24 June 2021
EMA/393532/2021
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Bimzelx

International non-proprietary name: bimekizumab

Procedure No. EMEA/H/C/005316/0000

Note

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

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List of abbreviations

ADCC	Antibody-dependent cell-mediated cytotoxicity
AET	Analytical Evaluation Thresholds
AEX	Anion exchange
AI	Autoinjector
ANOVA	Analysis of Variance
APG	Acid peak group
AQL	Acceptable quality limit
BET	bacterial endotoxins
BLF	Break-loose force
BW	Body weight
BPG	Basic peak group
BSE	Bovine spongiform encephalopathy
CCI	Container closure integrity
CDC	complement-dependent cytotoxicity
CEX	Cation exchange
CHO	Chinese hamster ovary
CoA	Certificate of analysis
CPP	Critical process parameter
CPP	Critical process parameter
CQA	critical quality attribute
CQA	Critical quality attribute
CTCAE	Common Terminology Criteria for Adverse Events
DILI	Drug-induced liver injury
DF	Diafiltration
DHFR	Dihydrofolate reductase
DO	Dissolved Oxygen
DoE	Design of Experiments
DP	Drug product
DS	Drug Substance
DS	Drug substance
EAIR	Exposure-adjusted incidence rate
EOSL	End of shelf life
EtO	Ethylene Oxide
FACS	fluorescence-activated cell sorting
GF	Gliding force
GMP	Good manufacturing practice
GOF	Goodness of fits plots
HDPE	High density polyethylene
HLT	High Level Term
HMWS	High molecular weight species
IBD	Inflammatory bowel disease
iCE	Imaged capillary electrophoresis
IIR	Inter-individual variability
IGA	Investigator’s global assessment
IgG1	Immunoglobulin G1
IGRA	Interferon gamma release assay
IL-17	Interleukin 17
IPC	in process control
IPC	In process control
IR	Infrared
IRT	interactive response technology
LER	Low endotoxin recovery
LFT	Liver function test
LMWS	Low molecular weight species
MCB	master cell bank
MFI	Microflow imaging
MVI	Manual visual inspection

NEC	Not elsewhere classified
NOR	Normal operating parameters
NOR	normal operating range
NR-CGE	Non-reduced capillary gel electrophoresis
PAR	proven acceptable range
PAR	Proven acceptable range
PASI	Psoriasis Area and Severity Index
PBMC	Peripheral blood mononuclear cell
PC	Polycarbonate
PCR	polymerase chain reaction
PCS	process characterisation studies
PDE	Permitted daily exposure
PDMS	polydimethylsiloxane
PFS	Pre-filled syringe
PHQ-9	Patients' Health Questionnaire 9
PP	Process Parameter
PP	Process parameter
PPQ	Process performance qualification
PS80	Polysorbate 80
PS-80	Polysorbate 80
PVDF	Polyvinylidene fluoride
QTPP	Quality target product profile
RABS	Restricted access barrier system
RSE	Relative standard error
RH	Relative humidity
RNS	Rigid needle shield
SAL	Sterility assurance level
SDM	Scale down model
SE-HPLC	Size exclusion high performance liquid chromatography
SE-HPLC	Size exclusion High performance liquid chromatography
SIB	Suicidal ideation and behavior
SRF	Small round flange
SS	Safety syringe
SVP	Sub visible particles
TEMA	Treatment-emergent markedly abnormal
TNFα	Tumour necrosis factor alpha
TSE	Transmissible spongiform encephalopathies
UF	Ultra-filtration
VCC	Viable cell concentration
VPC	Visual Predictive Check
VRF	Virus reduction filtration
WCB	Working cell bank
WCB	Working cell bank
WFI	Water for injection

1. Background information on the procedure

1.1. Submission of the dossier

The applicant UCB Pharma S.A. submitted on 15 July 2020 an application for marketing authorisation to the European Medicines Agency (EMA) for Bimzelx, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004. The eligibility to the centralised procedure was agreed upon by the EMA/CHMP on 28 February 2019.

The applicant applied for the following indication:

Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/0375/2019 on the agreement of a paediatric investigation plan (PIP).

At the time of submission of the application, the PIP P/0375/2019 was not yet completed as some measures were deferred.

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant 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.

New active Substance status

The applicant requested the active substance bimekizumab contained in the above medicinal product to be considered as a new active substance, as the applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union.

Scientific advice

The applicant received the following Scientific advice on the development relevant for the indication subject to the present application:

Date	Reference	SAWP co-ordinators
26 May 2016	EMEA/H/SA/3306/1/2016/III	Dr Carin Bergquist, Dr Jan Mueller-Berghaus and Dr Caroline Auriche
21 July 2016	EMEA/H/SA/3306/2/2016/II	Dr Kirstine Moll Harboe and Dr Peter Kiely
14 September 2017	EMEA/H/SA/3306/1/FU/1/2017/III	Dr Peter Kiely and Mr Christian Gartner
18 October 2018	EMEA/H/SA/3306/3/FU/1/2018/II	Prof Livia Puljak and Dr Mario Miguel Rosa
25 July 2019	EMEA/H/SA/3306/4/2019/II	Dr Carin Bergquist and Dr Stephan Lehr

The Scientific advice pertained to the following *quality, non-clinical, and clinical* aspects:

- *Acceptability of comparability studies for various vial sizes.*
- *Sufficiency of the nonclinical program,*
- *Sufficiency of relying on the sharps injury prevention study*
- *Acceptability of the phase 2 study design, the dose finding and confirmation approach,*
- *Acceptability of the overall clinical development strategy, safety assessment, the planned effectiveness study, patient reported outcomes, endpoints*
- *Acceptability of the bioequivalence study to bridge between study drug and marketed product*

1.2. Steps taken for the assessment of the product

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

Rapporteur: Peter Kiely Co-Rapporteur: Christophe Focke

The application was received by the EMA on	15 July 2020
The procedure started on	13 August 2020
The Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2020
The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on	3 November 2020
The PRAC Rapporteur's first Assessment Report was circulated to all PRAC members on	16 November 2020
The CHMP agreed on the consolidated List of Questions to be sent to the applicant during the meeting on	10 December 2020
The applicant submitted the responses to the CHMP consolidated List of Questions on	17 February 2021

The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Questions to all CHMP members on	29 March 2021
The PRAC agreed on the PRAC Assessment Overview and Advice to CHMP during the meeting on	09 April 2021
The CHMP agreed on a list of outstanding issues in writing to be sent to the applicant on	22 April 2021
The applicant submitted the responses to the CHMP List of Outstanding Issues on	19 May 2021
The Rapporteurs circulated the Joint Assessment Report on the responses to the List of Outstanding Issues to all CHMP members on	09 and 17 June 2021
The CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a marketing authorisation to Bimzelx on	24 June 2021

2. Scientific discussion

2.1. Problem statement

2.1.1. Disease or condition

Psoriasis (PSO) is a common, chronic inflammatory disease characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leucocytes in affected skin.

2.1.2. Epidemiology and risk factors

The reported prevalence of PSO in countries ranges between 0.09% and 11.43%, with at least 100 million individuals affected worldwide (WHO report on psoriasis, 2016). PSO affects approximately 3% of the adult US population (Rachakonda et al, 2014; Kurd and Gelfand, 2009). Prevalence varies in Europe, due in part to different study populations and variability in ascertainment methods, with rates ranging between 2% and 6% (Danielsen et al, 2013).

Individuals with PSO are at an increased risk of developing other chronic and serious health diseases. These comorbid diseases include psoriatic arthritis, metabolic syndrome or components of the syndrome, cardiovascular disorders, and several other diseases such as anxiety and depression, non-alcoholic fatty liver disease, Crohn's disease, and lymphoma.

Risk factors for the development of psoriasis include genetic, environmental, and behavioural factors, with genetic factors being the largest contributor.

2.1.3. Aetiology and pathogenesis

The hallmark of psoriasis is sustained inflammation that leads to uncontrolled keratinocyte proliferation and dysfunctional differentiation. The histology of the psoriatic plaque shows acanthosis (epidermal hyperplasia), which overlies inflammatory infiltrates composed of dermal dendritic cells, macrophages, T cells, and neutrophils. Neovascularization is also a prominent feature. The inflammatory pathways active in plaque psoriasis and the rest of the clinical variants overlap, but also display discrete differences that account for the different phenotype and treatment outcomes (Rendon and Schäkel, 2019).

2.1.4. Clinical presentation, diagnosis and stage/prognosis

There are a variety of forms of PSO including plaque, guttate, inverse, pustular, and erythrodermic. Plaque PSO (PSO vulgaris) is the most common, comprising approximately 80% to 90% of all cases. It is estimated that approximately 80% of patients with plaque PSO have mild to moderate disease while 20% of patients have more severe disease, which affects either greater than 5% of body surface area or is located on high impact areas including scalp, genitals, hands, and nails (Boehncke and Schon, 2015; Menter et al, 2008).

The disease usually manifests as raised, well-demarcated, erythematous oval plaques with adherent silvery scales (Nestle et al, 2009), commonly presents on the elbows, knees and scalp, and may remain localized or become generalized (Lowes et al, 2007). The scalp is the most frequently and earliest affected area of the body in both paediatric and adult patients with PSO (Merola et al, 2018).

Nail involvement is also common, with an estimated prevalence of 50% in patients with plaque PSO. Clinical characteristics can range from pits, being the most typical and frequent signs, to complete nail destruction with crumbling of the nail plate, resulting in pain and restrictions in daily activities (Haneke, 2017; Jiaravuthiasan et al, 2007; de Jong et al, 1996).

2.1.5. Management

Therapy for patients with PSO varies per the severity of disease. Limited or mild disease is often treated with topical therapies, such as corticosteroids and vitamin D analogs, fumarates, and retinoids. Patients with more severe disease are often treated with photochemotherapy, ciclosporin, MTX, or biologic agents. Each therapy has unique characteristics that contribute to benefits and risks of treatment (Stiff et al, 2018; Armstrong et al, 2017; Nast et al, 2015).

Biologics including, but not limited to, tumor necrosis factor alpha (TNFα) inhibitors and interleukin (IL) inhibitors (eg, IL-17 and IL-23), are available treatment options for patients with moderate to severe plaque PSO who are candidates for systemic therapy. The effectiveness of TNFα inhibitors in the treatment of PSO has been demonstrated in many Phase 3 clinical studies and has led to the approval of multiple TNFα inhibitors for use in patients with moderate to severe plaque PSO. Interleukin inhibitors approved for PSO include the IL-12/23 inhibitor ustekinumab, the IL-17A inhibitors secukinumab and ixekizumab, the IL-17 receptor antagonist brodalumab, and the IL-23p19 inhibitors guselkumab, tildrakizumab, and risankizumab. These products are injected subcutaneously (sc) or delivered via intravenous (iv) infusion. Key safety concerns associated with the use of these biologic treatments include an increased risk of developing serious infections and malignancies; however, the associated risks vary across the different classes of biologic treatments (Piaserico et al, 2014; Menter et al, 2011).

These agents provide therapeutic options for many patients with moderate to severe plaque PSO, allowing achievement of at least a 75% reduction on the Psoriasis Activity and Severity Index (PASI75). However, fewer patients experience greater improvement (PASI90) or complete clearance (PASI100), and as PSO affects all aspects of a patient's life, an inability to achieve clear skin also negatively impacts their QOL. Furthermore, not all patients respond to current therapies and loss of response often occurs over time, which leads to patients switching to another medication for symptom relief (Kragballe et al, 2014; Piaserico et al, 2014; Menter et al, 2011). Thus, despite the number of currently available therapies, there remains an unmet need in the PSO treatment landscape for therapeutic agents that can provide more meaningful improvement in the extent and severity of plaque PSO.

About the product

Bimzelx contains bimekizumab as active substance.

Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) subclass with 2 identical antigen binding regions that potently and selectively bind and neutralise interleukin-17A (IL-17A), IL-17F, and IL-17AF cytokines.

Bimekizumab is intended to be indicated for the treatment of moderate to severe plaque psoriasis in adult patients.

Bimekizumab is administered as a solution for injection (160mg/mL).

Type of Application and aspects on development

The application was submitted under the legal basis 8(3) of Directive 2001/83/EC which corresponds to a complete and independent application.

The development program for bimekizumab in the treatment of moderate to severe plaque psoriasis (PSO) was discussed with CHMP in two Scientific Advice procedures in May 2016 (EMEA/H/SA/3306/1/2016/III) and in September 2017 (EMEA/H/SA/3306/1/FU/1/2017/III). See section 1.1. 'Scientific advice'.

Two formulations, three device presentations have been used during the development of bimekizumab.

2.2. Quality aspects

2.2.1. Introduction

Bimzelx is presented as a solution for subcutaneous injection in single use pre-filled syringe (PFS) or pre-filled pen (PFP). The active substance bimekizumab is formulated with glycine, sodium acetate trihydrate, glacial acetic acid, polysorbate 80 and water for injections. Each PFS or PFP contains 160 mg of bimekizumab in 1 mL solution.

Bimekizumab is a humanised IgG1/κ monoclonal antibody produced in a genetically engineered Chinese hamster ovary (CHO) cell line by recombinant DNA technology

2.2.2. Active Substance

General information

Bimekizumab is an engineered, humanised full length IgG1 antibody (approximately 149.9 kDa) which is manufactured in a Chinese hamster ovary (CHO) DG44 cell.

Bimekizumab has a high affinity for human interleukin 17A (IL-17A) and human interleukin 17F (IL-17F) and selectively and potently binds and inhibits the activity of both isoforms. IL-17A and IL-17F are soluble targets and key pro-inflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases.

Manufacture, characterisation and process controls

Description of the manufacturing process and process controls

The sites for manufacture, quality control and storage of the active substance are listed in the dossier. Active substance manufacture occurs at Rentschler Biopharma (Germany).

The active substance manufacturing process steps are divided in an upstream (cell culture) and downstream processing (purification).

Active substance production starts with thawing of a vial of the working cell bank (WCB). Cells are expanded in flasks and bioreactors before being transferred to the production bioreactor. After the production phase, the harvest is collected and clarified.

After clarification of the harvest, further purification is performed via several chromatography and filtration steps. To remove/inactivate possible viruses, a low-pH step and a nanofiltration are performed.

After purification the active substance is formulated. At the end, the active substance is filtered (0.2µm) and filled into bottles. The active substance is stored frozen at ≤-60^{0}C.

Reprocessing procedures are established Examples of events that could lead to reprocessing are specified.

Control of materials

Information is provided on all compendial and non-compendial materials used in the active substance manufacturing process. For non-Ph. Eur. materials, quality controls (specifications and acceptance) are described in detail. No raw materials were used from animal or human origin. All raw materials and component materials used in the production of the active substance (except for the production cells) originate from non-animal and non-human sources or are compliant to the effective version of EMA/410/01 (European Commission: Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products), and thus pose no risk for transmission of TSE/BSE.

Porcine trypsin and bovine serum were used early in the cell line development. However, a risk assessment and testing showed that there is no risk for BSE/TSE or viral contamination. The qualitative composition of media components has been provided along with a confirmation that a quality agreement is in place with the vendor to notify the marketing authorisation holder in case of qualitative changes to the media composition.

The source, history and generation of the cell banking system (master cell bank (MCB) and WCB) is adequately described and the cell banks have been qualified. In addition, characterisation of end-of-production-cells (EOPC) has also been addressed and genetic stability beyond end-of production stage has been demonstrated. The applicant has also provided a release testing programme for future WCBs. The cell bank system tested negative for mycobacteria. The applicant has demonstrated (via PCR) that the cell banks tested negative for porcine parvovirus, porcine circovirus and hepatitis E virus. In line with the 3R principles and ICH Q5A, virology testing is not performed in animals on future WCBs and extended cell banks.

Control of critical steps and intermediates

The Applicant provided an overview of critical and key process parameters (KPPs), as well as of all IPCs. Overall, the control strategy is deemed sufficient.

Process validation

The validation of the bimekizumab active substance manufacturing process was successfully completed using three consecutive batches from three independent thaws of the WCB according to the proposed commercial active substance process. Results from CPPs and in-process monitoring were provided. All process verification results presented for CPPs and KPPs as well as in-process quality controls met the predefined acceptance criteria. In addition, the active substance manufacturing process showed sufficient capacity for removal of process-related impurities, such as residual host cell proteins (HCP), DNA and Protein A. Furthermore, hold times and hold conditions for processed intermediates in the purification process have been justified based on supportive data. The proposed maximum hold times for the intermediates are therefore acceptable. Hold times will be extended through additional validation studies. Adequate detail is provided on how these additional studies will be performed. Also reuse of chromatography resins and the shipping of the active substance to the finished product manufacturing site has been adequately validated.

For the 0.22 µm filter microbial retention study, the test microorganism has been specified and its appropriateness justified.

Based on the process validation results presented, it can be concluded that in general the commercial active substance manufacturing process is capable of consistently and reproducibly producing active substance that meets relevant specifications.

Manufacturing process development

There were versions of the active substance manufacturing process throughout the process development history.

Comparability studies have been performed in accordance with the principles of ICH Q5E. Analytical comparability was assessed using various protein characterisation methods, batch release results, and a comparison of accelerated and stressed stability results. The data demonstrate that the active substance used throughout development and proposed for commercialisation is comparable. The comparability analysis included evaluation of fucosylated glycans, but not afucosylation which is acceptable as it has been demonstrated that Fc-mediated functions do not contribute to the mechanism of action of bimekizumab.

Fc-mediated functions were also not included in the comparability, which is acceptable as it has been demonstrated that Fc-mediated functions do not contribute to the mechanism of action of bimekizumab.

An overview of all the active substance lots produced thus far has been provided.

Risk assessments to identify the critical quality attributes (CQAs) of bimekizumab were performed using an approach aligned with quality by design (QbD) principles described in ICH Q8, Q9, Q10, and Q11. Quality attributes were identified based on the quality target product profile (QTPP), knowledge of the bimekizumab molecule, and information gained during process development and manufacture. No design space is claimed.

Process evaluation studies using scale-down models, which were verified as representative of the large-scale manufacturing process, have been performed for the bimekizumab active substance manufacturing process, to increase process understanding, define the acceptable range for process parameters and to identify CPPs that have a significant impact on the CQAs of the product.

A summary has been provided for the data from the extractables & leachables (E&L) assessment of contact materials during the active substance process. The levels and a justification for the levels of any E&Ls were provided and are acceptable.

Characterisation

Elucidation of structure

Bimekizumab was characterised using a range of biochemical, biophysical and biological techniques. Also forced degradation studies were performed. Studies were performed using samples of bimekizumab selected as representative of the commercial process and/or used in Phase III clinical studies.

Peptide mapping and molecular weight analysis were performed. Bimekizumab is structurally composed of two identical heavy chains and two identical light chains. The heavy chain contains 455 amino acids and the light chain contains 214 amino acids. There are sixteen disulfide bonds in total in bimekizumab: twelve intra-molecular bonds and four inter-molecular bonds. Each heavy chain contains an N-linked glycan with a biantennary oligosaccharide structure at the consensus glycosylation site at asparagine 305. As bimekizumab is a monoclonal antibody of the IgG1 subclass expressed in a CHO cell line, the predominant glycans expected are asialylated biantennary core-fucosylated structures differing in terminal galactose content. As is typical with mammalian cell culture processes, the heavy chain C-terminal lysine 455 is mostly removed by carboxypeptidases as a post-translational change.

The secondary and tertiary structure of bimekizumab were evaluated with circular dichroism, Fourier Transform infrared (FTIR) spectroscopy, intrinsic fluorescence analysis and differential scanning calorimetry. These analyses confirmed the correct higher-order structures of the molecule.

Product-related variants were analysed using various techniques. Size-exclusion high-performance liquid chromatography (SEC-HPLC), analytical ultra-centrifugation (AUC) and non-reducing capillary gel electrophoresis (NR-CGE) demonstrated the high monomer purity, with only low amounts of aggregates and low molecular weight species (LMWS). Imaged capillary electrophoresis demonstrated consistent charge variant profiles among bimekizumab lots. Liquid chromatography electrospray ionisation mass spectrometry (LC-ESI-MS) showed consistent and low levels of deamidation and oxidation. N-glycans analysis was performed using ultra-performance liquid chromatography (UPLC) and LC-ESI-MS analysis. Also sialic acid content was measured; only low levels of N-acteylneuraminic acid (NANA) were detected (no N-glycolylneuraminic acid (NGNA) was detected). N-glycan analysis assay will be retained as a characterisation test in case of relevant future variations related to the upstream process.

Biological activity analyses of bimekizumab were performed for Il-17A and Il-17F.

Impurities

Removal of process-related impurities was adequately evaluated. During process validation, removal of residual HCP, DNA and Protein A has been successfully demonstrated. All process-related impurities were shown to be removed to very low levels (much lower than the toxicological threshold) which do not raise any concern for safety.

Product-related impurities were characterised and shown to be consistent between batches.

Specification

The specification for the active substance includes control of identity, purity and impurity, potency and other general tests.

The acceptance criteria of the specifications are based on batches that have been utilised in clinical studies and batches manufactured with the commercial process to define the release and shelf life acceptance criteria for the commercial active substance. The acceptance criteria for the compendial tests are based on pharmacopoeial standards.

The proposed active substance specifications for purity are deemed sufficient.

A test for HCP is included in the active substance specifications. The HCP antigen has been properly qualified. In addition, the polyclonal antiserum used in the HCP assay was shown to have coverage that was deemed sufficient and adequate for its use in the HCP assay. The HCP assay was adequately validated.

The cell-based assay (see below) is capable to accurately monitor batch consistency with regard to potency as well as to detect sub-potent batches. As such, Il-17A/Il-17F binding assays do not need to be included in the active substance specifications. The proposed acceptance criteria for potency have been sufficiently justified and are deemed acceptable.

Analytical methods

Method descriptions are provided for the analytical procedures used in the testing of bimekizumab active substance. Analytical procedures were validated in accordance with ICH Q2(R1) and USP<1033> for the relative potency assay. Compendial procedures have been qualified or validated for testing bimekizumab in accordance with applicable pharmacopeia requirements.

Potency assay

Bimekizumab binds and neutralises both IL-17A and IL-17F. This binding and neutralising activity (expressed in % relative potency) of bimekizumab to IL-17A and IL-17F is quantitatively measured by cell-based assay, which is suitable and properly validated for release and stability testing of active substance and finished product.

Batch analysis

An overview of all batches (28) and full release testing data were provided, including the process verification batches manufactured according to the final commercial process. All results were compliant with the specifications.

Reference material

Five consecutive reference standards derived from different manufacturing processes were used during the development of bimekizumab. Each reference standard was prepared according to an approved protocol and qualified to the active substance specification in place at the time of testing.

Reference standard was prepared. The reference standard has been utilised in release and stability testing of bimekizumab active substance and finished product batches. Reference standard was prepared from commercial process. Qualification data for reference standard are provided. All acceptance criteria were met.

Future reference standards will be prepared from active substance batches manufactured from an approved commercial process. Each new reference standard will be qualified against the current reference standard to ensure consistency. The initial qualification of the reference standard will be performed against the current active substance release specifications. Additional characterisation tests will also be performed. Periodic qualification of the reference standard will be performed every 2 years by testing against the current active substance shelf life specification.

Container closure

The bimekizumab active substance is stored in sterile bottles with high density polyethylene (HDPE) screw cap closures. The sterile primary packaging material elements (bottle and screw cap) are received as 'ready-to-use' container components. The compatibility of bimekizumab with the primary container closure system is confirmed through leachable/extractable studies. The containers and closures are tested by the manufacturers of the container closure system to pharmacopoeial standards, where applicable. They are USP class VI compliant and meet the requirements of USP <85> and Ph.Eur. 2.6.14 for bacterial endotoxins. The bottles additionally comply with USP <661> Plastic Packaging Systems and their Materials of Construction.

Stability

A shelf life of 42 months when stored at ≤-60° C is claimed for the active substance.

The Applicant has performed long term stability studies (≤-60°C), accelerated stability studies (5°C±3°C) and stressed stability studies (25°C±2°C/60%±5% relative humidity) in accordance with applicable ICH guidelines.

