast majority were mild-moderate and not leading to treatment discontinuation.	
IBD	TEAEs adjudicated as definite or probable IBD events	%, EAIR	Pool SP1: BKZ 0.0% (n=698) vs Placebo 0.0% (n=413) Pool SP2: BKZ 0.5% (n=1401) EAIR 0.3 per 100PY (95% CI: 0.1, 0.7) Updated Pool SP2: BKZ 0.5% (n=1413) EAIR 0.3 per 100PY (95% CI: 0.1, 0.5)	Incidence low but slightly higher than that seen in the PSO development program and higher than the expected disease background rates in the PSA population IR 7.68/10,000 PYs reported in the epidemiological study by Charlton et al 2018	
Hepatic events and elevated liver enzymes			Pool SP1: BKZ 4.0% (EAIR: 13.1/100 PYS) vs Placebo 2.7% (EAIR: 8.7/100PYs) Pool SP2: BKZ 9.3% (EAIR: 6.3/100 PYs) Updated Pool SP2: BKZ 10.5% (EAIR: 6.0/100 PYs) TEMA cases of liver enzyme elevations (ALT or AST >3×ULN)	Incidence low. Two participants in the bimekizumab Total group (459-02814 and 20036-10243) met laboratory criteria for PDILI. Both cases resulted in withdrawal from study and were considered possibly related to study medication. Both cases were confounded by concomitant medication. One case (participant	

			Pool SP1 :BKZ 1.3% vs 0% for placebo). Pool SP2: BKZ 3.8% Updated Pool SP2: BKZ 4.3%	09595) met Hy's law laboratory criteria but was not considered a confirmed Hy's law case as the LFT elevations were attributed to excessive alcohol consumption.	

ACR=American College of Rheumatology; BKZ=bimekizumab; BSA=body surface area; EAIR=exposure adjusted incidence rate; HAQ-DI=Health Assessment Questionnaire – Disability Index; HLGT=High Level Group Term; HLT=High level term; IBD=inflammatory bowel disease; LDI= Leeds Dactylitis Index; LEI=Leeds Enthesitis Index; LS=least squares; MACE=major adverse cardiac events; MDA=minimal disease activity; MedDRA=Medical Dictionary for Regulatory Activities; n=number of participants in the cohort; PASI=psoriasis area and severity index; PT=Preferred Term; SMQ=Standard MedDRA Query; SOC=System Organ Class; SPARCC=Spondyloarthritis Research Consortium of Canada; TEAEs=treatment-emergent adverse events; vdHmTSS=van der Heijde modified Total Sharp Score

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

Bimekizumab has demonstrated a statistically significant and clinically relevant improvement in the extent and severity of active PsA in a TNFα-IR population (Study PA0011) as well as a bDMARD naïve patient population (Study PA0010). The clinical development program also included study participants who had no prior exposure to cDMARDs 35.5% or had exposure to 1 or more prior cDMARDs (62.4%) however a limitation of this clinical development programme is the proportion of subjects with exposure to CDMARDs other than methotrexate (9.3%). As a result, the indication was restricted to monotherapy or combination with methotrexate.

The primary objective was met in both pivotal trials. In PA0010, Bimekizumab 160mg Q4W treatment demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.9% vs 10.0%, respectively). This difference is considered clinically meaningful, with a statistically significant odds ratio versus placebo of 7.082 ($p<0.001$). In PA0011, treatment with bimekizumab 160mg Q4W demonstrated a superior ACR50 responder rate at Week 16 (the primary efficacy variable) compared with the placebo group (43.4% vs 6.8%, respectively). This difference is also considered clinically meaningful, with a statistically significant odds ratio versus placebo of 11.086 ($p<0.001$). The results of all supportive analyses of the primary efficacy variable confirmed the primary efficacy results. Updated PA0010 Week 52 efficacy data demonstrated that efficacy outcomes achieved at Week 16 either continued to improve or were sustained up to 1 year (Week 52).

PA0010 and PA0011 also met all the ranked secondary efficacy objectives. Additionally, numerically greater improvements compared with placebo were observed for the non-ranked secondary efficacy endpoints following bimekizumab treatment. The results of all supportive analyses of the primary and secondary efficacy variables confirmed the results of the primary analyses, and subgroup analyses demonstrated consistent efficacy over placebo at Week 16 across multiple subgroups, with the exception of the age and gender subgroups in the phase 2 and phase 3 clinical studies, for which efficacy appeared less pronounced in some subgroups, however further rationale was provided by the MAH. Although lower efficacy in joint outcomes was observed in females and older patients, efficacy observed was still clinically relevant as compared to placebo. In addition, this phenomenon indeed is not unique to bimekizumab and is well known in the literature in studies with other biologics in PsA.

While there are a number of important identified and potential risks associated with bimekizumab, the current dataset in PsA patients is generally consistent with the previously known safety profile in PSO. No new safety issues have been identified during the review of this application. A number of post-authorisation measures are in place for further characterisation of important identified and potential risks.

The Product Information has been adequately updated with new information on PsA and already includes adequate warnings and precautions regarding the management of these risks.

3.7.2. Balance of benefits and risks

Although the availability of treatment options has expanded over the years, there is still an unmet need for a treatment that provides clinically meaningful improvement in the extent and severity of active PsA. The results on bimekizumab monotherapy and combination therapy with MTW show robust efficacy of bimekizumab compared to placebo up to 52-weeks. Hence, both the indication for monotherapy and combination therapy with MTX are considered acceptable to the CHMP. Overall, the favourable effects outweigh the unfavourable effects.

3.8. Conclusions

The overall B/R of Bimzelx is positive in the following indication:

'Psoriatic arthritis

Bimzelx, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adults who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs).'

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 active psoriatic arthritis in adults patients who have had an inadequate response or who have been intolerant to one or more disease-modifying antirheumatic drugs (DMARDs) for Bimzelx, based on results of a Phase III study in biological DMARD naïve study participants (PA0010; BE OPTIMAL) and a Phase III study in study participants who are inadequate responders (inadequate response or intolerant) to ⩽2 prior TNF inhibitors (PA0011; BE COMPLETE). Both Phase III studies are interventional studies aimed to evaluate the efficacy and safety of bimekizumab. For PA0010, the Initial Treatment Period was placebo- and no inferential active reference (adalimumab)-controlled, while PA0011 was placebo-controlled. As a consequence, sections 4.1, 4.2, 4.4, 4.5, 4.8, 5.1 and 5.2 to the SmPC have been updated. The Package leaflet is updated in accordance. The RMP version 1.7 is acceptable. Furthermore, the PI is brought in line with the latest QRD template version 10.2 rev.1.

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

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.0011'

Attachments

1. Product Information as adopted by the CHMP on 26/04/2023.