48-month data has been provided from long term stability studies (for 4 lots). All results comply with the specifications. No trends are observed. Even under accelerated and stressed conditions, the active substance is relatively stable; only a slight increase in HMWS is observed.

Based on the available results, the Applicant proposes a shelf life of 42 months (≤-60^{0}C) which is acceptably supported by the data provided.

The Applicant commits to continue the ongoing stability studies in accordance with the testing protocol.

Post-approval, 1 batch will be placed on annual stability. Appropriate stability-indicating tests are included. In addition, testing for appearance, content, pH and potency are also included.

2.2.3. Finished Medicinal Product

Description of the product and pharmaceutical development

Description of the finished product

Bimekizumab finished product is supplied as a sterile, preservative-free 1 mL solution in PFS and PFP (clear to slightly opalescent and pale brownish-yellow):

Pre-filled Syringe (safety syringe) – Type I glass with a fluoropolymer-laminated bromobutyl rubber stopper, staked 27G, ½" thin wall needle, and a polypropylene rigid needle shield assembled in a passive safety device.

Pre-filled pen (auto-injector) – containing a pre-filled syringe (Type I glass) with a fluoropolymer-laminated bromobutyl rubber stopper, staked 27G, ½" thin wall needle, and a polypropylene rigid needle shield.

Commercial bimekizumab is formulated as a nominal formulation at 160 mg/mL bimekizumab in sodium acetate trihydrate, glycine, glacial acetic acid, polysorbate 80 and water for injections. All the excipients are of compendial grade. None of the excipients used in the finished product are of human or animal origin.

Pharmaceutical development

Full details of the formulation history throughout clinical development is presented in the dossier. Two different formulations and two container closure systems (vial and PFS) have been used in non-clinical and clinical studies. The commercial formulation was used in phase III clinical trials. The selection of excipients and their concentrations are based on internal knowledge/experience with sodium acetate/acetic acid buffer systems and glycine as excipients, development studies, including formulation robustness studies (two design of experiments (DoE) studies) and shipping and freeze/thaw studies. Overall, the Applicant has presented a good understanding of each component used in the commercial formulation and justified their inclusion.

No preservatives are included in the Bimekizumab PFS. Bioburden and endotoxins are routinely tested as IPCs. Sterility and endotoxins are tested at release and over shelf life.

The parameters identified as influencing the long-term stability of the finished product are pH and concentration of the finished product, which are suitably controlled by the manufacturing process and included in the release specifications (P.5.1) hence no queries are raised.

The finished product does not contain an overage of the active pharmaceutical ingredient. The PFSs are filled with a volume in slight excess (overfill). Clinically relevant physico-chemical and biological parameters have been identified. Osmolality and pH adequately controlled at release of finished product. While viscosity is not specifically controlled, it is deemed acceptable as any clinically significant deviations in viscosity would be detected on release testing for break loose / glide force.

Manufacturing History

Manufacturing process development from the early development phase to the commercial production is clearly described. Early manufacturing processes (active substance /finished product were carried out.

Subsequently, there were two changes during the active substance manufacturing history – a site change which also resulted in a change of container closure (vial to PFS), and then minor changes for finished product process improvement Comparability is presented for the site change.

Process evaluation

The approach used for process evaluation for the finished product includes prior knowledge from other platform therapeutic protein processes. Specific bimekizumab finished product manufacturing steps were characterised to optimise process parameters for the following steps: active substance thaw, transfer through bioburden reduction filter in process tank and active substance pooling, sterile filtration and aseptic filling and stoppering. Details of the studies carried out are described in the dossier and considered acceptable. Batches and process verification batches were included in these studies. Proven acceptable ranges (PARs) and normal operating ranges (NORs) were identified for each of these steps and demonstrated that the finished product manufacturing process is robust and can deliver the required product quality and process consistency when operated within acceptable ranges. No negative impact on product quality (size variants, protein concentration, charge heterogeneity, subvisible particles, reducing/non-reducing bioanalyser, pH, visible particles, appearance) is observed. Filtration was shown to have no impact on the polysorbate 80 content or protein concentration (measured before and after filtration).

Comparability

Comparability data between the 160 mg/mL vial and PFS presentation is presented and supports comparability. PFS batches contains higher levels of particles than vials. No trends were observed with time at the recommended storage condition (5±3°C), although the overall levels of subvisible particles are higher in the PFS compared to the finished product in the vial.

Overall, the results presented confirm that quality of the finished product was consistently maintained or improved during development and that relocation of manufacturing sites had no negative impact on PFS-finished product.

Batch History

Details of the lot history of all clinical batches is listed in several tables in the dossier. Pivotal studies (PS008, PS009 and PS0013) were carried out. All phase III clinical studies were conducted using the commercial PFS assembled into the True North functional secondary packaging. Long-term safety studies are conducted using batches manufactured from finished product /commercial process. While none of the pivotal studies were carried out in the commercial safety syringe/auto-injector (SS/AI) device, supportive clinical studies (UP0033 – phase I bioequivalence study and DV002/DV006 participant self-injection phase III studies) were conducted using the final assembled devices and deemed supportive.

Finished product commercial safety syringe/auto-injector device

Details on the manufacturing history of the safety syringe and auto-injector devices, including identification of the CQAs, CPPs and critical materials is provided and considered acceptable. The same assembly process has been used throughout development. The control strategy is based on the relevant medicinal product guidance (ICH quality guidelines Q8, Q9, Q10) as well as medical device standards (ISO 13485 and ISO 14971).

Container closure

The primary packaging for the bimekizumab finished product consists of a long Type I glass PFS fitted with a staked 27G, ½" special thin wall needle. In general, adequate descriptions have been provided for the container closure system components, including supplier specifications, technical drawings and

dimensions. The components of bimekizumab primary packaging comply with the requirements of the relevant Ph. Eur. monographs and ISO 10993. The glass barrel used complies with Ph. Eur. 3.2.1 (Glass Containers For Pharmaceutical Use), the stopper and shield comply with Ph. Eur. 3.2.9 (Rubber Closures For Containers For Aqueous Parenteral Preparations); this is endorsed. The silicone oil used as lubricant for the PFS barrel, plunger stopper, and the outside surface of the needle complies with the Ph. Eur. 3.1.8 monograph.

The choice of container closure system for bimekizumab quality and safety has been demonstrated and is supported by functionality (break-loose and gliding force, optimal fill volume) and compatibility studies (silicone oil analysis including interaction with polysorbate 80, tungsten spike studies). Controlled extraction studies were also performed on each component of the container closure. No extractables were found above the safety threshold or permitted daily exposure.

The Applicant notes that the staked needle and rigid needle shield is supplied pre-assembled and sterilised with ethylene oxide and the plunger stoppers are supplied sterilised by gamma radiation. Further details on the sterilisation methods are provided in the certificates of analysis for each component provided in P.2.4, which confirm sterilisation can achieve a sterility assurance level (SAL) of 10^{-6}. The names and address of the site of sterilisation for the pre-sterilised container closure system components are provided.

Notified Body Opinions (NBOps) in relation to Article 117 of the Medical Device Regulation (EU) 2017/745 have been provided for the safety syringe and auto-injector. The NBOps were issued by BSI and confirm compliance with the relevant General Safety and Performance Requirements (GSPRs). No issue in relation to these NBOps has been identified.

Details on the design, risk management and development of the safety syringe and auto-injector final device presentations (conducted in collaboration with the device manufacturers) have also been provided and are considered acceptable. Both are single use, with a sharp protection feature for self-administration by subcutaneous injection and do not have any contact with the finished product contained within the PFS. Data is provided showing that a reproducible and accurate dose of the product is delivered and that all other CQAs for each device presentation are reproducible.

The final safety syringe and auto-injector device presentations do not have any contact with the finished product hence no compatibility studies were conducted.

Manufacture of the product and process controls

Manufacture

The finished product manufacturer is UCB Pharma (Belgium). sites have valid GMP certificates for the concerned activities. The bimekizumab finished product composition is identical to that of the active substance, as no further compounding or dilution is performed during the finished product manufacturing process.

The finished product manufacturing process consists of the following steps: active substance thaw, bioburden reduction filtration and pooling, sterile filtration, aseptic filling, stoppering and visual inspection and storage.

Up to three active substance batches can be pooled for the manufacture of a bimekizumab finished product batch.

The assembly steps of the two devices occur under controlled conditions (18-25°C) and are conducted at the assembly site in accordance with current Good Manufacturing Practice (cGMP).

CPPs have been identified. An overview of the in-process controls is provided. The control strategy is considered acceptable.

Process validation

Process verification of the finished product manufacturing process was demonstrated by the successful completion of four consecutive process verification batches according to a pre-approved protocol. All four process verification batches met the pre-determined acceptance criteria for the study, demonstrating that all steps of the finished product manufacturing process produced pre-filled syringes meeting the pre-determined quality attributes. Also, the hold times of the finished product manufacturing process have been properly validated.

Product specification, analytical procedures, batch analysis

The specification for the finished product includes control of identity, purity and impurity, potency and other general tests, including tests for the safety syringe and auto-injector.

The proposed specifications are deemed suitable for the control of the finished product. The acceptance ranges of the specifications were justified based on the available batch data including those of the clinical batches. For quality attributes that show trends during shelf life, also stability data were taken into account to set and justify the specification limits. Any impurities present in the finished product are carried over from the active substance.

The potential presence of elemental impurities in the active substance and finished product has been assessed on a risk-based approach in line with the ICH Q3D guideline for elemental impurities. Four finished product lots were screened by inductively coupled plasma mass spectrometry (ICP-MS). No elemental impurities were detected above 30% of the permitted daily exposure. The risk of carryover of elemental impurities from reagents and materials used for manufacture is considered negligible and no additional control is required.

A risk evaluation concerning the presence of nitrosamine impurities in the finished product has been performed considering all suspected and actual root causes in line with the "Questions and answers for marketing authorisation holders/Applicants on the CHMP Opinion for the Article 5(3) of Regulation (EC) No 726/2004 referral on nitrosamine impurities in human medicinal products" (EMA/409815/2020) and the "Assessment report - Procedure under Article 5(3) of Regulation EC (No) 726/2004 - Nitrosamine impurities in human medicinal products" (EMA/369136/2020). Based on the information provided, it is accepted that no risk was identified on the possible presence of nitrosamine impurities in the active substance or finished product. Therefore, no additional control measures are deemed necessary.

Analytical methods

Details of the analytical procedures applied to test bimekizumab finished product are provided. Many of the analytical procedures are common to testing both active substance and finished product. Analytical procedures were validated in accordance with ICH Q2(R1). Compendial procedures were verified and confirmed suitable for their intended use.

Batch analysis

An overview of all batches and full release testing data were provided, including the 4 finished product process validation batches manufactured according to the final commercial process. All results were compliant with the specifications.

Reference material

As the active substance and finished product have the same composition, the same reference standards are used for both active substance and finished product testing.

Container closure

The primary packaging for the bimekizumab finished product consists of a long Type I glass PFS fitted with a staked 27G, ½" special thin wall needle (see above). In general, adequate descriptions have been provided for the container closure system components, including supplier specifications, technical drawings and dimensions.

Stability of the product

A shelf life of 36 months when stored at 5°C±3°C is claimed for the finished product.

The Applicant has performed long-term stability studies (5°C±3°C), accelerated stability studies (25±2°C/60±5%RH) and stressed stability studies (30±2°C/75±5%RH or 40±2°C/75±5%RH) in accordance with the applicable ICH guidelines.

Currently data up to 36 months are available (six batches of real time data for the 36 month time point. All results comply with the specifications. A thermal-cycling stability study, using one batch of finished product, demonstrated no impact to the finished product over 3 cycles alternating between -5±3°C and 5±3°C.

Based on the data presented, the proposed shelf life of 36 months (5°C±3°C) for the finished product is considered acceptable. Bimzelx may be stored at room temperature (up to 25°C) for a single period of maximum 25 days with protection from light. Once removed from the refrigerator and stored under these conditions, the PFS or PFP should be discarded after 25 days or by the expiry date printed on the container, whichever occurs first.

A photostability study, performed according to ICH Q1B light source option 2 conditions on 1 batch of PFS, demonstrated that bimekizumab PFS is sensitive to light exposure. Therefore, the PFS and PFP should be kept in the outer carton in order to protect from light.

The device components do not have any fluid path and do not have any contact with the bimekizumab solution contained within the PFS. Therefore, the stability of the bimekizumab FP in the PFS is not impacted by assembly into the bimekizumab-safety syringe device or bimekizumab-auto-injector device.

The Applicant commits to continue the ongoing stability studies in accordance with the testing protocol.

Adventitious agents

The Applicant has taken adequate and sufficient measures to avoid possible contamination by adventitious agents. The cell bank system has been thoroughly screened for possible viral contaminants. During manufacture the combination of IPC (bioburden, mycoplasma, *in vitro* adventitious agents) and release testing (bioburden sterility, endotoxin) guarantees the absence of contaminating agents.

A viral clearance study in accordance with ICH Q5A was performed using a representative small-scale process. The choice of the 4 model viruses (MLV, PRV, Reo3 and MVM) is deemed acceptable. Four active substance process steps were shown and validated to remove or inactivate viruses. The scaled-down process steps were qualified to be representative of the full-scale process.

Overall, high clearance/inactivation factors were observed for all 4 model viruses. The results support the claimed viral clearance throughout the resin lifetime.

As such, the viral risk associated with bimekizumab is negligible.

The transmissible spongiform encephalopathy (TSE)/bovine spongiform encephalopathy (BSE) status for the raw materials used in the manufacture of bimekizumab active substance have been assessed and confirmed to be compliant with EMA/410/01 (current version): Note for guidance on minimizing the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products. The risk of transmitting TSE/BSE agents is considered very low.

Overall, the adventious agents safety is considered sufficiently assured.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Overall, the bimekizumab quality dossier is of high quality. The active substance manufacturing process is adequately controlled to ensure routine production of material that meets the intended quality and that is representative of material used in the clinical development programme. Therefore, the batches used in clinical trials are representative with regards to the commercial product to guarantee that the latter will be the same as the clinical batches. The active substance and impurities have been adequately characterised. The control strategy sufficiently guarantees consistent and satisfactory quality of the product. The release testing and methods will ensure material of adequate quality. The proposed shelf life of the active substance is adequately supported by stability data. The material is acceptably safe from an adventitious agents and viral safety perspective.

The documentation provided for the manufacture, control and stability of the finished product is sufficiently detailed. The product is formulated using commonly used excipients. Sufficient details are provided detailing the pharmaceutical development of the product from early formulations in a vial through to the commercial product. Data presented throughout the process development confirm that quality of the finished product was consistently maintained or improved during development and that the commercial product is the same as batches used in clinical studies. The process is well characterised and process validation data supports the proposed process. Release and stability specifications ensure adequate control of the finished product. The methods are suitably validated. The product is stable and safe for use for the proposed shelf life.

All issues raised during the procedure have been resolved.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of Bimzelx is considered acceptable when used in accordance with the conditions defined in the SmPC. Physico-chemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

In conclusion, based on the review of the quality data provided, the marketing authorisation application for Bimzelx is considered approvable from the quality point of view.

2.2.6. Recommendation(s) for future quality development

None.

2.3. Non-clinical aspects

2.3.1. Introduction

The non-clinical development was performed in accordance with the ICH S6(R1) guideline.

The non-clinical evaluation has been conducted in the Cynomolgus monkey only since bimekizumab has no or very low affinity for mouse IL-17A, IL-17F or IL-17AF.

The pharmacokinetics (PK) of bimekizumab was investigated after single and multiple intravenous (iv) and subcutaneous (sc) injections in the Cynomolgus monkey.

Toxicology studies included a single-dose study and repeat dose studies in the Cynomolgus monkey with dose levels up to 200mg/kg/week for up to 26 weeks of duration in support to chronic human dosing. Assessments included effects on cardiovascular variables (repeat-dose studies), clinical observations, laboratory safety variables, immunophenotyping, T cell-dependent response to immunization, reproductive endpoints (26-week study) and histopathological changes. Intravenous and subcutaneous routes of administration were explored.

No evaluation of the genotoxic potential was performed and no standard carcinogenicity bioassays were conducted since the standard tests used were considered inappropriate for a monoclonal antibody. A Carcinogenicity Assessment was presented based on literature review and an evaluation of the applicant own non-clinical and clinical data.

General toxicity studies were all conducted in accordance with GLP.

2.3.2. Pharmacology

Primary and secondary pharmacodynamic studies

Primary and secondary pharmacodynamics studies with bimekizumab were conducted *in vitro*.

Pharmacodynamic activity of bimekizumab was investigated in primary cultures of normal human dermal fibroblasts (NHEK) and epithelial keratinocytes (NHDF). Bimekizumab prevented CXCL-1 (chemokine (C-X-C motif) ligand 1) secretion in NHEKs and NHDFs incubated with activated Th17 cell serum. PCR analysis identified that bimekizumab altered gene expression responses with greater activity than inhibition of IL-17A only. Inhibition of IL-17F had minimal to no effect on gene expression responses). The presence of IL-17A/F expression on normal epidermal tissue and inflammatory cells in the lesioned psoriatic skin was qualitatively presented by the applicant.

Affinity studies were performed by surface plasmon resonance on BIAcore and using a cell-based assay with stimulated NIH-373 cells. BIAcore data identified Kd values for IL-17A, IL-17F and the heterodimer IL-17AF. Affinity for IL-17F was 8-fold lower than Il-17A and comparable to the affinity for the heterodimer AF.

Table 1 Affinity of bimekizumab against human IL-17A, IL-17F and IL-17A/F (mean values)

Cytokine	K_D (pM)[a]
Human IL-17A	3.5
Human IL-17F	28
Human IL-17AF	26

IL=interleukin; K_D=dissociation constant (measures affinity between a ligand and a protein)
[a] BIAcore; 4 to7 measurements

In the NIH-3T3 assay, which used IL-6 secretion as the readout, cells were stimulated with human IL-17A or IL-17F (in combination with recombinant tumor necrosis factor-alpha (TNFα)). Bimekizumab inhibited both secretion of IL-6 elicited by IL-17A or IL-17F; again, bimekizumab had higher affinity for

IL-17A, ~39-fold higher than IL-17F. A separate NIH-3T3 assay was conducted with UCB mAbs specific for IL-17A or a commercial IL-17F antibody; again bimekizumab inhibited Il-6 to a greater extent than the IL-17A and IL-17F inhibitors alone. A third type of potency assay was performed in NHDF however values could not be determined in this experimental system. A transwell assay with NHDFs investigated neutrophil and monocyte migration where bimekizumab demonstrated the greatest capacity to inhibit migratory activity, indicating that total IL-17 inhibition is important for this effect. In this setting, selective inhibition of IL-17F had minimal impact, whereas anti-IL-17A antibody notably suppressed the migratory capacity of human neutrophils and monocytes. Interestingly, dual blockade of both IL-7A and IL-17F with bimekizumab showed the greatest capacity to inhibit neutrophil and monocyte migration, indicating that to fully inhibit IL-17 mediated inflammation, both IL-17A and IL-17F must be neutralized.

A comparison of affinity and potency of bimekizumab in Cynomolgus monkeys was investigated using surface plasmon resonance in BIAcore and an NIH-3T3 bioassay. In the BIAcore analysis the affinity of bimekizumab for cynomolgus IL-17A and IL-17F was lower 3.5-fold and 12-fold, respectively compared to human. The capacity of bimekizumab to cross react with Cynomolgus monkey IL-17A and IL-17F was also determined in the NIH-3T3 cell bioassay, where affinity of bimekizumab for IL-17A was ~1.6-fold higher in monkeys, and ~2-fold lower for monkey IL-17F.

No *in vitro* data is available with regards to the binding of bimekizumab to other unrelated cytokines. This was justified by the selectivity of bimekizumab and by the lack of sequence homology across those cytokines as compared to the target ligands IL-17A and IL-17F. Furthermore, no cytokine mediated effect and no change in cytokine levels were noted in non-human primates (NHP) administered bimekizumab.

No *in vivo* pharmacodynamics assessment has been conducted given the low expression of IL- 17A and IL-17F in normal tissues, as no direct pharmacodynamics markers are available, and as no appropriate and relevant animal model of PSO is available. Furthermore, mice models of inflammation involving IL-17 do not seem appropriate since murine IL-17F has shown a different physiological role and regulation.

Secondary pharmacodynamics studies investigated the potential for antibody-dependent cell-mediated cytotoxicity (ADCC) in NHDFs co-cultured with hIL-17A or hIL-17F, with cetuximab as a positive control. There was no evidence of reduced cell viability indicating bimekizmab does not mediate ADCC. Similarly, the potential for complement-dependent cytotoxicity (CDC) was investigated in peripheral blood mononuclear cell (PBMCs) pre-stimulated with hIL-17A or hIL-17F. There was no effect of bimekizumab on PBMC viability at any dose level, compared to control and positive control alemtuzumab. The applicant states that Bimekizumab is devoid of Fc effector functions since its targets are soluble. An in vitro study (study 40001929) assessing the cell depletive potential of bimekizumab via ADCC or CDC on IL-17 producing CD4+ T cells was conducted. Activated PBMCs from two independent human donors were cultured with varying concentrations up to 100 µg/mL of either bimekizumab or secukinumab (IgG1 anti-IL-17A), and changes in IL-17 producing CD4+ T cells were monitored by flow cytometry after 24h. Rituximab and ocrelizumab, which are known B cell depletors active by ADCC and CDC mechanisms, were used as a positive control in this assay. The results indicated that both bimekizumab and secukinumab did not alter the number of CD4+ IL-17+ T cells whereas in the same assay rituximab, and ocrelizumab efficiently ablated CD20+ B cells. These results indicate a ligand (Class III IgGs)-mediated effect rather than an ADCC/CDC-related effect as the underlying mechanism of action of bimekizumab to inhibit IL-17A/IL-17F signalling. The absence of relevant toxicity in non-clinical studies supports these conclusions.

In vivo treatment with an anti-IL-17 antibody may be associated with neutropenia. Administration of anti-IL-17 antibodies in humans indicated that this potential risk was low and reversible. Furthermore,

no effects on circulating levels of neutrophils were observed in toxicity studies performed in Cynomolgus monkey. See section 2.6 on clinical safety.

Safety pharmacology programme

No dedicated safety pharmacology studies were conducted, instead safety endpoints were included in GLP-compliant repeat-dose toxicology studies. No effects on the central nervous system were noted and clinical observations in repeat-dose studies suggest bimekizumab did not alter respiration. Cardiovascular safety pharmacology was investigated in the 8-week and 26-week repeat dose studies in cynomolgus monkeys. No changes in cardiovascular variables (systemic arterial blood pressure [systolic, diastolic, and mean blood pressure] or heart rate), and no significant effects on electrocardiogram (ECG) Lead II parameters (PR, RR, QT, QTc intervals, and QRS duration) were produced at any dose. There were no abnormalities in the ECG waveform or morphology that could be directly attributed to administration of bimekizumab. Exposure to bimekizumab was adequate to ensure neutralization of IL-17A and IL-17F at levels sufficiently in excess of the KD of bimekizumab (in the picomolar range). No renal pharmacology studies have been conducted. The applicant considered that since antibodies are degraded by non-specific cell uptake followed by lysosomal degradation, the renal function is not expected to be impacted by their catabolism.

Pharmacodynamic drug interactions

Pharmacodynamic (PD) drug interactions are not expected with monoclonal antibodies, thus, no non-clinical PD drug interactions studies were conducted. Cytokines e.g. Il-6, can alter activity of CYP450, thus inhibition of IL-17A/F by bimekizumab could circumvent this in the psoriatic patient.

2.3.3. Pharmacokinetics

To support the non-clinical development of bimekizumab, several PK assays were developed and validated (see table below).

Table 2 - Pharmacokinetic assays

Format	Sandwich ECLA	Sandwich ECLA	Sandwich ECLA
Capture	Biotinylated recombinant human IL17A	Rabbit anti-idiotypic antibody to bimekizumab	Rabbit anti-idiotypic antibody to bimekizumab
Detection	Goat anti-human (kappa) SULFO-TAG	Sheep anti-human IgG1 SULFO-TAG	Sheep anti-human IgG1 SULFO-TAG
PK Assay Range	69.0 to 50,000ng/mL	150 to 18,000ng/mL	150 to 18,000ng/mL
Used in Studies	NCD2259, NCD2260	NCD2384, NCD2450	NCD2676

ECLA=electrochemiluminescence immunoassay

No dedicated pharmacokinetic studies have been performed with bimekizumab. The toxicokinetics of bimekizumab were characterised in single and repeat-dose toxicology studies in cynomolgus monkeys.

Doses of up to 200 mg/kg/week were administered i.v. or s.c., the latter reflecting the intended clinical route of administration. Dose proportionality was generally demonstrated; bimekizumab had a slow elimination and extended terminal half-life. Steady-state concentrations was reached after 7-9 weekly

doses in most animals. Following i.v. administration the mean volume of distribution (Vz) ranged between 93.7mL/kg and 109mL/kg, independently of the dose, and the mean clearance (CL) ranged between 4.5mL/day/kg and 5.5mL/day/kg. No sex differences in bimekizumab exposure were noted in repeat-dose studies. In the enhanced peri- and postnatal development (ePPND) study, bimekizumab exposure was evident in infants confirming significant in utero exposure, persisting into the postnatal period at concentrations considered sufficient to fully inhibit IL-17A and IL-17F.

Sustained exposure to bimekizumab is reported in all the toxicity studies conducted in the NHP administered monotherapy, including for high dose levels. Therefore, detection of ADA was not systematically evaluated. ADAs were measured in the 8-week study with adalimumab and the ePPND study. In the 8-week study with adalimumab, only co-treated animals displayed reduced bimekizumab exposure after repeated doses and select animals in 2 mg/kg/week and 20 mg/kg/week groups were positive for anti-bimekizumab antibodies. The presence of ADAs to bimekizumab was also evident in all mothers and infants in the ePPND study in the postnatal period, after cessation of treatment. However, the applicant considered that production of ADA in those studies does not represent a concern for the interpretation of the pivotal toxicity studies where sustained exposure was achieved.

2.3.4. Toxicology

The applicant submitted a toxicology package consisting of a single dose toxicity study, an 8-week repeat dose study, an 8-week repeat dose study with adalimumab, a 26-week repeat dose study and an ePPND toxicity study. All studies were in compliance with GLP and investigated the clinical route of administration (subcutaneous). A once weekly dosing regimen was employed in all studies (except for the single dose study) to achieve exposures in excess of those anticipated with the proposed clinical regimen. Cynomolgus monkeys were used in all studies as they were considered to be the only relevant non-clinical species by the applicant.

Single and repeat dose toxicity

The main finding in single and repeat dose studies was the increased risk of infection due to reduced muco-epidermal immunity. In the single dose and 8-week study with bimekizumab, the applicant concluded that *Balantidium coli* was the causative pathogen, considered to be species-specific and not relevant to humans. In the 8-week study, gastrointestinal (GI) lesions were noted as pathological correlate of *Balantidium coli* infection and resolved during the 12-week recovery period. To circumvent the issue of *Balantidium coli* infection, animals in the 26-week repeat dose study were pre-treated with metronidazole to reduce the *balantidium coli* load. Superficial dermatitis was the most prevalent finding in the 26-week study, likely resulting from on-target pharmacology and/ or hypersecretion of IL-21, IL-22, and/or IL-17C. This finding was generally considered to be low grade and improved in recovery phase but the effect was not completely reversible. While this finding was not observed in the 8-week study, despite significant bimekizumab exposure in the recovery period due to the extended half-life of the active substance, external factors that may have influenced this difference between the studies which were conducted at different facilities, including differences in the genetic background, housing conditions and age of the monkeys.

The no-observed adverse effect level (NOAEL) was the highest dose tested in the 8-week studies (200mg/kg/week and 20mg/kg/week, respectively, for Study NCD2260 and Study NCD2384).

Due to the severity of skin findings in some high-dose animals and mortalities in the low dose group consecutive to GI infection, no NOAEL could be determined in the 26-week study.

However, if it is considered that infections and microorganism-related changes are not directly translatable from NHP to humans, the safety ratio can be calculated using the exposure at the high dose in this study (corresponding to AUC0-7days of 23967 day.µg/mL and Cmax of 4303µg/mL).

One animal was euthanized at Day 115 of the treatment phase due to repeated enteritis in the 26-week study. A second animal was euthanized in the recovery phase due to the same issue. No causative pathogen was identified in either case. A NOAEL was not defined in this study. The applicant postulates that reduced mucosal immune surveillance as a consequence of on-target pharmacology of bimekizumab, and similar to marketed IL-17A inhibitors could underlie these findings.

Genotoxicity

No genotoxicity studies have been conducted with bimekizumab in line with ICH S6 (R1) guideline.

Carcinogenicity

The applicant submitted a carcinogenicity assessment document (CAD) reviewing the weight-of-evidence for IL-17A and IL-17F in carcinogenesis and tumour progression. Although the information published on the role of IL-17 in tumour promotion is still confusing, based on the weight of the evidence available to date, neutralizing IL-17A does not suggest an increased tumour promoting risk. Bimekizumab is also pharmacologically active in the inhibition of IL-17F. There is minimal evidence on the potential tumorigenic role of IL-17F. Generally, IL-17F functions are less potent than IL-17A and have not been reported to recruit leukocytes or promote angiogenesis. In addition, no pre-neoplastic or neoplastic lesions are reported from the chronic repeat-dose toxicity study monkeys, following 26 weeks of sc dosing up to 200mg/kg/week, with exposure at the high dose in this study (corresponding to AUC0-7days of 23967 day.µg/mL and Cmax of 4303µg/mL) 109 times the human exposure at 320 mg every 4 weeks. Malignancy is identified as an important potential risk in the RMP.

Reproduction Toxicity

Reproductive and developmental toxicity studies are supported by an evaluation of fertility in sexually mature animals used in the 26-week repeat dose toxicology study and an enhanced peri- and postnatal development (ePPND) study. There was no evidence of impaired fertility parameters in either sex in the 26-week study (i.e. no effects were observed on semen quality, testicular size, and spermatic staging in males and menstrual cycle duration in females following bimekizumab treatment.). The ePPND study was carried out in cynomolgus monkeys; female animals were dosed weekly from GD20 to parturition. No effects on survival rate, external or internal morphology, or skeletal formation were noted. Steady state concentrations of bimekizumab was achieved in maternal animals between GD83 and GD139. Comparable bimekizumab concentrations were detected in mothers and infants at PND7 indicating significant in utero exposure via placental transfer and pharmacologically-relevant concentrations persisted for a minimum of 2 months in post-natal period. In maternal animals, the main finding was dose-related mild non-adverse skin changes representative of superficial dermatitis. In infants, the main finding was transient discolouration of the lips; this was considered non-adverse. Exposure achieved in this study represents a 27-fold safety margin to the anticipated clinical exposure. No juvenile toxicity studies were conducted as the ePPND study was considered sufficient to cover the developmental period of the immune system and no effects were observed.

Toxicokinetic data

Toxicokinetic analysis was performed in all pivotal studies. Exposure-based safety margins were derived on the basis of exposure at the maximum dose (200 mg/kg/week) in the 26-week repeat dose study and the NOAEL in ePPND study. Exposures were significantly in excess of anticipated clinical exposure.

Local Tolerance

Local tolerance after iv and sc administration of bimekizumab was investigated as part of the 8- week- and 26-week repeat dose toxicology studies in Cynomolgus monkeys. There was no evidence of macroscopic changes at the injection site after treatment.

Other toxicity studies

Tissue cross-reactivity was investigated using a panel of 37 tissues from human and cynomolgus monkey. There was no evidence of specific or non-specific staining in any tissues from human and Cynomolgus monkey. Bimekizumab did not demonstrate haemolytic potential on human or cynomolgus monkey blood *in vitro*.

Immunotoxicity was investigated as part of repeat dose toxicity studies (Studies NCD2260, NCD2384 and NCD2450).

2.3.5. 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. The CHMP considered this acceptable.

2.3.6. Discussion on non-clinical aspects

The non-clinical package for bimekizumab includes *in vitro* pharmacology studies demonstrating the affinity of the active substance for Il-17A and Il-17F and neutralizing activity against human and cynomolgus Il-17A, IL-17F and the heterodimer IL-17A/F. No dedicated PK studies were conducted in line with ICH S6 (R1). PK was characterised as part of toxicokinetic assessment in single and repeat-dose toxicology studies. The toxicology package is composed of a single dose study, an 8-week repeat-dose study, another 8-week repeat-dose study in combination with adalimumab, a 26-week repeat-dose study and an ePPND in cynomolgus monkeys. The non-clinical package is in line with requirements set out in relevant guidance including ICH M3 (R2) and ICH S6 (R1).

All pivotal studies were performed in compliance with GLP.

Pharmacology

Pharmacodynamic studies indicated that bimekizumab is a potent inhibitor of IL-17A and to a much lesser extent, of IL-17F. Studies illustrated that dual inhibition of IL-17A and IL-17F elicited greater reductions in IL-6 release and inhibitory migratory activity compared to proprietary IL-17A- and IL-

17F-inhibitors. Bimekizumab binding affinity was approximately 12-fold and 3.5-fold lower for IL-17F and IL-17A, respectively in cynomolgus monkeys compared to humans, but *in vitro* efficacy in inhibiting IL-6 secretion was similar between the species, suggesting that this difference in binding affinity is not clinically relevant. The binding profile of bimekizumab to other IL-17 family members and other cytokines has not been evaluated thus, no *in vitro* data is available with regards to the binding of bimekizumab to other unrelated cytokines. This is acceptable to the CHMP based on the lack of sequence homology with other cytokines as compared to the target ligands IL-17A and IL-17F. Furthermore, no cytokine mediated effect and no change in cytokine levels were noted in NHP administered bimekizumab. Therefore, the applicant's justification for not performing binding studies with other unrelated cytokines is agreed by the CHMP. There is no evidence of ADCC or CDC, data suggested that bimekizumab is mediating its biological and therapeutic effects solely through the inhibition of IL-17A and IL-17F signalling, without involvement of a depleting effect on IL-17-producing cells. There was no evidence of non-specific binding of bimekizumab in a range of human tissues.

Safety pharmacology evaluation is in line with relevant guidance for monoclonal antibodies. CNS and respiratory safety pharmacology endpoints were included in GLP-compliant repeat-dose studies; no overt findings were observed. Cardiovascular safety was also investigated in the studies and no abnormalities in blood pressure or ECG waveform were noted. The exposure achieved in the studies is considered significantly in excess of anticipated clinical exposure and thus the safety pharmacology investigation is considered acceptable by the CHMP.

Pharmacokinetics

The PK of bimekizumab were investigated in repeat-dose and ePPND toxicity studies. Intravenous and subcutaneous administration were employed, the latter reflecting the proposed clinical route of administration. Exposure to bimekizumab was generally dose-proportional, with slow elimination and a long terminal half-life. Steady state concentrations were typically achieved after 7-9 weekly doses. There was no sex difference in bimekizumab exposure across the studies. ADAs were measured only in studies were decreased exposure indicated ADA measurement was warranted. This included the 8-week study with adalimumab; reduced bimekizumab exposure in co-treated animals was associated with anti-bimekizumab antibodies. In the ePPND study, ADAs were present in the postnatal period for maternal and infant animals, after the cessation of treatment. However, the production of ADA in these studies does not represent a concern for the interpretation of the pivotal toxicity studies where sustained exposure was achieved. In addition, the maintained exposure of bimekizumab during the treatment phase was associated in some animals with signs of exaggerated pharmacodynamics but not with toxicities related to immune-complex formation. Therefore, the lack of further investigation on ADAs with regards to their neutralising potential, timing of occurrence and relationship with the dose of bimekizumab is acceptable, in particular since the occurrence of ADA in animal species is not predictive for the human.

Toxicology

The toxicology package for bimekizumab is comprised of a single-dose toxicity study, and repeat dose toxicity studies including two 8-week studies (one with adalimumab, 12-week recovery in both), a 26-week study (21-week recovery) and an ePPND study. Reduced muco-epidermal immunity was a common observation in all studies, due to exaggerated pharmacological action of bimekizumab. Findings of note include GI lesions in the 8-week study (attributed to *balantidium coli* infection) and superficial dermatitis was the predominant finding in the 26-week study, emerging at a treatment timepoint that achieved bimekizumab exposure that was likely to be present in the recovery period of the 8-week study due to the long-terminal half-life of bimekizumab. This differential finding of superficial dermatitis in the 8-week and 26-week studies is likely the result of external factors (including differences in the genetic background, housing conditions and age of the monkeys) due to

the conduct of the studies in different testing facilities. The definition of a NOAEL in the 26-week study was confounded by the finding of repeated enteritis (requiring euthanasia of 2 animals) in the 50 mg/kg/week dose group. The applicant's position is that this finding is representative of reduced muco-epidermal immunity due to exaggerated pharmacology of bimekizumab. While a causative pathogen has not been identified, given the high GI sensitivity of the monkey as compared to human, together with the fact that the GI tract was not identified as a target organ in humans with inborn errors of IL-17 immunity, the translation of the severe GI toxicity findings noted in the monkey to the human situation is considered of limited relevance.

No genotoxicity studies were conducted for bimekizumab in line with ICH S6 (R1). A carcinogenetic assessment has been submitted in lieu of formal carcinogenicity studies reviewing the potential pro- and anti-tumorigenic effects of IL-17A and IL-17F inhibition; this is considered acceptable by the CHMP. The evidence on the carcinogenic potential of IL-17F is minimal. There is conflicting evidence for IL-17A and dual IL-17/IL-17F inhibition in tumorigenesis carcinogenic potential. Malignancy has been identified as an important potential risk in the RMP and will be further followed-up as part of ongoing studies (PS0014 and PS0015) and planned PASS study (see sections 2.6 on Clinical Safety and 2.7 on Risk Management Plan). This is considered appropriate by the CHMP.

The ePPND study did not identify any effects in maternal or infant animals. At birth, serum bimekizumab concentrations in infant monkeys were comparable to those of mothers. Adequate exposure was achieved and in utero exposure was thus confirmed. Superficial dermatitis (maternal) and transient discolouration of the lips (infants) were the notable observations in this study. ADAs were present in maternal and infant animals. The safety margin to the anticipated clinical exposure was 27-fold (based on AUC). No other toxicology studies were performed. Local tolerance and immunotoxicity were assessed as part of repeat-dose studies which is acceptable.

Bimekizumab is a natural substance, the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, bimekizumab is not expected to pose a risk to the environment.

The results of the toxicity studies are reflected in section 5.3 'Pre-clinical safety data' of the SmPC.

2.3.7. Conclusion on the non-clinical aspects

Overall, the non-clinical data is sufficient for authorisation of bimekizumab in adult patients with psoriasis. Malignancy is an important potential risk and additional pharmacovigilance activities is expected to address this safety concern in the post marketing setting.

2.4. Clinical aspects

2.4.1. Introduction

The bimekizumab clinical pharmacology programme characterized the PK, PD, immunogenicity, dose-exposure-response, and dose-exposure-safety properties of bimekizumab based on data from Phase 1, 2, and 3 studies in healthy study participants and study participants with moderate to severe plaque PSO. Clinical responses (PASI and IGA) were used as PD assessments throughout the development of bimekizumab. No other PD or PD biomarker analyses outside of efficacy assessments were conducted.

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

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

- Tabular overview of clinical studies

Table 3 ***Tabular listing of relevant clinical studies***

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Biophar-maceutic	RA0124/ NA/ Netherlands	5.3.1.1	To evaluate the absolute BA, dose proportionality, and safety and tolerability of 2 dose levels of BKZ given by sc injection vs BKZ given by iv infusion	OL, parallel-group, single-dose	Healthy study participants	BKZ/ BKZ 80mg and 160mg/ sc injection BKZ 160mg/ iv infusion	30 study participants enrolled: 10 BKZ 80mg sc 10 BKZ 160mg sc 10 BKZ 160mg iv	Single dose	Complete/ Final
Biophar-maceutic	UP0031/ NA/ UK	5.3.1.2	To evaluate the relative BA, safety and tolerability of a 160mg sc dose of BKZ given as 2x80mg or 1x160mg injection	Randomized, OL, parallel-group, single-dose	Healthy study participants	BKZBKZ 160mg/ BKZ 2x80mg or BKZ 1x160mg sc injection	12 study participants randomized: 6 BKZ 2x80mg 6 BKZ 1x160mg	Single dose	Complete/ Final
Biophar-maceutic	UP0033/ NCT03707717/ Germany and US	5.3.1.2	To confirm the BE between BKZ administered sc in the BKZ-TN device presentation and the BKZ-SS-1mL and BKZ-AI-1mL device presentations	Randomized, OL, parallel-group, 3-arm, single-dose, BE	Healthy study participants	BKZ/ BKZ 320mg/ BKZ-TN, BKZ-SS-1mL or BKZ-AI-1mL / sc injection	189 study participants randomized: 63 BKZ-TN 63 BKZ-SS-1mL 63 BKZ-AI-1mL	Single dose	Complete/ Final

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
PK	UP0042/ NA/ Japan	5.3.3.1	To evaluate the safety, tolerability, and PK of BKZ	Randomized, DB, PBO-controlled, single-dose, parallel-group	Japanese and Caucasian healthy male study participants	BKZ or PBO/ BKZ 80mg, 160mg, or 320mg or PBO/ sc injection	48 study participants randomized: 12 BKZ 80mg 12 BKZ 160mg 12 BKZ 320mg 12 PBO Each dose group had 6 Caucasian and 6 Japanese participants	Single dose	Complete/ Final
PK	UP0008/ NCT02529956/ UK	5.3.3.2	To evaluate the safety, PK, and PD of BKZ	Randomized, participant-blind, Investigator-blind, PBO-controlled, single-dose, dose-escalating	Mild to moderate plaque PSO	BKZ or PBO/ BKZ 8mg, 40mg, 160mg, 480mg, or 640mg or PBO/ iv infusion	39 study participants randomized: 4 BKZ 8mg 4 BKZ 40mg 6 BKZ 160mg 6 BKZ 480mg 6 BKZ 640mg 13 PBO	Single dose	Complete/ Final Addendum to final report
PK	PA0007/ NCT02141763/ Bulgaria, Republic of Moldova, and UK	5.3.3.2	To evaluate the safety, tolerability, PK, and PD of multiple doses of BKZ	Randomized, participant-blind, Investigator-blind, PBO-controlled, multiple-dose	PsA	BKZ or PBO/ BKZ LD at W1 plus 2 maintenance doses at W4 and W7, or PBO BKZ 80mg/40mg/40mg, BKZ 160mg/80mg/80mg, BKZ 240mg/160mg /160mg, BKZ 560mg/320mg /320mg, or PBO/ iv infusion	53 study participants randomized: 6 BKZ 80mg/40mg/40mg 6 BKZ 160mg/80mg/80mg 21 BKZ 240mg/160mg/160mg 6 BKZ 560mg/320mg/320mg 14 PBO	6 weeks	Complete/ Final Amendment to final report

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
PK	UP0034/ NCT03895385/ US	5.3.3.4	To evaluate the effectiveness of influenza vaccination following concomitant exposure to a single dose of BKZ	Randomized, OL, parallel-group, single-dose	Healthy study participants	BKZ or no treatment/ BKZ 320mg/ sc injection No treatment (vaccination only)	56 study participants randomized: 28 BKZ 320mg 28 No treatment	Single dose	Complete/ Final
Efficacy and safety	PS0016/ NCT03025542/ Australia, Canada, Republic of Moldova, and US	5.3.5.1	To evaluate the time course of PD response, safety and PK of BKZ	Randomized, participant-blind, Investigator-blind	Moderate to severe plaque PSO who were candidates for systemic PSO therapy and/or phototherapy and/or chemo-phototherapy	BKZ and PBO/ BKZ 320mg at BL, W4, and PBO at W16, BKZ 320mg at BL, W4, W16/ sc injection	49 study participants randomized: 32 BKZ 320mg/PBO 17 BKZ 320mg	28 weeks	Complete/ Final
Efficacy and safety	PS0018/ NCT03230292/ Australia, Canada, Republic of Moldova, and US	5.3.5.2	To evaluate the long-term safety, tolerability, and efficacy of BKZ	OL extension	Participants who completed PS0016	BKZ/ BKZ 160mg Q4W option to increase to 320mg Q4W if inadequately controlled/ sc injection	43 study participants enrolled: 28 BKZ 320mg+PBO Q4W[c] 15 BKZ 320mg Q4W[c]	48 weeks	Complete/ Final

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	PS0010 (BE ABLE 1)/ NCT02905006/ Canada, Czech Republic, Hungary, Japan, Poland, and US	5.3.5.1	To evaluate the safety, efficacy, PK, and PD of BKZ	Randomized, DB, PBO-controlled, parallel-group, dose-ranging	Moderate to severe plaque PSO who were candidates for systemic PSO therapy and/or phototherapy and/or chemo-phototherapy	BKZ or PBO/ BKZ 64mg, 160mg, 320mg, or 480mg Q4W, or 320mg LD then 160mg Q4W, or PBO Q4W/ sc injection	250 study participants randomized; 39 BKZ 64mg 43 BKZ 160mg 43 BKZ 320mg 43 BKZ 480mg 40 BKZ 320mg/160mg 42 PBO	12 weeks	Complete/ Final Addendum to final report
Efficacy and safety	PS0011 (BE ABLE 2)/ NCT03010527/ Canada, Czech Republic, Hungary, Japan, Poland, and US	5.3.5.1	To evaluate the long-term safety, tolerability, and efficacy of BKZ	DB, PBO-controlled, parallel-group, extension study	Participants who completed PS0010	BKZ or PBO/ Participants who received PBO or BKZ 64mg, 160mg, or 320mg LD then 160mg Q4W in PS0010 and achieved a PASI90 response at W12 entered PS0011 on the same treatment dose Participants with <PASI90 response at W12 in PS0010 while receiving PBO or BKZ 64mg Q4W were assigned to BKZ 160mg Q4W in PS0011 Participants with <PASI90 response at W12 in PS0010 while receiving	217 study participants enrolled: 15 BKZ 64mg 111 BKZ 160mg 91 BKZ 320mg	48 weeks	Complete/ Final Addendum to final report

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
						BKZ 160mg or 320mg LD then 160mg Q4W were assigned to BKZ 320mg Q4W in PS0011 Participants who received BKZ 320mg or 480mg Q4W in PS0010 were assigned to BKZ 320mg Q4W in PS0011, regardless of PASI90 response at W12 in PS0010/ sc injection			
Efficacy and safety	PS0008 (BE SURE)/ NCT03412747/ Australia, Canada, Germany, Hungary, Poland, Republic of Korea, Russian Federation, Taiwan, and US	5.3.5.1	To evaluate the efficacy, safety, and PK of BKZ compared with ADA	Randomized, DB, active-controlled, parallel-group	Moderate to severe plaque PSO who were candidates for ADA or for systemic PSO therapy and/or phototherapy	BKZ or ADA/ BKZ 320mg Q4W (and PBO at certain weeks) throughout the study/ BKZ 320mg Q4W until W16, then 320mg Q8W (and PBO at certain weeks) continuing through W52/ ADA 80mg LD, and 400mg Q2W (and PBO at certain weeks) starting 1 week after initial dose until W24,	478 study participants randomized: <u>Initial Treatment Period (16 weeks)</u> 158 BKZ 320mg Q4W 161 BKZ 320mg Q4W/Q8W 159 ADA <u>Maintenance Treatment Period (40 weeks)</u> 152 BKZ 320mg Q4W 149 BKZ 320mg Q4W/Q8W 149 ADA/BKZ 320mg Q4W	56 weeks for BKZ; 24 weeks for ADA	Ongoing/ Interim[d]

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
						then BKZ 320mg Q4W through W52/ sc injection			
Efficacy and safety	PS0009 (BE VIVID)/ NCT03370133/ Australia, Belgium, Canada, Germany, Hungary, Italy, Japan, Poland, Russian Federation, UK, and US	5.3.5.1	To evaluate the efficacy, safety, PK, and PD of BKZ compared with PBO and ustekinumab	Randomized, DB, PBO- and active-controlled, parallel-group	Moderate to severe plaque PSO who were candidates for ustekinumab or for systemic PSO therapy and/or phototherapy	BKZ, ustekinumab, or PBO/ BKZ 320mg Q4W (throughout study)/ Ustekinumab 45mg or 90mg (weight based) at BL and 4 weeks later, then Q12W/ PBO Q4W until W16, then BKZ 320mg Q4W through W48 sc injection	567 study participants randomized: Initial Treatment Period (16 weeks) 321 BKZ 320mg Q4W 163 ustekinumab 83 PBO Maintenance Treatment Period (36 weeks) 306 BKZ 320mg Q4W 157 ustekinumab 74 PBO/BKZ 320mg Q4W	52 weeks	Ongoing/ Interim[d]
Efficacy and safety	PS0013 (BE READY)/ NCT03410992/ Australia, Canada, Germany, Hungary, Poland, Republic of Korea, Russian Federation, UK, and US	5.3.5.1	To evaluate the efficacy, safety, and PK of BKZ compared with PBO, including a Randomized-Withdrawal Period	Randomized, DB, PBO-controlled	Moderate to severe plaque PSO who were candidates for systemic PSO therapy and/or phototherapy	BKZ or PBO/ Initial Treatment Period (16 weeks): BKZ 320mg or PBO Q4W/ sc injection Randomized-Withdrawal Period (40 weeks): If initially randomized to BKZ 320mg Q4W and achieved a PASI90 response, then at W16 rerandomized (1:1:1) to BKZ	435 study participants randomized: Initial Treatment Period: 349 BKZ 320mg Q4W 86 PBO Randomized-Withdrawal Period: 106 BKZ 320mg Q4W/Q4W 100 BKZ 320mg Q4W/Q8W 105 BKZ 320mg Q4W/PBO 1 PBO/PBO	56 weeks	Ongoing/ Interim[d]

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
						320mg Q4W or Q8W, or PBO (ie, treatment withdrawal) If initially randomized to PBO and achieved a PASI90 response at W16, then continued PBO Q4W If PASI90 not achieved at W16, allocated to OL BKZ 320mg Q4W for 12 weeks (escape arm) If relapsed (<PASI75) during randomized withdrawal period, allocated to OL BKZ 320mg Q4W for 12 weeks (escape arm) sc injection	Escape Treatment Period: Week 16 responders: 67 BKZ 320mg Q4W/PBO 4 BKZ 320mg Q4W/Q8W 7 BKZ 320mg Q4W/Q4W Week 16 nonresponders: 23 BKZ 320mg Q4W 81 PBO		

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	PS0014/ NCT03598790/ Australia, Belgium, Canada, Germany, Hungary, Italy, Japan, Poland, Republic of Korea, Russian Federation, Taiwan, UK, and US	5.3.5.2	To evaluate the long-term safety, tolerability, and efficacy of BKZ	OL extension	Moderate to severe plaque PSO who completed 1 of the Phase 3 feeder studies (PS0008, PS0009, or PS0013)	Dependent on participant's treatment regimen and PASI response in the feeder study: BKZ 320mg Q4W or Q8W/ sc injection	1343 study participants enrolled at the time of data cut	144 weeks	Ongoing/ clinical data cut on 01 Nov2019 (safety data included in Pool S2)
Efficacy and safety	DV0002/ NCT03766685/ Canada and US	5.3.5.2	To evaluate the safe and effective use of the investigational device presentations for self-injection of BKZ after training in self-injection technique	OL, 2-arm (BKZ-AI-1mL; BKZ-SS-1mL), randomized, noncomparator (substudy of PS0014)	Moderate to severe plaque PSO	BKZ/ Depending on participant's treatment regimen in the feeder study: BKZ 320mg Q4W or Q8W using BKZ-AI-1mL or BKZ-SS-1mL/ sc injection	134 study participants randomized: 47 BKZ 320mg Q4W (BKZ-AI-1mL) 46 BKZ 320mg Q4W (BKZ-SS-1mL) 21 BKZ 320mg Q8W (BKZ-AI-1mL) 20 BKZ 320mg Q8W (BKZ-SS-1mL)	16 weeks	Ongoing/ 1ml CSR is complete
Efficacy and safety	DV0006/ NA/ Germany, Hungary, Poland, and Japan	5.3.5.2	To evaluate the safe and effective use of the investigational device presentations for self-injection of BKZ after training in self-injection technique	OL, 2-arm (BKZ-AI-1mL; BKZ-SS-1mL), randomized, noncomparator (substudy of PS0014)	Moderate to severe plaque PSO	BKZ/ Depending on participant's treatment regimen in the feeder study: BKZ 320mg Q4W or Q8W using BKZ-AI-1mL or BKZ-SS-1mL/ sc injection	88 study participants randomized: 32 BKZ 320mg Q4W (BKZ-AI-1mL) 36 BKZ 320mg Q4W (BKZ-SS-1mL) 11 BKZ 320mg Q8W (BKZ-AI-1mL) 9 BKZ 320mg Q8W (BKZ-SS-1mL)	16 weeks (Europe) 9 weeks (Japan)	Ongoing/ 1ml CSR is complete

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	PA0008/ NCT02969525/ Czech Republic, Germany, Hungary, Poland, Russia, and US	5.3.5.1	To evaluate the efficacy, safety, tolerability, PK, PD, and immunogenicity of BKZ	Randomized, DB, PBO-controlled, parallel-group, dose-ranging	Active PsA who were candidates for systemic PsA therapy	BKZ or PBO/ DB Period (12 weeks) BKZ 16mg, 160mg, or 320mg Q4W, or BKZ 320mg LD at BL, then 160mg Q4W, or PBO Q4W/ sc injection Dose-blind Period (36 weeks) If randomized to BKZ 160mg, 320mg or 320mg LD, then 160mg Q4W in DB Period, continued on the same treatment dose If received PBO during DB Period, rerandomized (1:1) to BKZ 160mg or 320mg Q4W If received BKZ 16mg Q4W during DB Period, rerandomized (1:1) to BKZ 160mg or 320mg Q4W/ sc injection	206 study participants randomized: DB Period 41 BKZ 16mg 41 BKZ 160mg 41 BKZ 320mg 41 BKZ 320mg/160mg 42 PBO Dose-blind Period 40 BKZ 160mg/160mg 41 BKZ 320mg/320mg 37 BKZ 320mg/160mg/160mg 20 PBO/BKZ 160mg 20 PBO/BKZ 320mg 22 BKZ 16mg/160mg 19 BKZ 16mg/320mg	48 weeks	Complete/ Final Amendment to final report

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

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	HS0001/ NCT03248531/ Australia, Belgium, Denmark, Germany, Norway, Russia, and US	5.3.5.1	To assess the efficacy, safety, tolerability, immunogenicity, and PK of BKZ	Randomized, Investigator-blind, participant-blind, PBO-controlled, active-reference arm (ADA)	Moderate to severe HS	BKZ, ADA or PBO/ BKZ 640mg at BL (LD), then 320mg at W2, W4, W6, W8, and W10 (PBO to match ADA dosing schedule) ADA 160mg at BL (LD), 80mg at W2, then 40mg at W4, W5, W6, W7, W8, W9, and W10 (PBO to match BKZ dosing schedule) PBO at BL (LD, then at W2, W4, W5, W6, W7, W8, W9 and W10 sc injection	90 study participants randomized: 46 BKZ 22 ADA 22 PBO	12 weeks	Complete/ Final
Efficacy and safety	RA0123/ NCT02430909/ Czech Republic, Hungary, Poland, Republic of Moldova, Russia, Slovak Republic, and UK	5.3.5.4	To evaluate the safety, PK, PD and efficacy of multiple doses of BKZ administered as add-on to stable CZP therapy	DB, randomized, PBO-controlled, multiple dose	Moderate to severe RA	BKZ or PBO/ Part 1 (W0 toW8): OL, Run-In Period with sc CZP treatment of 400mg at W0, W2, and W4, and 200mg at W6/ sc injection (CZP) Part 2A (W8 to W20): If low disease activity not achieved after CZP treatment at W8, randomized to BKZ	159 study participants enrolled: 52 CZP/BKZ+CZP/CZP 27 CZP/PBO+CZP/CZP 80 CZP/CZP/CZP	12 weeks	Complete/ Final

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
						240mg (LD) and 120mg Q2W or PBO as an add-on to background CZP 200mg Q2W treatment/ iv infusion (BKZ) sc injection (CZP) <u>Part 3A (W20 to W32):</u> CZP 200mg Q2W Treatment Period (for those who completed Part 2A)/ sc injection (CZP) <u>Part 2B/3B (W8 to W32)</u>: CZP 200mg Q2W Treatment Period for those who completed Part 1 but did not qualify for randomization into Part 2A/ sc injection (CZP)			

Type of study	Study number/ NCT number/ Country(ies)	Location of study report	Objectives of the study	Study design and type of control	Population studied	Test product(s)/ Dosage regimen/ Route of administration	Number of study participants	Duration of treatment	Study status/ Type of report
Efficacy and safety	UC0011/ NA/ Bulgaria, Czech Republic, Georgia, Italy, Poland, Republic of Moldova, Romania, South Africa, Spain, and UK	5.3.5.4	To evaluate the efficacy, safety, tolerability, and PK of an iv LD followed by sc administration of BKZ	Randomized, participant-blind, Investigator-blind, PBO-controlled	Moderate to severe active UC who have failed to respond to conventional therapy	BKZ or PBO/ BKZ 560mg LD (D1), then 420mg on D22 and D43 or PBO on D1, D22 and D43/ LD iv infusion followed by sc injections	23 study participants enrolled: 15 BKZ 8 PBO Early termination	8 weeks	Complete/ Final

ADA=adalimumab; AI=autoinjector; AS=ankylosing spondylitis; BA=bioavailability; BE=bioequivalence; BKZ=bimekizumab; BL=Baseline; CSR=clinical study repor; CZP=certolizumab pegol; D=day; DB=double-blind; HS= hidradenitis suppurativa; iv=intravenous; LD=loading dose; NA=not applicable; OL=open-label; PASI= Psoriasis Area and Severity Index; PASI90=90% reduction in PASI score; PBO=placebo; PD=pharmacodynamics; PFS=prefilled syringe; PK=pharmacokinetics; PsA= psoriatic arthritis; PSO=psoriasis; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; RA=rheumatoid arthritis; sc=subcutaneous; SFU=Safety Follow-Up; SS=safety syringe; TN=True North; UC=ulcerative colitis; W=week

Note: BKZ-TN consists of the PFS containing 1mL of BKZ drug product and the True North functional secondary packaging. BKZ-AI-1mL is a combination of the PFS containing 1mL of BKZ drug product and the autoinjector components. BKZ-SS-1mL is a combination of PFS containing 1mL of BKZ drug product and the safety syringe device components.

[c] PS0016 randomized treatment group

[d] Note that treatment periods are completed; however, a small number of study participants were ongoing in the SFU Period at the time of the cut-off date for the submission.

2.4.2. Pharmacokinetics

A total of 16 clinical studies provided data to characterise the PK and PD of bimekizumab in patients with psoriasis. These included 4 clinical pharmacology studies and 12 studies (biopharmaceutics, efficacy and safety studies) providing supportive data including PK, PD, and immunogenicity of bimekizumab. In addition, three population PK and PK/PD analyses have been completed.

Analytical methods

Three PK methods were used throughout the clinical programme. Method #1 was an ECLIA assay used in Phase 1 and Phase 2 studies (except the BE study UP0033 and vaccine study UP0034). Method #2 was used in Phase 3 studies and employed a similar platform to Method #1 but used an anti-bimekizumab idiotypic antibody for detection rather than an anti-human IgG in order to achieve a higher assay passing rate. Method #3 was only used for study UP0034. It is the same as Method #2 but conducted at a different CRO.

The methods covered a suitable range and were validated for accuracy, precision, dilution linearity, parallelism and selectivity. Target interference was studied by spiking samples with IL-17A and IL-17F; the serum levels of IL-17 are below the levels shown to interfere with the assay. Cross-validation performed between method 1 and 2 was successfully demonstrated. Finally, PK Method 2 was transferred successfully to another vendor and validated as PK Method 3. Long term sample stability data covered the storage period of all the study samples.

The presence of ADAs in human plasma was determined using solution-ligand binding assays utilizing the MSD platform. A tiered-based assay approach was used, involving screening, confirmatory, and titre assays. Only samples that were positive in the screening assay were taken forward to a confirmatory assay. The presence of neutralizing antibodies was detected using a competitive ligand binding assays (CLBAs) for both IL-17A and IL-17F. The evaluation of the neutralizing capacity of the confirmed ADA positive samples has been investigated in the phase III clinical studies (PS0008, PS0009 and PS0013).

The ADA assay has been developed and progressively optimized to improve target and drug tolerance up to the ADAb-5 assay used in the phase 3 clinical studies. ADAb against UCB4940 in human plasma are detected using an electrochemiluminescent (ECL) immunoassay. In this assay, the samples are incubated in acetic acid and then neutralized with Master Mix containing Biotin-UCB4940, Sulfo-Tag-UCB4940, the 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 mitigating any target interference. This complex is then bound to a blocked MSD-Streptavidin plate and detected by a chemiluminescent signal that is generated when voltage is applied. The resulting electrochemiluminescent signal (ECL or relative light units, RLU) is directly proportional to the amount of ADA present in the human plasma.

A competitive ligand binding (CLB) assay format has been used to investigate the neutralizing potential of binding anti-drug antibodies. The CLBA method comprises 2 NAb assays, with specificity for IL-17AA and IL-17FF, respectively. In these NAb assays, ADAb compete with labeled target to bind to the drug. Neutralization 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.

Population PK analyses

CL0453

A population PK analysis to estimate the absolute bioavailability of subcutaneous bimekizumab administration. Data collected from four single-dose bimekizumab clinical studies [UP0008 (IV), UP0031 (SC), UP0042 (SC) and RA0124 (SC and IV)] were pooled and analysed.

The final model was a two-compartment model with first-order absorption after SC administration, bioavailability of SC administration and first-order elimination. Weight was included as a covariate on both CL and V2. The absolute bioavailability was estimated to 70.1%. Parameter estimates for the final 2-compartment model are provided in ***Table 4***. Visual predictive checks (VPCs) are presented in **Figure 1** (IV administration and SC administration).

Table 4 – Population PK parameter estimates of the final model

Population estimates			Inter-individual variability (IIV)			
Parameters	Value	RSE%	Parameters	Value (CV)	RSE%	Shrinkage
[CL] L/Day	0.179	4.061	[CL]	0.0461 (21.4%)	19.349	9.0%
[V2] L	3.03	3.597	[V2]	0.0572 (23.9%)	24.825	20.2%
[Q] L/Day	0.296	8.851	[KA]	0.0650 (25.5%)	32.308	36.4%
[V3] L	2.13	6.056	[F1]	0.211 (45.9%)	36.919	42.0%
[KA] 1/DAY	0.172	4.698				
[F1]	0.701	5.007				
[proportional error]	0.128	7.125				
[additive error] (µg/ml)	0.173	14.393				
V2WT	0.598	28.93				
CLWT	0.535	28.972				

CV=coefficient of variation; RSE=relative standard error; CL=elimination clearance; V2=volume of central compartment; Q=inter-compartment clearance; V3=volume of peripheral compartment; KA=sc absorption rate; F1=bioavailability of sc administration; V2WT=allometric exponent of body weight as covariate on V2; CLWT=allometric exponent of CL as covariate on V2

Figure 1 – Prediction corrected visual predictive check for the final model iv/sc bimekizumab administration

Figure 5-8: Prediction corrected visual predictive check for the final model -iv bimekizumab administration

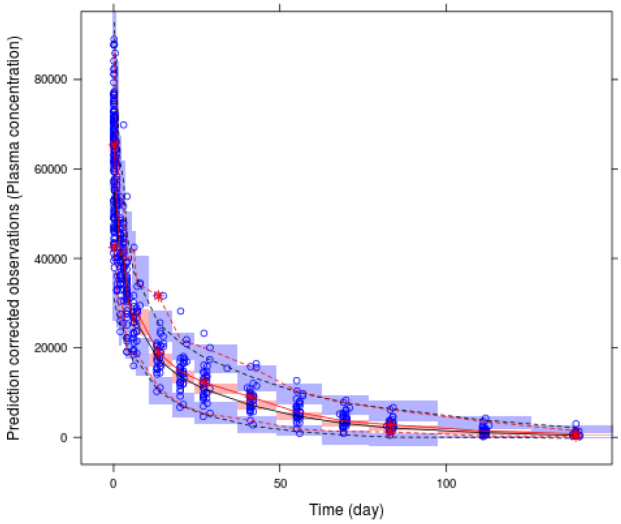
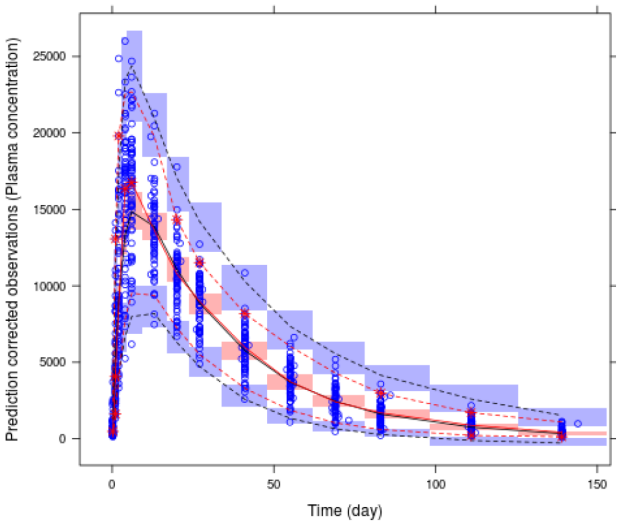


Figure 5-9: Prediction corrected visual predictive check for the final model -sc bimekizumab administration



Note: The solid red line represents the median observed plasma concentration (prediction corrected), and the semi-transparent red field represents a simulation-based 95% confidence interval for the median. The solid black line represents the model predicted median plasma concentration. The observed 2.5% and 97.5% percentiles are presented with dashed red lines. The model predicted 2.5% and 97.5% percentiles are presented with dashed black lines, and the 95% confidence intervals for the corresponding model predicted percentiles are shown as semi-transparent blue fields. The observed plasma concentrations (prediction corrected) are represented by blue circles.

CL0466

The popPK model was developed using combined data from the Phase 2B study PS0010 and the Phase 2A study PS0016. The model was initially developed using a pre-final dataset including data up to Week 16. The pre-final model was then rerun with the final dataset once the data after Week 16 from PS0016 became available.

The structural model was a one compartment model with first order absorption and first order elimination. At the end of the stepwise covariate modelling procedure, the only covariate kept in the model was WT on CL/F and V/F. The parameters characterising the pre-final population PK model are listed in **Table 5**. VPCs by dose of the pre-final model is shown in **Figure 2**. Similar results were obtained when the model was re-run once data after Week 16 became available; the final model.

Table 5 – Parameter estimates of the pre-final PK model

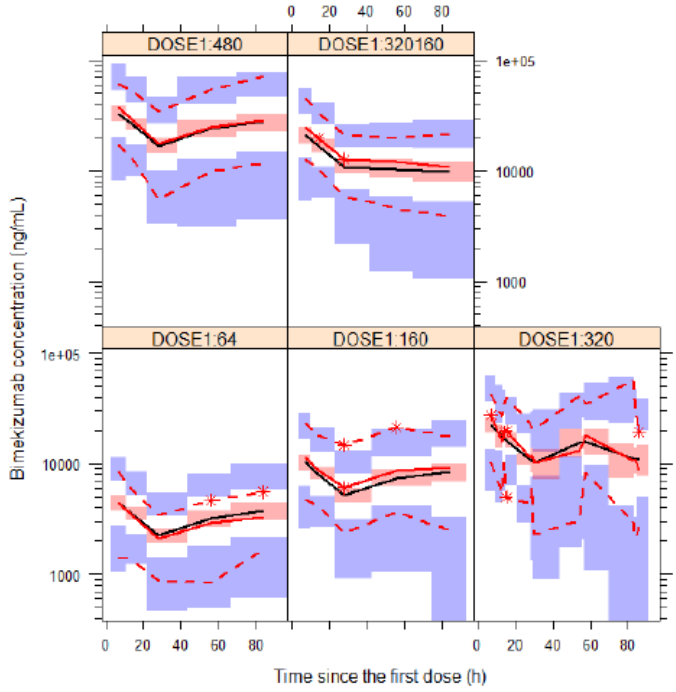
Parameter (unit)	Estimate	95%CI	Precision [a] (CV%)	Shrinkage (%)
Structural PK model				
K_a (day^{-1})	1.61	1.29; 1.93	10.0	-
CL/F (L/day)	0.364	0.347; 0.381	2.38	-
V/F (L)	11.6	10.9; 12.3	3.2	-
WT on CL/F	0.882	0.664; 1.1	12.6	-
WT on V/F	0.811	0.588; 1.03	14.1	-
IIV in K_a (%CV) [b]	140	123 ; 154	11.2	81.8
IIV in CL/F (%CV) [b]	32.6	28.5; 36.2	12.0	6.7
IIV in V/F (%CV) [b]	42.5	32.1; 50.9	22.1	7.4
Prop. Error (%)	39.4	36.9; 41.7	6.22	21.0

[a] Precision was calculated as the standard error (SE) divided by the parameter estimate x 100 (i.e. relative standard error [RSE])

[b] % CV for both inter-individual and residual variability is an approximation taken as the square root of variance x100

CI: confidence interval, CL/F: apparent clearance, CV: coefficient of variation, IIV: Inter-individual variability, K_a: first-order absorption rate constant, Prop. Error: proportional residual error, V/F: apparent volume of distribution, WT: bodyweight

Figure 2 – Visual predictive check by dose from the pre-final population PK model, semi-log scale



Solid red lines: observed median bimekizumab concentrations
Dotted red line: 5th and 95th percentiles of the observed concentrations
Solid black line: median simulated bimekizumab concentrations,
Red area: 95% prediction interval of the median simulated bimekizumab concentrations,
Blue area: 95% prediction interval of the 5th and 95th percentiles of the simulated bimekizumab concentrations

CL0485

The population PK model was developed based on data from three Phase 2 studies (PS0010, PS0011, and PS0016) and interim data from two Phase 3 studies (PS0008 and PS0009).

The final popPK model was a one-compartment model with first-order absorption and elimination. Covariate effects included in the final model were body weight (WT), sex, race and anti-drug-antibodies (ADAbs) status on apparent clearance (CL/F), and WT on apparent volume of distribution (V/F). Parameter estimates for the final popPK model are provided in table below.

Table 6 – Parameter estimates of the final population PK model for bimekizumab

Run		21		
OFV		31580.73		
Condition number		65.85		
	Unit	**Value**	**RSE (%)**	**SHR (%)**
CL/F[a]	L/day	0.337	1.56	
V/F[a]	L	11.2	1.28	
k_a	/day	0.882	22.7	
Exponent for WT on CL/F		1.12	4.19	
Exponent for WT on V/F		0.779	5.81	
CL/F: ADAb positive[b]		0.0834	21.7	
CL/F: Japanese or Asian[c]		0.222	12.5	
CL/F: Female[d]		0.0993	19.9	
IIV CL/F	CV	0.327	2.99	2.56
IIV V/F	CV	0.305	4.36	11.5
Corr. IIV CL/F-V/F		0.703	4.53	
Prop RUV	CV	0.189	2.95	8.86

The RSE for IIV and RUV parameters are reported on the approximate CV scale
[a] For an 87 kg study participant, with allometric exponents for CL/F ($Par_i = Par_{pop} \cdot (WT_i/87)^{1.12}$), and for V/F ($Par_i = Par_{pop} \cdot (WT_i/87)^{0.779}$).
[b] Proportional change compared to ADAb negative.
[c] Proportional change compared to Caucasian, American Indian or Alaska Natives or Native Hawaiian or other Pacific Islander .
[d] Proportional change compared to males.
k_a: first-order absorption rate constant; CL/F: apparent clearance; V/F: apparent volume of distribution; WT: body weight; ADAb: anti-drug-antibody; CV: coefficient of variation; IIV: interindividual variability; OFV: objective function value; RSE: relative standard error; RUV: residual unexplained variability

Figure 3 – Prediction corrected visual predictive check of bimekizumab concentration for the final population PK model stratified by study

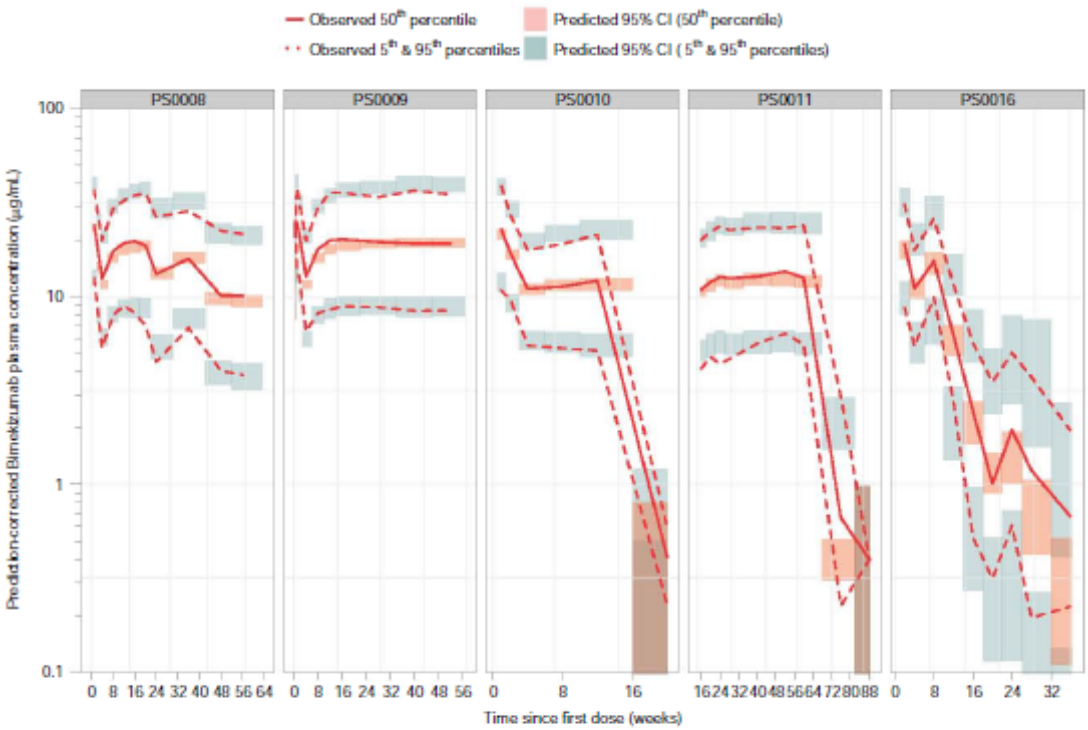


Figure 15: Prediction corrected visual predictive check of bimekizumab concentrations, for the final population PK model (run 21), stratified by study. Bimekizumab concentrations are displayed versus time after dose, on a semi-logarithmic scale. The solid and dashed red lines represent the median, 5th and 95th percentiles of the observations; the shaded red and blue areas represent the 95% confidence interval of the median, 5th and 95th percentiles predicted by the model. The y-axis has been limited between 0.1 and 100.

Absorption

Peak plasma concentrations (tmax) were achieved between 4 to 7 days following SC administration of bimekizumab to healthy volunteers.

Based on population pharmacokinetic analysis, following a single subcutaneous dose of 320 mg in plaque psoriasis patients, bimekizumab reached a median (2.5th and 97.5th percentile) peak plasma concentration of 25 (12 -50) µg/mL, between 3- and 4-days post dose.

Based on simulated data, the median (2.5th and 97.5th percentile) peak and trough concentration at steady-state following subcutaneous administration of 320 mg every 4 weeks are 43 (20-91) µg/mL and 20 (7-50) µg/mL respectively and steady-state is reached after approximately 16 weeks with every 4 weeks dosing regimen. Compared with exposure after a single dose, the population pharmacokinetic analysis showed that patients exhibited a 1.74-fold increase in peak plasma concentrations and area under the curve (AUC) following repeated four weekly dosing.

After switching from the 320 mg every 4 weeks dosing regimen to 320 mg every 8 weeks dosing regimen at week 16, steady-state is achieved approximately 16 weeks after the switch. Median (2.5th and 97.5th percentile) peak and trough plasma concentrations are 30 (14 -60) µg/mL and 5 (1-16) µg/mL respectively.

- **Bioavailability**

Study RA0124 was an open-label, parallel-group, single-dose absolute bioavailability study 30 healthy subjects were randomized to 1 of 3 treatment groups (10 subjects per group): bimekizumab 80mg SC, 160mg SC, and 160mg IV.

When compared with the parenteral bimekizumab 160mg IV dose, the bimekizumab 80mg and 160mg SC doses had absolute bioavailabilities of 0.656 (95% CI: 0.539, 0.798) and 0.631 (95% CI: 0.511, 0.780), respectively. This is consistent with the result of the popPK analysis CL0453 (bioavailability of 70.1%).

- **Bioequivalence**

In early Phase 1 studies, an formulation was used instead of the formulation used in the remaining studies.

Study UP0031

This was an open-label, parallel group, single-dose study to evaluate the relative bioavailability of bimekizumab 160 mg SC in healthy study participants administered as 2x80 mg (N=6) or 1x160 mg (N=6).

The GeoMeans for AUC were similar between the bimekizumab 2x80mg (Formulation A) and 1x160mg (Formulation B) treatment groups (653.8day*µg/mL and 628.3 day*µg/mL, respectively). A similar Cmax was observed between the bimekizumab 2x80mg and 1x160mg treatment groups (GeoMeans of 21.29µg/mL and 18.20µg/mL, respectively). The relative BA of bimekizumab Formulation B vs Formulation A was 96.1% (95% CI: 72.7, 127.0%); suggesting no clinically relevant differences between both formulations and processes.

The population PK analysis that combined Phase 2 and Phase 3 data (**CL0485**) included data collected from studies that used and studies that used. However, the process was not specifically tested as a covariate in the analysis. In its response to the day 120 LOQ, the Applicant provided additional data that demonstrated similar PK across the investigational medicinal product used in Phase 2 and Phase 3 studies.

In the pivotal Phase 3 clinical studies, the bimekizumab-True North (TN) device presentation was used for administration. For commercial use, the applicant developed 2 different device presentations: bimekizumab-SS-1mL (safety syringe) and bimekizumab-AI-1mL (auto-injector). The conduct of a bridging **BE study UP0033**, as part of the applicant's comparability strategy, was previously agreed in CHMP scientific advices. UP0033 was a three-arm single dose study in healthy volunteers comparing exposure after subcutaneous administration of 320 mg bimekizumab with 3 different devices. Both bimekizumab-SS-1mL and bimekizumab-AI-1mL were bioequivalent to bimekizumab-TN, as the 95% CI for the ratios of AUC, AUC(0-t), and Cmax were fully included within the acceptance range of 80% to 125%.

Studies **DV0002** and **DV0006** (see section 2.5.2) investigated the impact of self-injection and injection sites (thigh, abdomen) on the bimekizumab PK and did not suggest clinically relevant differences. Dose administration was allowed in the thigh, abdomen, or the upper arm in the pivotal phase 3 studies.

Distribution

The volume of distribution (V) ranged from 4.2 to 5.8 L following single dose IV administration of 8-640 mg bimekizumab in patients with mild to moderate psoriasis (study UP0008). The apparent volume of distribution (V/F) following a single SC dose of 80mg or 160 mg bimekizumab to healthy subjects was 8.655 L and 10.15 L, respectively (study RA0124). In the population PK analysis

(CL0485), V/F was estimated to 11.2 L (IIV 30.5%) for a typical subject with psoriasis weighing ~90 kg.

Elimination

Terminal elimination half-life ranged from 19 to 26 days (median values) in healthy study participants. In the population PK analysis (CL0485), apparent clearance (CL/F) was estimated to 0.337 L/day (IIV 32.7%) and the model-predicted half-life was 23 days.

As a monoclonal antibody, bimekizumab is not expected to undergo significant renal or hepatic elimination.

Dose proportionality and time dependencies

Dose proportionality

Phase 1 studies

Bimekizumab exhibited linear PK with dose-proportional or approximately dose-proportional increases in systemic exposure in the following Phase 1 clinical trials: UP0008, PA0007, RA0124 and UP0042.

In Study UP0008, 26 subjects with mild to moderate psoriasis were randomized to single IV doses of bimekizumab (8, 40, 160, 480, or 640mg). Exposure in terms of AUC and Cmax increased with increasing dose in a linear fashion and was dose proportional between 8mg and 640mg (**Table 7**).

Table 7 – Dose proportionality for PK parameters of UCB4940 (Analysis Set: PK Per protocol Set)

Analysis Parameter	Effect	Estimate	Estimated standard error	95% CI	CV (%)
AUC(0-inf) [day*ug/ml]	Intercept	1.60	0.257	[1.07,2.13]	40.2
	Dose (beta)	1.04	0.050	[0.94,1.14]	
AUC(0-t) [day*ug/ml]	Intercept	1.37	0.257	[0.84,1.91]	40.2
	Dose (beta)	1.08	0.050	[0.97,1.18]	
Cmax [ug/ml]	Intercept	-1.01	0.143	[-1.31,-0.71]	21.9
	Dose (beta)	1.02	0.027	[0.96,1.08]	

Phase 2 studies

In the Phase 2b study (PS0010), bimekizumab was administered SC Q4W for 12 weeks at doses of 64mg, 160mg, 320mg loading dose at baseline followed by 160mg, 320mg, and 480mg. The observed plasma concentrations of bimekizumab at Week 1 and Week 12 at different doses are shown in **Table 8**. These data indicate a dose proportional increase in plasma concentrations following SC administration in subjects with moderate to severe psoriasis.

Table 8 – Summary of bimekizumab plasma concentrations at Week 1 and Week 12 in PS0010 (PK-PPS)

BKZ concentration (µg/mL) GeoMean (GeoCV%)	BKZ 64mg	BKZ 160mg	BKZ 160mg w/LD	BKZ 320mg	BKZ 480mg
Week 1 [n]	4.45 (56.3) [39]	9.25 (112.4) [42]	20.8 (139.1) [40]	21.9 (131.4) [43]	31.8 (131.9) [43]
Week 12 [n]	2.31 (156.6) [38]	9.53 (54.3) [38]	10.3 (49.7) [33]	18.3 (64.6) [40]	28.1 (63.7) [39]

BKZ=bimekizumab; CSR=clinical study report; GeoCV%=geometric coefficient of variation; GeoMean=geometric mean; LD=loading dose; PK-PPS=Pharmacokinetic Per-Protocol Set; w=with

Time dependency

Phase 3 clinical studies

In the Phase 3 studies (PS0008, PS0009 and PS0013) bimekizumab trough concentrations increased in a linear fashion and appeared to achieve steady state between Week 12 and Week 16. Trough plasma concentration accumulations between Week 4 and Week 16 were 1.57-1.65 and 1.54 for bimekizumab 320mg Q4W and Q4W/Q8W, respectively.

Population PK analysis (CL0485)

Based on simulated data, steady-state is achieved by Week 16 on a Q4W regimen and subjects on 320mg Q4W followed by a 320mg Q8W regimen achieved a new steady-state 16 weeks after the switch. The mean accumulation ratio for Q4W dosing in a typical patient with psoriasis was 1.74. The overall accumulation ratio for all simulated subpopulations receiving 320mg Q4W was 1.67.

Intra- and inter-individual variability

No information was provided on intra-individual variability. In the population PK analysis (CL0485), the estimated inter-individual variabilities of apparent clearance (CL/F) and apparent volume of distribution (V/F) were moderate, with a CV% of 32.7% for CL/F and 30.5% for V/F.

Pharmacokinetics in the target population

A comparison of PK following single doses of bimekizumab indicated no apparent differences between healthy subjects and subjects with moderate to severe psoriasis (**Table 9**).

Table 9 – Bimekizumab plasma PK paramters following administration of single SC doses in healthy study participants and study participants with moderate to severe PSO

	Healthy study participants										Study participants with PSO
Parameter	80mg (N=5) Japanese UP0042	80mg (N=6) Caucasian UP0042	160mg (N=6) Japanese UP0042	160mg (N=6) Caucasian UP0042	320mg (N=6) Japanese UP0042	320mg (N=6) Caucasian UP0042	320mg BKZ-TN (N=63) UP0033	320mg BKZ-SS (N=63) UP0033	320mg BKZ-AI (N=63) UP0033	320mg (N=28) UP0034	320mg CL0485
t_{max} (days)[a]	4.021 (4.02, 6.05)	5.041 (4.03, 6.06)	6.038 (4.03, 6.20)	6.052 (4.03, 6.05)	6.035 (4.01, 6.04)	6.043 (4.04, 6.05)	5.031 (1.97, 12.1)	5.999 (2.95, 15.0)	6.963 (2.99, 13.0)	7.000 (2.00, 14.0)	3.28 (2.72, 3.52)
C_{max} (µg/mL)[b]	9.294 (17.6)	8.808 (20.2)	19.80 (8.9)	17.17 (20.6)	41.33 (16.0)	33.60 (19.7)	31.18 (30.5)	30.10 (28.0)	30.63 (22.9)	33.44 (23.1)	26.8 (36.8)
AUC (µg.day/mL)[b,c]	342.3 (29.6)	284.8 (14.2)	679.4 (19.0)	673.2 (22.9)	1278 (17.8)	1450 (13.2)	1080 (32.0)	1083 (31.1)	1129 (29.9)	1200 (33.4)	953 (43.2)
$t_{1/2}$ (days)[a]	21.99 (16.3, 28.2)	20.81 (16.6, 33.1)	22.35 (19.1, 24.3)	25.00 (20.4, 32.4)	19.06 (14.8, 30.6)	25.91 (23.2, 32.6)	22.48 (14.7, 35.5)	24.14 (10.3, 37.2)	23.56 (13.2, 39.8)	22.96 (14.2, 35.7)	23

AUC=area under the plasma concentration-time curve from time 0 to infinity; AUCss=area under the plasma concentration-time curve at steady state; BKZ-AI=bimekizumab auto-injector; BKZ-SS=bimekizumab safety syringe; BKZ-TN=bimekizumab True North device presentation; C_{max}=maximum concentration; CSR=clinical study report; CV=coefficient of variation; PK=pharmacokinetic; PSO=psoriasis; sc=subcutaneous; $t_{1/2}$=apparent terminal half-life; t_{max}=time of occurrence of C_{max}

Note: The healthy study participant study UP0033 is described in Module 2.7.1 Appendix Table 4-6.

[a] median (minimum, maximum) for t_{max} and $t_{1/2}$

[b] Geometric mean (GeoCV%) for UP0042, UP0033, and UP0034, and mean (CV%) for CL0485

[c] AUCss for study participants with PSO

Immunogenicity

Phase 2 clinical studies

In the Phase 2 studies (PS0010, PS0011, PS0016, and PS0018), the overall incidence of ADAb was between 1.9% and 38.8%. The earliest time point at which ADAb were observed was 4 weeks post first dose, which was the first post-baseline time point at which ADAb were measured. The majority of ADAb were seen at 1 time point. In PS0010 and PS0016, only 2 study participants had their PK

impacted by the presence of ADAb. In a population PK analysis (CL0466), combining data from PS0010 and PS0016, ADAb status was not included as a covariate on clearance in the final model. The immunogenicity results from PS0018 suggested no risk for increased immunogenicity upon retreatment with bimekizumab.

Phase 3 clinical studies

Treatment-emergent ADAb occurred as early as 4 weeks post first dose at the earliest sampling time point, and cumulative counts increased over time. There was a tendency for higher incidences of ADAb in study participants receiving lower doses of bimekizumab (i.e., <160mg) and in study participants who switched from receiving bimekizumab 320mg Q4W to Q8W at Week 16 compared with study participants receiving bimekizumab 320mg Q4W continuously.

The overall incidence of ADAb in the pooled Phase 3 studies was 22.6% during the Initial Treatment Period and 37.6% and 45.1% following 1 year of treatment with bimekizumab 320mg Q4W and bimekizumab 320mg Q4W switching to Q8W at Week 16, respectively. The PK of bimekizumab was impacted in the presence of ADAb, with slightly lower bimekizumab plasma concentrations observed in ADAb-positive study participants. This is in line with an 8% higher apparent clearance of bimekizumab in ADAb-positive compared with ADAb-negative study participants, as shown by population PK analysis (CL0485). Simulations based on the final population PK/PD model (CL0485) indicated that ADAb status had negligible impact on PASI100 and IGA0/1 response rates.

The overall incidence of NAb-positive study participants in the pooled Phase 3 studies following 1 year of treatment was 14.6% in the group receiving bimekizumab 320mg Q4W throughout and 15.6% in the group switching from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W at Week 16. In all studies, the majority of participants were positive for both IL-17AA and IL-17FF. The PK of bimekizumab was impacted in the presence of NAb, and this impact was larger than the impact of ADAb positivity on PK.

Special populations

- **Renal and hepatic impairment**

No specific studies have been conducted to determine the effect of renal or hepatic impairment on the PK of bimekizumab. As a mAb, the renal elimination and metabolism of bimekizumab is expected to be low and of minor importance. Hence, no dose adjustments are proposed in renally or hepatically impaired patients.

- **Gender**

In the population PK analysis (CL0485), gender was found to be a statistically significant covariate on CL/F, with females predicted to have approximately 10% greater CL/F compared to males. This difference was not considered to be clinically meaningful. Hence, no dose adjustment is proposed.

- **Race**

Study UP0042

This study evaluated the PK of bimekizumab following single SC doses of 80mg, 160mg, 320mg bimekizumab in healthy Japanese (N=24; 6 study participants per dose) and Caucasian (N=24; 6 study participants per dose) subjects.

The results indicated that the PK of bimekizumab was linear and dose proportional in Japanese and Caucasian healthy study participants in the tested dose range. The dose- and body weight-normalized PK of bimekizumab was generally similar between Japanese and Caucasian subjects. The point

estimates of the Geo LSMean ratios of dose-normalized AUC and Cmax were approximately 1 (1.014 and 1.140, respectively) [90% CI ranged from 0.91-1.25). The point estimates of the Geo LSMean ratios of dose-normalized and body-weight normalized AUC and Cmax were both approximately 1 (0.9017 and 1.014) [90% CI ranged from 0.81-1.1).

Population PK and PKPD analysis (CL0485)

The popPK model found that race was a statistically significant covariate on CL/F (Asian/Japanese study participants had 22% higher CL/F than non-Asian/Japanese study participants). However, Asian/Japanese subjects had typically lower body weights compared to non-Asian/Japanese, which is likely to compensate for faster clearance in this group.

Based on simulations using the popPK model, the impact of race on exposure was not considered to be clinically meaningful. The impact of race on clinical response (PASI and IGA), based on simulations using the PK/PD model, was also not considered to be clinically meaningful (**Figure 4** and **Figure 8**).

Figure 4 – PASI100 response rate versus time for different weight categories

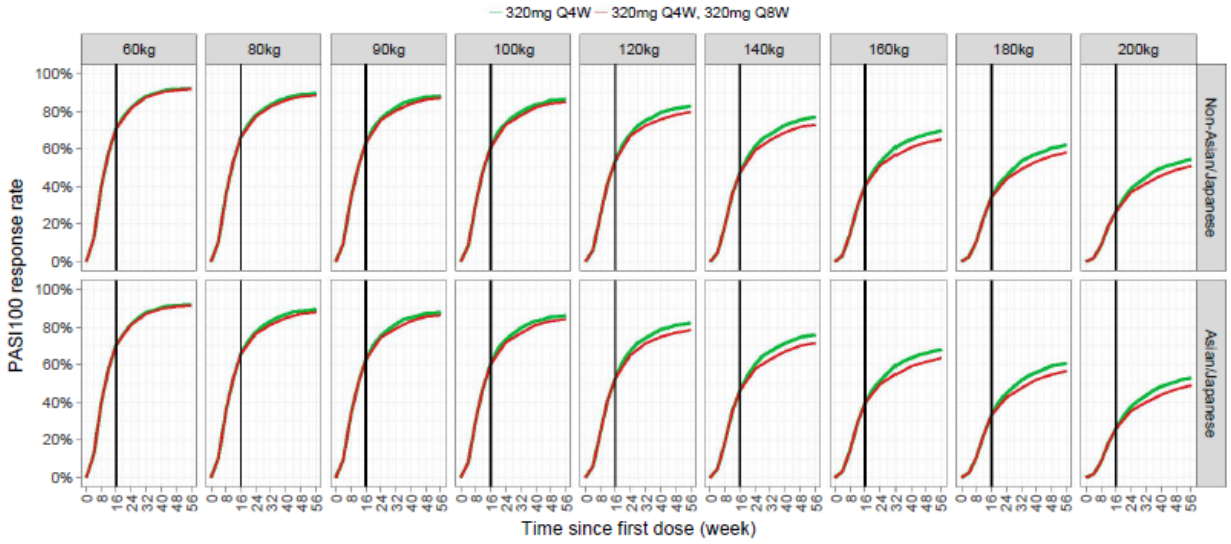


Figure 39: PASI100 response rate versus time for different weight categories for a 65 year male study participant from Central/Eastern Europe, with ADAb negative status and a baseline PASI of 18.5, based on the final exposure response model for PASI, colored by the treatment groups and stratified by race. The vertical line shows the time (Week 16) when the study participants in the second treatment group switch from 320mg Q4W regimen to 320mg Q8W regimen. PASI: Psoriasis Area and Severity Index; PASI100: 100% improvement from baseline in PASI; Q4W: every 4 weeks; Q8W: every 8 weeks; ADAb: anti-drug-antibody; 320 mg Q4W, 320 mg Q8W: 320mg Q4W followed by 320mg Q8W from week 16 onwards.

Figure 5 – Boxplots of the simulated IGA response rate versus race categories at Week 56

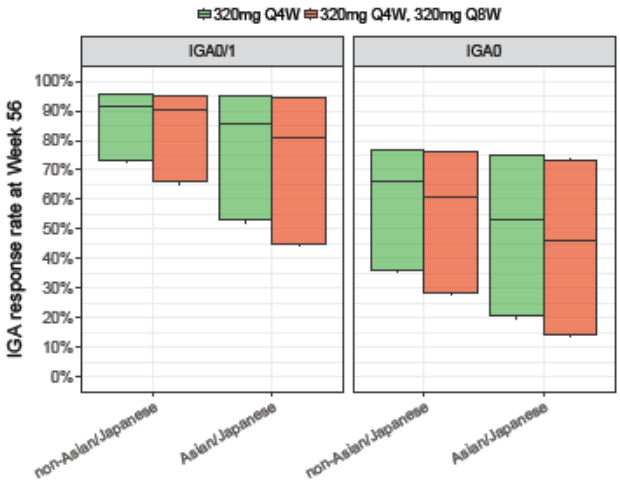


Figure 58: Boxplots of the simulated IGA response rate versus race categories at Week 56, based on the final exposure response model for IGA, colored by the treatment groups and stratified by IGA response variable. In the box plots, the line corresponds to the median, the upper and lower hinges correspond to the 97.5th and 2.5th percentiles. IGA: Investigator's Global Assessment; IGA0: IGA score of 0; IGA0/1: IGA score of ≤1; Q4W: every 4 weeks; Q8W: every 8 weeks; 320 mg Q4W, 320 mg Q8W: 320mg Q4W followed by 320mg Q8W from week 16 onwards.

Based on the overall data, no dose adjustment is proposed in terms of race.

- **Weight**

The population PK analysis (CL0485) indicated that both CL/F and V/F of bimekizumab change with bodyweight (median of 87.0kg [range: 40.1-237kg]). Compared to a typical patient (~90 kg kg), patients weighing 120kg are expected to have Cav which is 30% lower and patients weighing 200 kg are expected to have Cav which is 60% lower. Similarly, a 60kg subject is expected to have 50% higher Cav and 40% higher Cmax, compared to a typical subject.

Figure 6 and **Figure 7** present the results of the simulations based on the population PKPD model (CL0485) for PASI and IGA, respectively, with 2 dose regimens (i.e. continuous 320mg Q4W and 320mg Q4W up to Week 16 followed by Q8W) for non-Asian male patients, stratified by different weight categories. These show that the median model-predicted PASI90, PASI100 and IGA0/1 responder rates overlap at body weights lower than 120kg and then start diverging. This indicates that some patients with body weight ≥120kg may benefit from the Q4W regimen in the Maintenance Phase.

Figure 6 – PASI response rate versus time for different weight categories

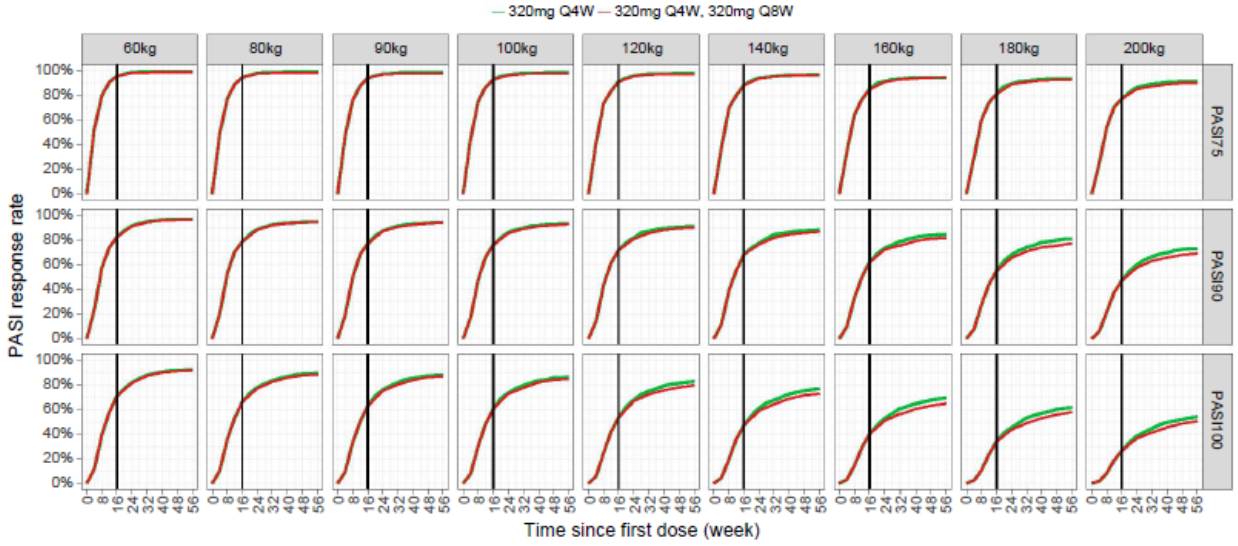


Figure 34: PASI response rate versus time for different weight categories for a 65 year old non-Asian male study participant from Central/Eastern Europe, ADAb negative status and a baseline PASI of 18.5, based on the final exposure response model for PASI, colored by the treatment groups. The vertical line shows the time (Week 16) when the study participants in the second treatment group switch from 320mg Q4W regimen to 320mg Q8W regimen. PASI: Psoriasis Area and Severity Index; PASI75: 75% improvement from baseline in PASI; PASI90: 90% improvement from baseline in PASI; PASI100: 100% improvement from baseline in PASI; Q4W: every 4 weeks; Q8W: every 8 weeks; ADAb: anti-drug-antibody; 320 mg Q4W, 320 mg Q8W: 320mg Q4W followed by 320mg Q8W from week 16 onwards.

Figure 7 – Simulated IGA response rate versus time for different weight categories

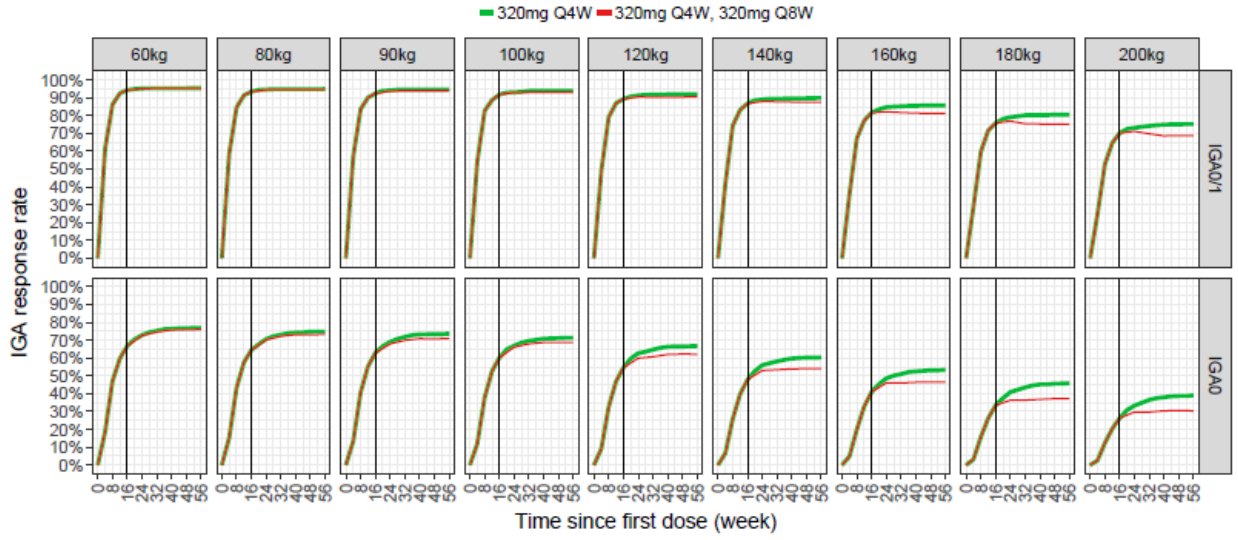


Figure 53: Simulated IGA response rate versus time for a typical non-Asian/Japanese 65 year old male study participant with ADAb negative status and baseline IGA of 3, based on the final exposure response model for IGA, colored by the treatment groups and stratified by body weight categories and IGA response variable type. The vertical line shows the time (Week 16) when the study participants in the second treatment group switch from 320mg Q4W regimen to 320mg Q8W regimen. IGA: Investigator's Global Assessment; IGA0: IGA score of 0; IGA0/1: IGA score of ≤1; Q4W: every 4 weeks; Q8W: every 8 weeks.

- **Elderly**

In the population PK analysis (CL0485), bimekizumab CL/F and V/F were not impacted by age. The median age of the subjects was 44 years (ranging from 18–83 years). 110 of the 1348 patients included in the analysis were ≥65 years (8.2%) and 14 were ≥75 years (1.0%). No dose adjustment is proposed.

Pharmacokinetic interaction studies

Interactions

No DDI studies were conducted. Although direct DDIs between therapeutic proteins and small molecules have not been reported, there is the possibility that cytokines or cytokine modulators may indirectly modify the metabolism of small molecules that are substrates for CYP enzymes and/or transporters.

A limited effect on the exposure of CYP substrates following treatment with bimekizumab is anticipated. Therefore, the applicant considered that current diligence to monitor the exposure of narrow therapeutic index drugs such as warfarin should suffice. This has been reflected in section 4.5 of the SmPC.

Exposure relevant for safety evaluation

Based on simulated data, median (2.5th and 97.5th percentile) peak and trough concentrations at steady-state following sc administration of 320mg Q4W are 43µg/mL (20-91µg/mL) and 20µg/mL (7-50µg/mL), respectively, and steady-state is reached after approximately 16 weeks with Q4W dosing regimens.

2.4.3. Pharmacodynamics

Clinical responses (PASI and IGA) were used as PD assessments throughout the development of bimekizumab (no other PD or PD biomarker analyses outside of efficacy assessments were conducted).

Mechanism of action

Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) subclass with 2 identical antigen binding regions that potently and selectively bind and neutralize IL-17A, IL-17F, and IL-17AF cytokines.

Primary pharmacology

PS0010

A statistically significant and clinically relevant difference in PASI90 responder rate at Week 12 was observed for bimekizumab-treated study participants compared with placebo-treated study participants. Maximum clinical response on PASI90 responder rate was achieved at 320mg Q4W. A further increase in dose would not be expected to provide additional clinical benefit. No clinically relevant difference was observed in the PASI90 responder rate at Week 12 between the bimekizumab 160mg and 160mg w/LD groups.

PS0011

Week 12 PASI90 non-responders in the placebo group quickly achieved improvements with bimekizumab treatment in PS0011, which were maintained over 48 weeks. Week 12 PASI90 non-responders in the bimekizumab group who continued to receive bimekizumab experienced improvements. Week 12 PASI90 responders in the bimekizumab group maintained improvements throughout the study.

PS0016

Bimekizumab was administered to study participants as follows:

- Bimekizumab 320mg+placebo: bimekizumab 320mg administered sc at Baseline and Week 4, and placebo administered at Week 16 (N=32)

- Bimekizumab 320mg: bimekizumab 320mg administered sc at Baseline and Weeks 4 and 16 (N=17)

Maximum PASI100 responder rates were achieved across all study participants at Week 12 (ie, 8 weeks after the second dose in the study) and loss of response had begun by Week 16 (ie, 12 weeks after the second dose in the study) indicating dosing intervals greater than Q8W would result in loss of PASI response.

PS0018

The PASI responder rates (PASI100, PASI90, PASI75, and PASI50) steadily increased from Week 0, followed by a plateau through Week 48/Withdrawal (WD) Visit, and a decrease at the SFU Visit. PASI100 responder rates reached 46.5% at Week 12, PASI90 responder rates reached 79.1% at Week 8, PASI75 responder rates reached 88.4% at Week 4, and PASI50 responder rates reached 95.3% at Week 4. The IGA responder rates steadily increased from Week 0 (18.6%) through Week 4 (62.8%) and Week 8 (79.1%), then plateaued through Week 48/WD Visit (79.1%), followed by a decrease at the SFU Visit (51.2%).

No PD analyses (outside of efficacy analyses) were conducted in PS0008, PS0009 and PS0013. Please see Clinical Efficacy section for details.

Secondary pharmacology

Bimekizumab is a mAb and is not expected to interact with the hERG channel. A thorough QT/QT interval corrected (QTc) clinical study has therefore not been conducted.

Pharmacodynamic interactions

Study UP0034

This was a Phase 1, open-label, randomized, parallel-group, single-dose study to evaluate the effectiveness of influenza vaccination following concomitant exposure to a single dose of bimekizumab (320mg) administered SC in healthy subjects (18-55 years of age). After measurement of antibody titers at Baseline, study participants were randomized in a 1:1 ratio to receive either bimekizumab 320mg (N=28) or no treatment (N=28). Inactivated influenza vaccine was administered intramuscularly 2 weeks after the dose of investigational medicinal product (IMP)/no treatment.

There was no significant difference in the proportion of participants exhibiting a seroconversion response between the bimekizumab 320mg group and the group of participants who received no treatment prior to their vaccination.

Table 10 – Primary analysis: Proportion of participants exhibiting a seroconversion response 4 weeks post vaccination (PD-PPS)

Treatment	n/Nsub (%)	Comparison	Difference estimate (95% CI)	p-value (Chi-square test)	p-value (Fisher's exact test)
BKZ 320mg (N=28)	24/28 (85.71)	BKZ 320mg/ No treatment	-3.17 (-20.74, 14.39)	0.724 [a]	>0.999
No treatment (N=27)	24/27 (88.89)				

BKZ=bimekizumab; CI=confidence interval; HI=hemagglutination inhibition; PD-PPS=Pharmacodynamic-Per Protocol Set; sc=subcutaneous

Note: n=number of participants exhibiting a seroconversion response at 4 weeks post vaccination, with seroconversion defined as participants with either a pre-vaccination HI titer ≤1/10 and a 4-week post-vaccination HI titer ≥1/40 or a pre-vaccination HI titer >1/10 and a ≥4-fold increase in HI titer 4 weeks after vaccination in at least 2 out of 4 serotypes. Nsub=number of participants with a nonmissing measurement at the visit.

Note: Chi-square test was performed on the proportion of study participants who achieved seroconversion. Noninferiority was concluded, as the lower 95% CI excluded a difference of 40% (lower confidence limit was above -40%) or more at 4 weeks post vaccination.

Note: No treatment: Single intramuscular dose of inactivated influenza vaccine on Day 15. BKZ 320mg: Single sc dose administered as a 2x1mL 160mg/mL injection on Day 1 followed by single intramuscular dose of inactivated influenza vaccine on Day 15.

[a] Chi-square test produced expected responder counts below 5; therefore, results from this test should be interpreted with caution.

There were no observed differences between the 2 groups for any of the 4 influenza serotypes of vaccine-specific antibodies. Within each individual influenza serotype, the influenza antibody geometric mean titers were generally similar between the 2 groups at all time points.

Relationship between plasma concentration and effect

Population PK/PD analysis CL0466

The population PKPD model was developed using combined data from 2 Phase 2 studies (PS0010 and PS0016) in adult subjects with moderate to severe adult plaque psoriasis. The aim was to perform simulations to inform the dose and dosing regimen/s to use in the Phase 3 clinical studies.

All data up to Week 16 were used to develop the "pre-final" PKPD model that was used to perform the dosing simulations. The parameters characterising the pre-final model are listed in Table 11. Results of the VPC from the pre-final PKPD model by dose level are shown in Figure 8Figure 9.

Table 11 – Model parameter estimates of the pre-final PKPD model

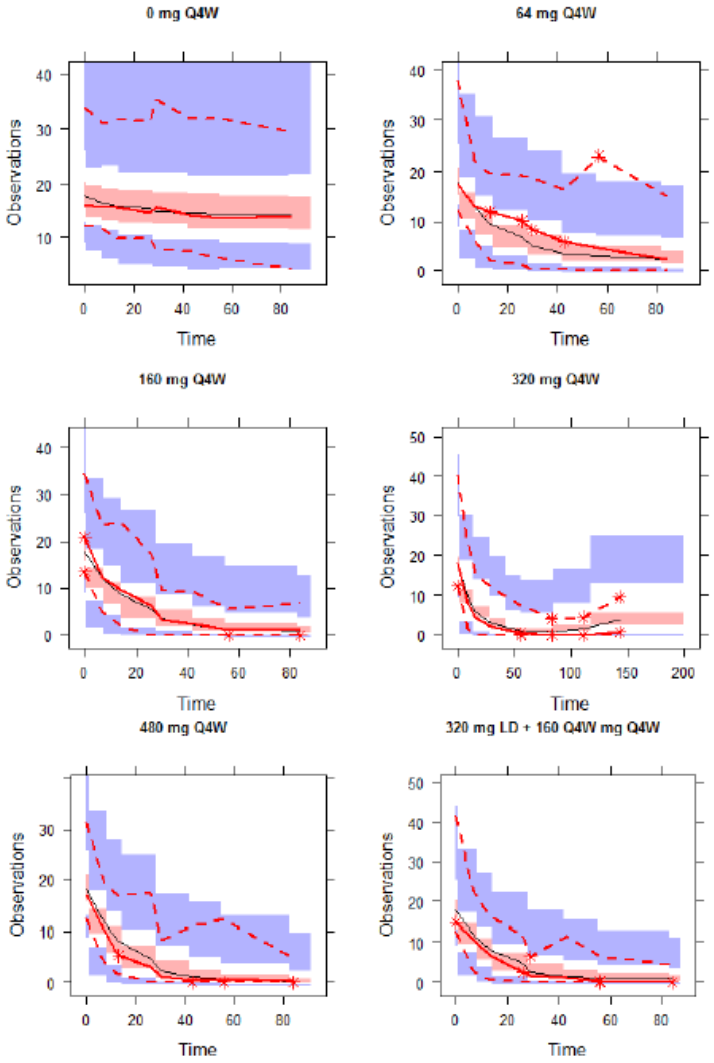
Parameter (unit)	Estimate	95%CI	Precision [a] (RSE%)	Shrinkage
Structural PK model				
Baseline PASI	17.7	[17.0;18.4]	2.1	-
Placebo effect	0.212	[0.041;0.383]	41.3	-
Turnout half-life	10.5	[9.41;11.6]	5.3	-
EC_{50} (µg/mL)	0.55	[0.39;0.71]	14.9	-
Stochastic PK model [b]				
IIV on baseline	0.944 (97%CV)	[0.73;1.16]	11.5	16.6
IIV on placebo	0.159 (40% CV)	[0.007;0.311]	48.8	66.4
IIV on turnout half-life	0.489 (70%CV)	[0.343;0.635]	15.3	12.1
IIV on EC_{50}	1.6 (126%CV)	[1.21;1.99]	12.3	17.9
Prop. Error (%)	0.112 (33%CV)	[0.099;0.125]	5.76	
Add. Error	0.171 (0.41 SD)	[0.128;0.214]	12.9	

[a] Precision was calculated as the standard error (SE) divided by the parameter estimate x 100 (i.e. relative standard error [RSE])

[b] The % CV for both inter-individual and residual variability is an approximation taken as the square root of variance x100

CI: confidence interval, CV: coefficient of variation, IIV: Inter-individual variability, K_a: first-order absorption rate constant, Prop. Error : proportional residual error, SD: standard deviation

Figure 10 – Visual predictive check by dosing regimen



Solid red lines: observed median PASI
Dotted red line: 5th and 95th percentiles of the observed PASI
Solid black line: median simulated PASI,
Red area: 95% prediction interval of the median simulated PASI,
Blue area: 95% prediction interval of the 5th and 95th percentiles of the simulated PASI

Simulations indicated that doses above 320mg Q4W may not provide a clinically relevant increase (>10 percentage points) in PASI90 or PASI100 responder rates at Week 16 (Figure 5:22). However, the 320 mg dose provides a greater than 10 percentage points benefit on PASI90 and PASI100 compared to 160 mg dose. The simulations also indicated that a loading dose at baseline may not impact PASI90 or PASI100 response at Week 16. For the maintenance period, simulations indicated that a Q4W regimen is likely to maintain PASI75, PASI90 and PASI100 response, whilst patients on both Q8W and Q12W are likely to lose PASI90 and PASI100 response.

Population PKPD analysis CL0485

This analysis was based on the data from three Phase 2 studies (PS0010, PS0011, and PS0016), and interim data from two Phase 3 studies (PS0008 and PS0009). Population PKPD models were developed to describe the bimekizumab exposure-response relationships for PASI and IGA.

PASI model

The final population PKPD model for PASI was a bounded integer model with a placebo effect model, described with maximum placebo effect (PLmax), and a treatment effect maximum effect (Emax)

model of bimekizumab average concentration (Cav) over the dosing intervals. Covariates included in the model were baseline body weight (WT), region and baseline PASI score on Emax, and age and region on EFhalf. However, body weight was the only clinically relevant covariate that impacts PASI90 and PASI100 response rates.

The parameter estimates of the final exposure-response model for PASI are presented in **Table 12**. Figures below present the categorical VPC for PASI response rate versus Cav deciles at Week 16 and Week 56, respectively.

Table 12 – Parameter estimates of the final exposure-response model for PASI

	Run 202 (Condition number = 58.1)		
	Unit	Value	RSE (%)
Scaling parameter (SP)		0.193	2.09
BASE		-0.630	1.52
PL_{max}		-0.273	21.3
EF_{half}	Week	4.92	5.02
E_{max}		-2.14	2.54
EC_{50}	µg/mL	0.148	18.0
Baseline PASI on E_{max}		0.210	15.2
Baseline WT on E_{max}		-0.225	17.9
North America region on E_{max}		-0.150	15.2
Western Europe/Asia/Australia region on E_{max}		-0.217	10.7
Baseline age on EF_{half}		0.383	20.1
Non-Central/Eastern Europe region on EF_{half}		-0.271	17.1
IIV SP	CV	0.461	4.84
IIV BASE	SD	0.222	4.87
IIV PL_{max}	SD	0.511	14.8
IIV EF_{half}	CV	0.833	3.59
Corr EF_{half}-E_{max}	Corr	-0.555	9.08
IIV E_{max}	SD	0.589	5.37
Corr EF_{half}-EC_{50}	Corr	0.166	58.3
Corr E_{max}-EC_{50}	Corr	-0.541	13.0
IIV EC_{50}	CV	2.18	6.76

Additive IIV and covariances are reported on the SD/Correlation scale ($\sqrt{\omega^2}$)
RSEs of the IIV parameters are calculated according to: abs(SD/estimate)*100.
PL_{max}: maximum placebo effect
EF_{half}: time to reach half maximum effect
E_{max}: maximum effect
EC_{50}: concentration at half maximum effect
IIV: interindividual variability

Figure 11 - categorical VPC for PASI response rate versus Cav deciles at Week 16

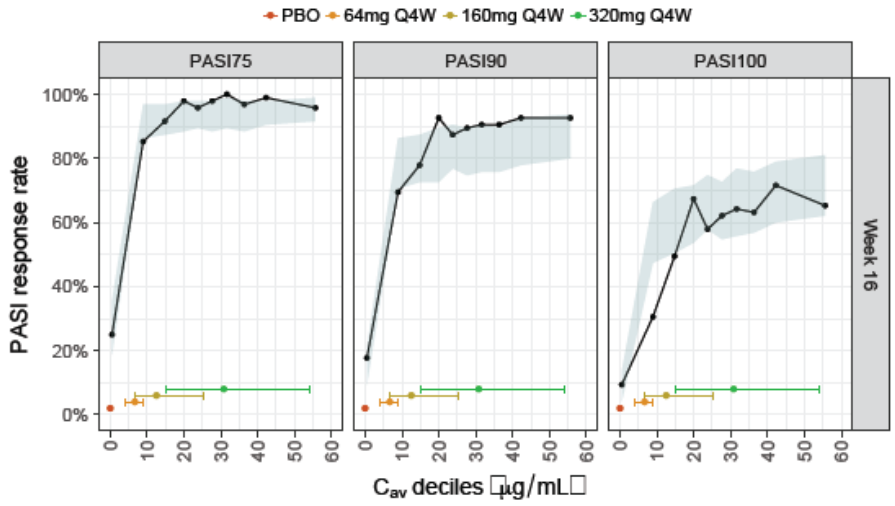


Figure 26: VPC of the PASI response rate at Week 16 based on the final PKPD model (run 202) for PASI versus deciles of average bimekizumab concentration, stratified by PASI response categories. The solid black lines connect the observed fraction of observations within each response category. The shaded areas are the 95% confidence intervals. 200 data-sets were simulated. The horizontal lines represent the median and 5th and 95th percentiles of C_{av} at Week 16 (irre-spective of PASI response variable type), colored by different treatment groups. VPC: visual predictive check; PKPD: pharmacokinetic-pharmacodynamic; PASI: Psoriasis Area and Severity Index; PASI75: 75% improvement from baseline in PASI; PASI90: 90% improvement from baseline in PASI; PASI100: 100% improvement from baseline in PASI; C_{av}: average concentration; PBO: Placebo; Q4W: every 4 weeks.

Figure 12 - categorical VPC for PASI response rate versus Cav deciles at Week 56

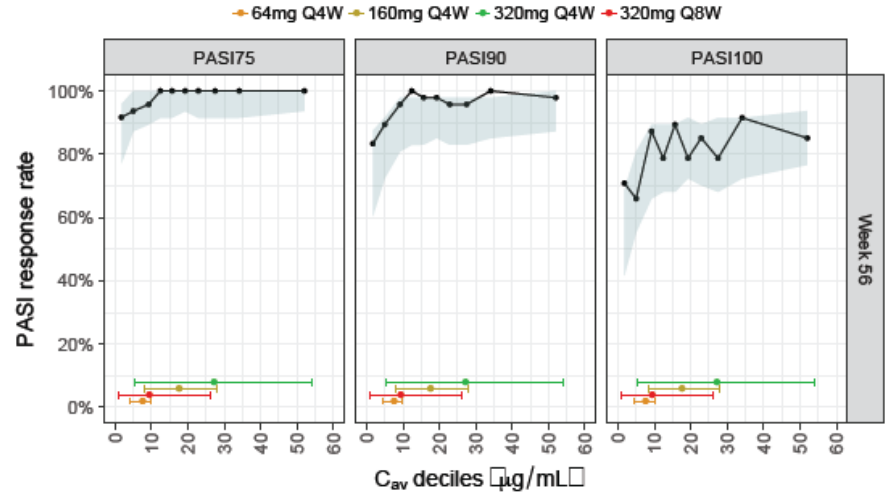


Figure 27: VPC of the PASI response rate at Week 56 based on the final PKPD model (run 202) for PASI versus deciles of average bimekizumab concentration, stratified by PASI response categories. The solid black lines connect the observed fraction of observations within each response category. The shaded areas are the 95% confidence intervals. 200 data-sets were simulated. The horizontal lines represent the median and 5th and 95th percentiles of C_{av} at Week 56 (irre-spective of PASI response variable type), colored by different treatment groups. VPC: visual predictive check; PKPD: pharmacokinetic-pharmacodynamic; PASI: Psoriasis Area and Severity Index; PASI75: 75% improvement from baseline in PASI; PASI90: 90% improvement from baseline in PASI; PASI100: 100% improvement from baseline in PASI; C_{av}: average concentration; Q4W: every 4 weeks; Q8W: every 8 weeks.

IGA model

The final population PKPD model for IGA was a bounded integer model with a mono-exponential time-dependent placebo effect described by PLmax and time to reach half maximum placebo effect (PLhalf). Bimekizumab exposure response was described with an indirect response model with stimulation of zero-order production rate constant (Kin) using an Emax effect model of bimekizumab Cav over the

dosing intervals. Covariates in the model were baseline IGA score on first-order removal rate constant (Kout), and baseline WT and Asian/Japanese race on concentration at half maximum effect (EC50).

The parameter estimates of the final PKPD model for IGA are presented in **Table 13**.

Figures below present the categorical VPC for IGA response rate versus Cav deciles at Week 16 and Week 56, respectively.

Table 13 – Parameter estimates of the final population PKPD model for IGA

	Run 24 (Condition number = 133)		
	Unit	Value	RSE (%)
Scaling parameter (SP)		0.211	3.44
Baseline parameter (BASE)		0.657	1.97
PL_{max}		-0.160	39.4
PL_{half}	Week	7.14	**FIXED**
Markov probability		0.334	4.69
E_{max}		-3.12	2.76
EC_{50}	µg/mL	0.451	21.2
K_{out}		0.0358	4.48
Baseline IGA score on K_{out}		-0.336	11.2
Baseline WT on EC_{50}		2.54	22.5
Asian/Japanese race on EC_{50}		1.19	60.3
IIV SP	CV	0.578	5.22
IIV BASE	SD	0.139	8.34
IIV PL_{max}	SD	0.576	13.4
IIV PL_{half}	CV	0.150	**FIXED**
IIV Markov	CV	0.150	**FIXED**
IIV E_{max}	SD	1.03	6.42
Corr E_{max}-EC_{50}	Corr	-0.614	14.6
IIV EC_{50}	CV	2.08	6.47
Corr E_{max}-K_{out}	Corr	0.546	13.4
Corr EC_{50}-K_{out}	Corr	-0.102	105
IIV K_{out}	CV	0.830	4.97

Additive IIV and covariances are reported on the SD/Correlation scale ($\sqrt{\omega^2}$)

RSEs of the IIV parameters are calculated according to: abs(SD/estimate)*100.

CV: coefficient of variation; E_{max}: maximum effect; EC_{50}: concentration at half maximum effect; IIV: interindividual variability; K_{out}: first-order removal rate constant; OFV: objective function value; PL_{half}: time to reach half maximum placebo effect; PL_{max}: maximum placebo effect; RSE: relative standard error; SD: standard deviation; WT: body weight

Figure 13 - categorical VPC for IGA response rate versus Cav deciles at Week 16

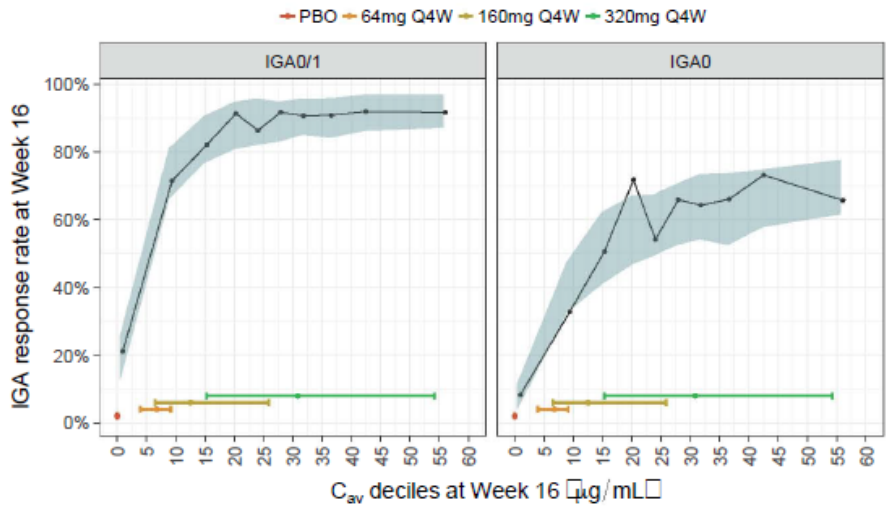


Figure 44: VPC based on the final bimekizumab exposure response model for IGA response rate versus bimekizumab C_{av} deciles at Week 16, stratified by IGA response variable type. The solid black lines connect the observed IGA response rates. The shaded areas are the 95% prediction intervals of the IGA response rates based on 200 simulated data sets.The horizontal lines represent the median and 5th and 95th percentiles of C_{av} at Week 16 (irrespective of IGA response variable type), colored by different treatment groups. IGA: Investigator's Global Assessment; IGA0: IGA score of 0; IGA0/1: IGA score of ≤1; PBO: Placebo; Q4W: every 4 weeks; C_{av}: average concentration.

Figure 14 - categorical VPC for IGA response rate versus Cav deciles at Week 56

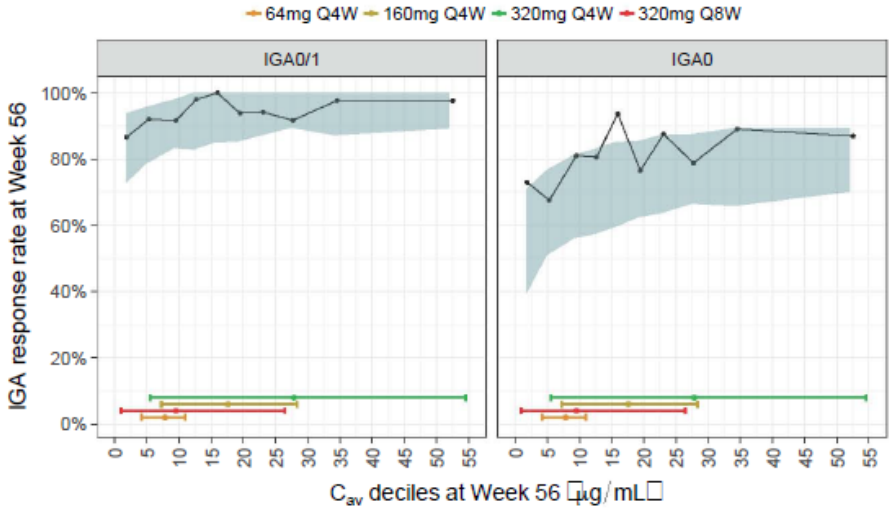


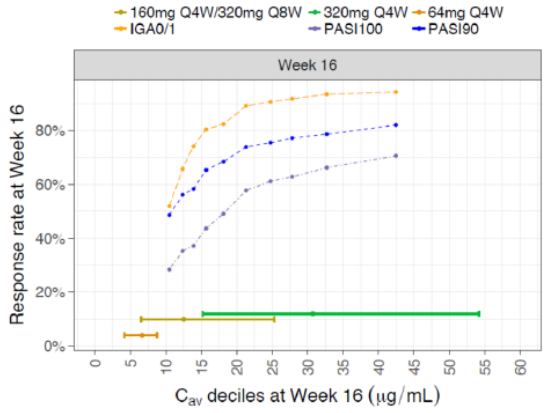
Figure 45: VPC based on the final bimekizumab exposure response model for IGA response rate versus bimekizumab C_{av} deciles at Week 56, stratified by IGA response variable type. The solid black lines connect the observed IGA response rates. The shaded areas are the 95% prediction intervals of the IGA response rates based on 200 simulated data sets. The horizontal lines represent the median and 5th and 95th percentiles of C_{av} at Weeks 56 (irrespective of IGA response variable type), colored by different treatment groups. IGA: Investigator's Global Assessment; IGA0: IGA score of 0; IGA0/1: IGA score of ≤1; PBO: Placebo; Q4W: every 4 weeks; Q8W: every 8 weeks; C_{av}: average concentration.

Dose simulations based on the exposure-response models for PASI and IGA

Figure 16 represent simulated PASI90, PASI100 and IGA0/1 response rates versus bimekizumab Cav deciles at Weeks 16 and 56, respectively. The plots indicate that 320mg Q4W was an appropriate dose for the initial treatment period and 320mg Q8W was appropriate for the maintenance period for the majority of moderate to severe plaque psoriasis subjects.

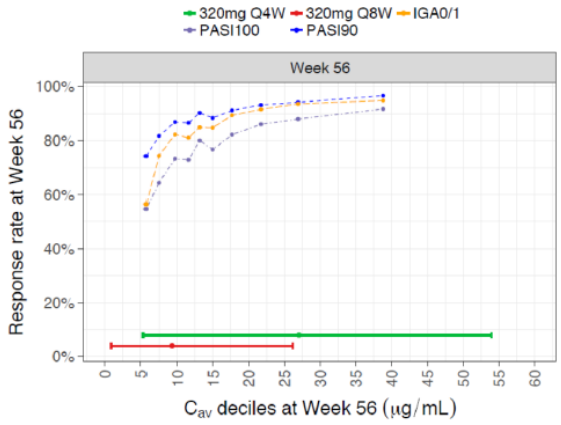
Figure 15 – Simulated PASI90, PASI100, and IGA 0/1 response rates vs bimekizumab Cav deciles at week 16 and week 56, respectively (CL0485)

Figure 2-16: Simulated PASI90, PASI100, and IGA 0/1 response rates vs bimekizumab C_{av} deciles at Week 16 based on the final bimekizumab exposure response model (CL0485)



C_{av}=average concentration; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks
Note: The lines connect the simulated median response rates and colored by the response variable types. The horizontal lines represent the median and 90th percentile boundaries of observed bimekizumab plasma concentrations at Week 16, colored by different treatment groups.

Figure 2-17: Simulated PASI90, PASI100, and IGA 0/1 response rates vs bimekizumab C_{av} deciles at Week 56 based on the final bimekizumab exposure response model (CL0485)



C_{av}=average plasma concentration; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks
Note: The lines connect the simulated median response rates and colored by the response variable types. The horizontal lines represent the median and 90th percentile boundaries of observed bimekizumab plasma concentrations at Week 56, colored by different treatment groups.

Simulations also showed that the difference between the two dosing regimens (i.e, continuous 320mg Q4W and 320mg Q4W up to Week 16 followed by Q8W) with regards to PASI75, PASI90 and IGA0/1 were negligible at Week 56 for a typical patient. The differences were slightly larger for PASI100 and IGA0 response (**Figure 17** and **Figure 18**).

Figure 16 – Simulated PASI response rate versus time

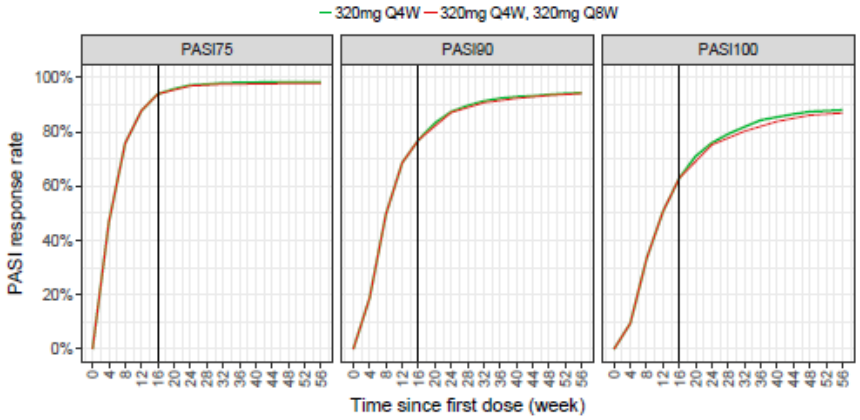


Figure 33: Simulated PASI response rate versus time for a typical 65 year old non-Asian male study participant from Central/Eastern Europe with 90kg WT, ADAb negative status and a baseline PASI of 18.5, based on the final exposure response model for PASI, colored by the treatment groups. The vertical line shows the time (Week 16) when the study participants in the second treatment group switch from 320mg Q4W regimen to 320mg Q8W regimen. PASI: Psoriasis Area and Severity Index; PASI75: 75% improvement from baseline in PASI; PASI90: 90% improvement from baseline in PASI; PASI100: 100% improvement from baseline in PASI; Q4W: every 4 weeks; Q8W: every 8 weeks; ADAb: anti-drug-antibody; WT: body weight; 320 mg Q4W, 320 mg Q8W: 320mg Q4W followed by 320mg Q8W from week 16 onwards.

Figure 17 – Simulated IGA response rate versus time

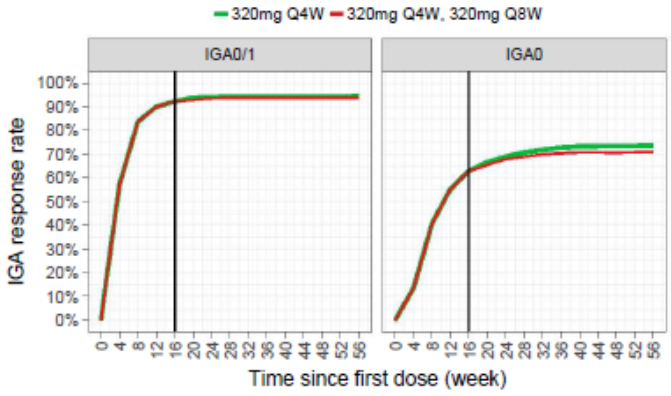


Figure 52: Simulated IGA response rate versus time for a typical non-Asian/Japanese 65 year old male study participant with 90kg body weight, ADAb negative status and baseline IGA of 3, based on the final exposure response model for IGA, colored by the treatment groups and stratified by IGA response variable type. The vertical line shows the time (Week 16) when the study participants in the second treatment group switch from 320mg Q4W regimen to 320mg Q8W regimen. IGA: Investigator's Global Assessment; IGA0: IGA score of 0; IGA0/1: IGA score of ≤1; Q4W: every 4 weeks; Q8W: every 8 weeks.

Dose-exposure-safety of bimekizumab

This analysis was based on pooled safety data collected while on blinded bimekizumab from Phase 2 and Phase 3 studies. TEAEs by bimekizumab trough concentrations quartiles at Week 52 or 56 are summarised in **Table 14**. A trend was observed towards higher Candida infection rates in the higher plasma concentration quartiles.

Table 14 – TEAEs during the combined initial and maintenance treatment period by week 52/56 bimekizumab trough concentration quartile (Pool S2A)

Plasma concentration quartile	First Quartile	Second Quartile	Third Quartile	Fourth Quartile	Any concentration
	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]	n (%) [#]
BKZ 320mg Q4W/Q4W					
	<12.6µg/mL N=124	≥12.6 to <19µg/mL N=124	≥19 to <27.8µg/mL N=124	≥27.8µg/mL N=125	N=497
Any TEAE	100 (80.6) [476]	101 (81.5) [401]	101 (81.5) [394]	105 (84.0) [431]	407 (81.9) [1702]
Any TEAE coding into the HLT of Candida infections	20 (16.1) [39]	24 (19.4) [34]	25 (20.2) [53]	25 (20.0) [46]	94 (18.9) [172]
BKZ 320mg Q4W/Q8W					
	<3.77µg/mL N=54	≥3.77 to <6.19µg/mL N=55	≥6.19 to <9.05µg/mL N=54	≥9.05µg/mL N=55	N=218
Any TEAE	41 (75.9) [180]	49 (89.1) [197]	49 (90.7) [231]	47 (85.5) [186]	186 (85.3) [794]
Any TEAE coding into the HLT of Candida infections	6 (11.1) [14]	7 (12.7) [9]	13 (24.1) [25]	9 (16.4) [17]	35 (16.1) [65]

BKZ=bimekizumab; HLT=high-level term; ISS=Integrated Summary of Safety; Q4W=every 4 weeks; Q8W=every 8 weeks; TEAE=treatment-emergent adverse event

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

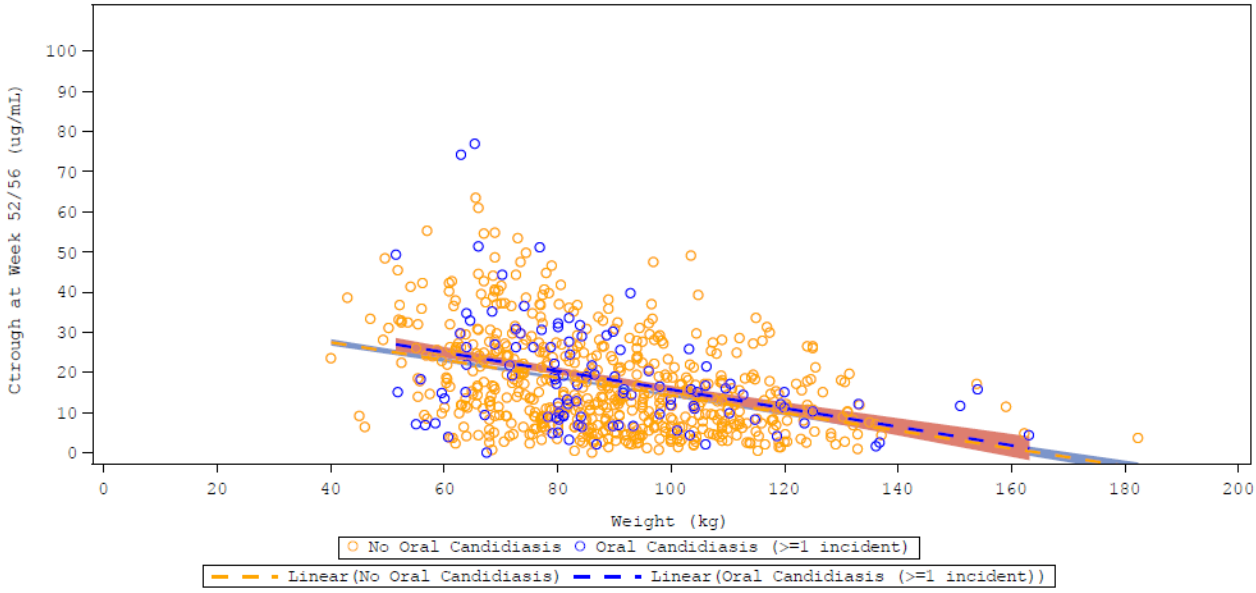
Note: This table summarizes data through Week 52 for PS0009 and through Week 56 for PS0008 and PS0013. For the BKZ 320mg Q4W/Q4W group, quartiles are based on the plasma concentrations from Week 52. For the BKZ 320mg Q4W/Q8W group, quartiles are based on the plasma concentrations from Week 56.

An inverse relationship for the risk of Candida infections with body weight was observed, particularly for oral candidiasis, with higher incidences reported in the lower weight categories. The applicant considered that this could potentially be due to lower concentrations of bimekizumab in heavier subjects compared to lower body weight subjects.

Additional analyses demonstrated that, while a higher exposure is expected in lower-weight patients, this has minimal clinical relevance as any concentration-driven effect on oral candidiasis is weak (**Figure 18**). Further, the vast majority of oral candidiasis cases were mild or moderate and did not lead to discontinuation. This observation includes oral candidiasis cases experienced by study participants <70kg. While the overall impact of dose adjustment on the risk profile is limited, a dose lower than the current proposed posology may result in loss of benefit in lower-weight patients. Hence, the current proposed posology provides the most favourable benefit/risk profile across the broadest range of the target population of adult patients with moderate to severe psoriasis (PSO), including lower-weight patients.

This is further discussed in section 2.4.4 'Discussion on clinical pharmacology'.

Figure 18: Bimekizumab plasma concentrations (ug/mL) at Week 52/56 vs Baseline weight (kg) – Pool S2A



2.4.4. Discussion on clinical pharmacology

Pharmacokinetics

Bioanalytical methods

The three PK methods are considered validated in accordance with the EMA Guideline on bioanalytical method validation (EMEA/CHMP/EWP/192217/2009 Rev. 1).

The overall approach to measuring immunogenicity is in line with the recommendations of EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for *in vivo* clinical use (EMA/CHMP/BMWP/86289/2010). For both the ADA and NAb assays, sufficient details have been provided on the cut-point determinations. Details of assay precision, sensitivity, range, selectivity, and drug tolerance have been provided and are considered acceptable to the CHMP. The drug tolerance of the assays was investigated and the serum concentration of bimekizumab was below the assay tolerances. No effect from target interference on the detection of anti-drug antibodies (ADAb) and neutralizing anti-drug antibodies (Nab) was observed. The validated target concentrations in the ADAb and Nab assays are expected to cover anticipated IL-17AA and IL-17FF levels in study participant samples from the reported clinical studies.

Population PK analyses

In each of the three population PK analyses (CL0453, CL0466 and CL0485), the methods used for model development and evaluation are considered acceptable to the CHMP.

CL0453

Bimekizumab PK were adequately described by a 2-compartment model with first-order absorption and elimination. The absolute bioavailability of SC administration was estimated to be 70.1% (CV 45.9%), which is comparable to that estimated from RA0124 data based on non-compartmental analysis.

CL0466

This popPK model was developed using pooled data from two Phase 2 clinical studies (Phase 2B study PS0010 and the Phase 2A study PS0016). The final model was a one-compartment model with linear absorption and elimination. Weight was found to be a significant covariate on CL/F and V/F, indicating that patients with higher body weight may have reduced bimekizumab exposure. No other significant covariates were identified including race (Japanese vs Caucasian).

All PK parameters of the pre-final model were estimated with good precision (Relative standard error (RSE) <23%). Shrinkage was acceptably low for CL/F and V/F (6.7% and 7.4%, respectively), but high for Ka (81.8%). Inter-individual variability (IIV) estimates were reduced compared to the base model. All Goodness of fits plots (GOF) plots showed that the model adequately described the observed bimekizumab concentrations. The Visual Predictive Check (VPCs) showed that the model captured the global trend and the variability of the concentration vs time data reasonably well. Therefore, the pre-final population PK model is deemed adequate for simulations.

The final model, based on all available data, is also deemed adequate, with similar parameter estimates to pre-final model. GOF and VPCs further support the adequacy of the model.

CL0485

This popPK model was developed using pooled data from three Phase 2 (PS0010, PS0011, and PS0016) and two Phase 3 studies (PS0008 and PS0009). The final model was a one-compartment model with first-order absorption and elimination. The applicant considered that the PK of bimekizumab in the target patient population was well characterised by a 1-compartment PK model with linear absorption and that all the model parameters were well estimated with adequate precision. Further, the volume of distribution of the peripheral compartment could not be adequately estimated (RSE > 50%) with the 2-compartment model. The choice of a one-compartment rather than a two-compartment model was considered to be adequately justified by the applicant.

All PK parameters, both fixed and random effects, were estimated with good precision (all RSEs <25%). IIV shrinkage was low for both CL/F and V/F (2.6% and 11.5%, respectively). The GOF plots show that the model describes the observed data well. The VPCs suggest that the predictive performance of the model is adequate.

Among the tested covariates, baseline body weight, sex, race and ADAb status were statistically significant covariates on CL/F, and body weight was a statistically significant covariate on V/F.

Absorption

- **Bioavailability**

The bioavailability of bimekizumab administered sc was assessed in healthy subjects in study RA0124 using non-compartmental methods. The absolute bioavailability of the 80mg and 160mg dose of bimekizumab reported was similar with values of 0.656 (95% CI: 0.539, 0.798) and 0.631 (95% CI:

0.511, 0.780), respectively. These values are comparable to the absolute bioavailability of SC administration (70.1%) estimated by population PK analysis.

- **Bioequivalence**

Two formulations and three device presentations have been used during the development of bimekizumab. The relative bioavailability study UP0031 showed no clinically relevant difference between the early formulation and the formulation used in most of the studies. In addition, bioequivalence was demonstrated in study UP0033 between processes and devices used in the pivotal phase 3 studies (TN device) and those planned for commercialisation (bimekizumab safety syringe or auto-injector).

No clinically relevant differences are expected after administration in the thigh, abdomen or upper arm. Rotated use of these injections sites as indicated in the SmPC section 4.2 is therefore endorsed by CHMP.

Distribution

The population estimate for the apparent V/F in patients with psoriasis is 11.2L, which is similar to V/F estimated in healthy subjects (8.7-10.2 L). The relatively small volume of distribution is typical of monoclonal antibodies, which are largely confined to the vascular and interstitial spaces due to their large molecular size and poor lipophilicity.

Elimination

The terminal elimination half-life of bimekizumab ranged from 19-26 days and was independent of dose. This half-life is consistent with non-specific (not target-mediated) elimination of human IgG by the reticuloendothelial system.

The lack of specific excretion or metabolism studies is acceptable because bimekizumab is a protein which is primarily cleared by proteolytic catabolism and broken down into small peptides and individual amino acids.

Dose proportionality and time dependency

In single-dose and multiple-dose studies, bimekizumab exhibited dose-independent linear PK. Simulated data based on the final popPK model indicated that steady-state is achieved by Week 16 and the accumulation ratio is ~1.7, which is consistent with the results of the Phase 3 studies.

Pharmacokinetics in the target population

There were no apparent differences observed in bimekizumab PK between healthy subjects and subjects with moderate to severe psoriasis.

Immunogenicity

Immunogenicity data were collected throughout the clinical development programme and the results were generally consistent across studies.

The overall approach to measuring immunogenicity is in line with the recommendations of the EMA Guideline on Immunogenicity assessment of therapeutic proteins (EMEA/CHMP/BMWP/14327/2006 Rev 1) and the EMA Guideline on immunogenicity assessment of monoclonal antibodies intended for in vivo clinical use (EMA/CHMP/BMWP/86289/2010).

For both the ADA and NAb assays, sufficient details have been provided on the cut-point determinations. Details of assay precision, sensitivity, range, and selectivity have been provided and are considered acceptable to the CHMP. The drug tolerance of the assays was investigated and the serum concentration of bimekizumab was below the assay tolerances. Target interference levels were

validated up to a 1:1 combined concentration of 4000pg/mL of IL-17AA and IL-17FF, respectively. No effect from target interference on the detection of anti-drug antibodies (ADAb) was observed. The validated target concentrations in the ADAb assay are therefore expected to cover all anticipated IL-17AA and IL-17FF levels in study participant samples from the reported clinical studies.

The PK of bimekizumab was altered by the presence of ADAb, with slightly lower bimekizumab plasma concentrations observed in ADAb-positive study participants. This is in line with an 8% higher apparent clearance of bimekizumab in ADAb-positive compared with ADAb-negative study participants determined in the population PK analysis (CL0485). Despite the impact on bimekizumab PK, ADAb positive status appears to have a very minor impact on clinical response rates (PASI100 and IGA0/1) according to simulations based on the final PKPD model (CL0485).

The PK of bimekizumab was also impacted in the presence of NAb, and this impact was larger than the impact of ADAb positivity on PK. The Applicant assessed the impact of NAb as a covariate on CL/F in the final population PK model based on the final Phase 3 dataset. NAb status for IL-17FF binding was statistically significant. The model predicted NAb-positive subjects to have 16% higher CL/F. This increase in clearance was not considered to be clinically relevant since only 9% of the total population were both NAb positive for the IL-17FF binding. Further, model-predicted Cav using the legacy model (without NAb covariate) and the final model (with NAb covariate) were similar, suggesting minimal differences in efficacy.

The ADAb and NAb analyses were updated with the immunogenicity data for the safety follow-up (SFU) Periods of PS0008, PS0009, and PS0013, which were ongoing at the time of the data cut-off date. When SFU samples were included, the overall incidences of ADAb- and NAb-positive subjects were similar to those reported in the initial submission.

In summary, there were 2 additional ADAb-positive study participants (1 only positive at SFU) and 1 additional NAb-positive study participant in the updated analyses compared with the initial submission. For all Phase 3 studies combined, the overall incidence of ADAb in study participants who switched from bimekizumab 320mg Q4W to Q8W after Week 16 was 45.1% with and without SFU samples. For all Phase 3 studies combined, the overall incidence of NAb-positive study participants in the group who switched from bimekizumab 320mg Q4W to Q8W at Week 16 was 15.6%, with and without SFU samples; corresponding to 34.2% (40 of 117) of ADAb-positive participants.

The below information included in Section 4.8 of the SmPC is considered acceptable by CHMP.

Immunogenicity

Approximately 45% of plaque psoriasis patients treated with bimekizumab up to 56 weeks at the recommended dosing regimen (320 mg every 4 weeks up to Week 16 and 320 mg every 8 weeks thereafter) developed anti-drug antibodies. Of the patients who developed anti-drug antibodies, approximately 34% (16% of all patients treated with bimekizumab) had antibodies that were classified as neutralizing. No evidence of altered clinical response, or safety profile was associated with anti-bimekizumab antibodies development.

Special populations

The conclusions on special populations are largely based on the testing of covariates (body weight, sex, race and ADAb status) in the popPK analysis.

- **Renal and hepatic impairment**

The lack of dedicated studies in subjects with renal and hepatic impairment is justified. It is agreed that a dose adjustment in these patient populations is not warranted.

- **Gender**

Despite a 10% higher CL/F in females compared to males determined in the population PK analysis, the difference did not translate into a clinically relevant effect on bimekizumab exposure. Therefore, it is agreed that no dosage adjustment is warranted in terms of gender.

- **Race**

It is agreed that there was no clinically meaningful difference in bimekizumab exposures between Asian/Japanese and non-Asian/Japanese subjects after accounting for body weight. Simulations based on the final PK/PD model (CL0485) indicated that there may be some differences in clinical response rates particularly for IGA response. However, upon request by the CHMP, the applicant adequately justified that the apparent effect of race on clinical response is not clinically relevant. Therefore, it is agreed that a dose adjustment is not necessary in Asian/Japanese patients.

- **Weight**

A strong impact of body weight (BW) on drug distribution and elimination was observed in the popPK model in addition to a strong effect on the two PD endpoints (PASI and IGA) according to the PK/PD models. Therefore, the applicant proposed that some patients (with an incomplete skin clearance at week 16) with BW ≥120kg may benefit from the Q4W regimen in the Maintenance Phase. This is supported by the PK/PD simulations. The recommendation for overweight patients in SmPC section 4.2 is agreed by CHMP.

The applicant did not propose a dose adjustment for patients of low BW (40-60 kg), despite an expected ≥50% higher Cav and ≥40% higher Cmax compared to a typical subject of ~90 kg. An inverse relationship between BW and oral candidiasis was observed with a higher incidence in the lower BW groups. However, the applicant conducted additional analyses in support of the current proposed dose regimen for lower weight patients. These showed that any concentration-driven effect on oral candidiasis is weak and a dose adjustment in lower weight patients will likely have a limited effect on the incidence of oral candidiasis. Further, efficacy data suggest that using a lower dose in lower weight patients may result in reduced efficacy. Finally, the majority of oral candidiasis cases were mild or moderate and did not result in treatment discontinuation. Therefore, the applicant's position that the current proposed posology for bimekizumab (i.e. 320mg at weeks 0, 4, 8, 12, 16 and every 8 weeks thereafter) provides the most favourable benefit/risk profile in adult patients with moderate to severe psoriasis, including lower-weight patients, is supported by CHMP. The SmPC - Section 4.8 informs the prescriber about the slightly higher incidences of oral candidiasis in patients weighing <70kg (8.5% *versus* 7.0% in patients ≥70 kg). This is agreed by CHMP.

- **Elderly**

It is agreed with the applicant that a dosage adjustment is not warranted in older patients. This has been adequately reflected in SmPC section 4.2.

Interactions

The lack of non-clinical DDI studies is acceptable to the CHMP. It is not expected that bimekizumab will directly interact with other drugs. The expected consequence of metabolism of biological products is degradation to small peptides and amino acids. As these processes typically have high capacity, they are not likely to be impacted by other co-administered medications. Further, any potential small molecule co-dosed with bimekizumab is unlikely to share the same elimination mechanisms as this antibody.

As a cytokine modulator, however, bimekizumab may indirectly modify the metabolism of drugs by altering CYP expression. The applicant considers that bimekizumab would not be expected to have an impact on the exposure of drugs metabolized by the CYP system. It is agreed that the recommendation

in Section 4.5 of the SmPC, to monitor the exposure of narrow therapeutic index drugs, is sufficient to mitigate any risk of a DDI.

Pharmacodynamics

Primary pharmacology

In the Phase 2b study PS0010, 5 sc doses of bimekizumab at Q4W for 12 weeks were studied: 64mg, 160mg, 320mg loading dose at Baseline followed by 160mg thereafter, 320mg, and 480mg. The 64mg dose showed the lowest PASI90 response, and the response increased with increasing doses up to 320mg Q4W. The 480mg dose did not result in a higher response rate than 320mg. Also, the loading dose did not show a clinically meaningful impact on PASI90 response at Week 12 compared to 160mg with no loading dose.

The results from study PS0016 indicated that dosing intervals greater than Q8W would result in loss of PASI response. This was further supported by PASI90 data from the bimekizumab 320mg group (where a dose was received at Week 16), where maintenance of PASI90 response was achieved for a further 8 weeks following the Week 16 dose but reduced 12 weeks after dosing.

These results support the selection of dosage regimens for the Phase 3 studies; 320mg Q4W up to Week 16 followed by either 320mg Q4W or 320mg Q8W as the maintenance regimen.

Secondary pharmacology

No secondary clinical pharmacology studies were conducted with bimekizumab. This is acceptable to the CHMP.

Pharmacodynamic interactions

Study UP0034 aimed to verify the lack of interference of IL-17 blockade on the ability to produce clinically relevant influenza titers (defined as a ≥4 times Baseline levels) following a therapeutic dose of bimekizumab. The design and conduct of the study is acceptable. The results demonstrated non-inferiority of bimekizumab versus placebo with respect to the immunogenic response to the influenza vaccine, based on the predefined non-inferiority margin of -40%. The conclusion that bimekizumab showed no effect on the immunogenic response to the influenza vaccine is agreed. The information included in Section 4.4 of the SmPC is considered acceptable to the CHMP.

Relationship between plasma concentration and effect - Population PKPD analyses

CL0466

The aim of this PK/PD analysis, using pooled data from two phase 2 clinical studies (the Phase 2B study PS0010 and the Phase 2A study PS0016), was to determine a dose and dosing regimen for the Phase 3 clinical studies in patients with psoriasis.

The methods used for development and evaluation of both the prefinal and final PK/PD models are acceptable. The pre-final model is deemed adequate for dosing simulations.

The simulations indicated that for the initial dosing phase up to Week 16, a 320mg dose Q4W is likely to be the optimal dose. A loading dose did not appear to improve the clinical response. Between week 16 and week 52, simulations suggested that a Q4W regimen should maintain response rates, while Q8W and Q12W regimens may lead to a loss of response. Nevertheless, both Q4W and Q8W regimens were selected for Phase 3 trials. Simulations also suggested that body weight does not have a significant impact on PASI response rate and, therefore, weight-based dosing was not selected for the phase 3 studies. The dose and dosing regimens selected for the Phase 3 studies appear reasonable.

CL0485

This population PKPD analysis was based on the data from three Phase 2 studies (PS0010, PS0011, and PS0016), and interim data from two Phase 3 studies (PS0008 and PS0009).

A bounded integer model was used to describe the relationship between bimekizumab plasma concentration (Cav) and PASI and IGA over time. The model structures were different for PASI and IGA. The estimated half maximal effective concentrations (EC50) for PASI and IGA were higher when estimated over the first 16 weeks compared to over 56 weeks.

Simulated PASI90, PASI100 and IGA0/1 response rates versus bimekizumab Cav deciles at Weeks 16 and 56, respectively, support the proposed dosing regimen of 320 mg Q4W for the first 16 weeks followed by 320 mg Q8W thereafter for the majority of patients with moderate to severe plaque psoriasis.

Exposure-safety analysis

The exposure-safety analysis suggested a positive relationship between Candida infection rates and bimekizumab exposure, which may explain the higher incidence of Candida infections observed in subjects in the lower body weight categories. However, additional analyses showed that any concentration-driven effect on oral candidiasis is weak and a dose adjustment in lower weight patients will likely have a limited effect on the incidence of oral candidiasis. This is accepted by the CHMP. Thus, no dose adjustment is deemed necessary for psoriasis patients with a lower body weight.

2.4.5. Conclusions on clinical pharmacology

The PK/PD profile of bimekizumab has been adequately characterised. Based on the PK-PD data presented in this application, the proposed posology of 320 mg (two 160 mg injections) Q4W followed by 320 mg administered every eight weeks for the majority of patients with moderate to severe plaque psoriasis as SC injection is agreed. For some patients with a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response. Appropriate information relevant for the prescribers and patients has been included in the SmPC and package leaflet accordingly.

2.5. Clinical efficacy

The clinical development programme included four Phase 2 studies to investigate dose-response, long-term safety, PK, and PD: PS0010, PS0011, PS0016, and PS0018. The doses of bimekizumab studied in Phase 2 (ranging from 64mg to 480mg every 4 weeks [Q4W]), as well as the PK/PD modelling of the Phase 2 data, were used to support the decision for the initial and maintenance dosing regimens studied in the Phase 3 programme.

Furthermore, three pivotal Phase 3 studies were conducted to assess the efficacy and safety of bimekizumab for the treatment of moderate to severe plaque PSO: **PS0008** (BE SURE), **PS0009** (BE VIVID), and **PS0013** (BE READY). An interim safety cut of the ongoing Phase 3 open-label extension (OLE) study (PS0014) also contributed to the body of evidence supporting the safety evaluation for bimekizumab in this population.

Table 15: Studies evaluating efficacy of bimekizumab in adult study participants with moderate to severe plaque PSO

Study number/clinical development phase/study design	Study Period	Number of study participants receiving			Maximum duration of treatment
		BKZ	PBO	Active control	
Primary efficacy studies					
PS0008/ Phase 3/ multicenter, randomized, double-blind, parallel-group, active comparator-controlled study	Initial Treatment	320mg Q4W: 319	NA	ADA: 159[a]	16 weeks
	Maintenance Treatment	320mg Q4W/320mg Q4W: 153 320mg Q4W/320mg Q8W: 154 ADA/320mg Q4W: 149	NA	NA[a]	40 weeks
PS0009/ Phase 3/ randomized, double-blind, placebo- and active comparator-controlled study	Initial Treatment	320mg Q4W: 321	83	Uste 45mg/90mg[b]: 163	16 weeks
	Maintenance Treatment	320mg Q4W/320mg Q4W: 306 PBO/320mg Q4W: 74	NA	Uste 45mg/90mg[c]: 157	36 weeks
PS0013/ Phase 3/ multicenter, randomized, double-blind, placebo-controlled study	Initial Treatment	320mg Q4W: 349	86	NA	16 weeks
	Randomized Withdrawal Treatment	320mg Q4W/320mg Q4W: 106 320mg Q4W/320mg Q8W: 100	320mg Q4W/PBO: 105 PBO/PBO: 1	NA	40 weeks
Total exposed during primary efficacy studies		320mg Q4W: 1293 320mg Q8W: 257 Overall total: 1293	169	ADA: 159 Uste 45mg/90mg: 163	
Supporting efficacy studies					
PS0010/ Phase 2b/ multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study	Treatment Period	64mg Q4W: 39 160mg Q4W: 43 320mg LD at Baseline followed by 160mg Q4W: 40 320mg Q4W: 43 480mg Q4W: 43	42	NA	12 weeks

Study number/clinical development phase/study design	Study Period	Number of study participants receiving			Maximum duration of treatment
		BKZ	PBO	Active control	
PS0016/ Phase 2a/ multicenter, randomized, study participant-blind and Investigator-blind study	Treatment Period	320mg at Baseline and Week 4, PBO at Week 16: 32 320mg at Baseline, Week 4, and Week 16: 17	NA	NA	28 weeks
Long-term studies					
PS0011/ Phase 2b/ multicenter, double-blind, placebo-controlled, parallel-group extension study	Treatment Period	64mg Q4W: 15 160mg Q4W: 111 320mg Q4W: 91	NA	NA	48 weeks
PS0018/ Phase 2a/ multicenter, OLE study	Treatment Period	160mg Q4W: 43	NA	NA	48 weeks
PS0014/ Phase 3/ multicenter, OLE study	Treatment Period	320mg Q4W and 320mg Q8W: NA (study is ongoing)	NA	NA	144 weeks

2.5.1. Dose response studies

The bimekizumab dose and dosing regimens tested in the Phase 3 studies were selected based on safety, efficacy, and PK data from the two Phase 2 studies (PS0010 and PS0016) in study participants with plaque psoriasis (PSO), as well as PK/PD analyses performed at the end of Phase 2b.

The population investigated in the phase 2 dose finding studies was similar to those investigated in pivotal studies. The study enrolled adults patients with Psoriasis Area and Severity Index (PASI) score ⩾12 and Body Surface Area (BSA) affected by PSO ⩾10%, an Investigators Global Assessment (IGA) score ⩾3 on a 5-point scale, who were candidates for systemic psoriasis therapy and/or phototherapy.

In the **study PS0010,** 8-fold dose range was tested. Patients received either 64, 160, 320 and 480mg of bimekizumab administered subcutaneously (sc) at Baseline, Week 4, and Week 8. The arm with an initial loading dose of 320mg followed by 160mg Q4W was also introduced in this study to investigate whether a loading dose may lead to a faster and/or increased efficacy.

The primary efficacy endpoint was PASI 90 at Week 12. The secondary efficacy variables were IGA response (Clear or Almost Clear with at least 2 category improvement from Baseline) at Week 12 and Week 8, PASI 90 response at Week 8, PASI 75 response at Week 12 and PASI 100 response at Week 12.

A total of 250 subjects were randomized to this study. The mean age of subjects was 44.3 years and similar as in the pivotal studies the majority of the subjects enrolled were white male. The mean body weight and mean BMI were 88.13kg and 29.531kg/m2, respectively.

Based on the results of this study, the320mg dose Q4W is likely to be the optimal dose for the initial treatment period. For this dose the highest percentage of responses were reported for the primary endpoint (PASI 90-79.1% responders) as well as for the majority of secondary endpoints. The increase in the dose to 480 mg was not associated with increased efficacy.

In addition, a loading dose did not appear to improve significantly clinical response. No clinically relevant differences between the bimekizumab 160mg and 160mg with Loading Dose groups were observed for PASI and IGA responder rates investigated in the study (with the exception of PASI100 at Week 12).

In the **study PS0016**, subjects received either Bimekizumab 320mg administered sc at Baseline and Week 4, and placebo administered at Week 16 (in arm A) or Bimekizumab 320mg administered sc at Baseline and Weeks 4 and 16 (in arm B). The primary endpoint of this study was change from Baseline in PASI at Week 28. The percentage PASI and IGA responses at week 16 and changes over time in the percentage of responders (week 2- 36) were assessed as secondary endpoints in this study.

At Week 28, mean changes and mean percentage changes from Baseline in PASI score were larger for the bimekizumab 320mg group (-19.74 points and -86.68%, respectively) compared with the bimekizumab 320mg+PBO group (-10.76 points and -62.07%, respectively). At week 16 there was no significant differences in the percentage of responses which was expected taking into consideration that up to week 16 the treatment in both groups was the same.

In the study, patients received their treatment at baseline and at week 4 but not at week 8 and 12. For PASI 90, PASI 75 a loss of response had begun by Week 16 (i.e., 12 weeks after the second 320mg dose at Week 4 in the study). For PASI 100 and IGA score a loss of response was started earlier (around 8 weeks after the second 320mg dose at Week 4 in the study). Q4W and Q8W regimens were selected for Phase 3 trials, which according to the applicant is considered justified based on the presented results of PS0016 study.

The dose selection is further supported by the PK/PD analysis which was performed using combined data from PS0010 and PS0016.

The performed simulations indicated that in the Initial Treatment Period a 320mg Q4W was predicted to have a clinically meaningful benefit ($\geqslant$10%) on both the PASI 90 and PASI 100 response compared to the 160mg dose with or without a loading dose. Doses greater than 320mg did not provide additional benefit indicating plateauing of efficacy at 320mg.

Three different maintenance treatment regimens were evaluated using simulations, 320mg Q4W, 320mg Q8W, and 320mg every 12 weeks (Q12W). Simulations from the PK/PD model showed that a Q8W regimen would maintain PASI 90 response in a majority of patients (85%) and a Q4W regimen would maintain response in all the study participants. A longer duration between the doses such as Q12W, would lead to study participants losing PASI 90 response. Thus, the recommended dose for adult patients with PSO is, as proposed by the applicant, 320 mg (given as 2 subcutaneous injections of 160 mg each) at week 0, 4, 8, 12, 16 and every 8 weeks thereafter. For some patients with a body

weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response.

2.5.2. Main studies

The clinical development programme consisted in three randomised phase 3 studies to evaluate the efficacy and safety of bimekizumab (PS0008, PS0009 and PS0013) in subjects with moderate to severe PSO. In this assessment report, Studies PS0008 and PS0009 will be presented together as many similarities between these two studies exist. Study PS0013 will be presented separately. Pooled results and results in pooled subgroups for the three main Phase 3 pivotal studies (PS0008, PS0009, PS0013) are discussed in the "Analysis performed across trials" sub-section.

PS0008 and PS0009

Methods

Study PS0008 – "BE SURE"

PS0008 is a Phase 3, multicenter study consisting of a 16-week, randomized, double-blind, parallel-group, active comparator-controlled Initial Treatment Period followed by a 40-week Maintenance Treatment Period to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque PSO. The active comparator was adalimumab. See study schema below.

Study PS0009 – ("BE VIVID")

Study PS0009 is a Phase 3, multicenter study consisting of a 16-week, randomized, double-blind, placebo- and active comparator-controlled Initial Treatment Period followed by a 36-week Maintenance Treatment Period to evaluate the efficacy and safety of bimekizumab administered subcutaneously (s.c.) to study participants with moderate to severe chronic plaque PSO. The active comparator was ustekinumab. See study schema presented below.

Study Participants

Study PS0008

Key inclusion criteria

- Male or female at least 18 years of age.
- Chronic plaque PSO for at least 6 months prior to the Screening Visit.
- PASI ≥12 and BSA affected by PSO ≥10% and IGA score ≥3 on a 5-point scale.
- Study participant was a candidate for systemic PSO therapy and/or phototherapy.
- Study participant must have been considered, in the opinion of the Investigator, to be a suitable candidate for treatment with adalimumab per regional labelling and had no contraindications to receive adalimumab as per the local label.
- Women of child-bearing potential had to use highly effective contraception.
- Study participant agreed not to change their usual sun exposure during the course of the study and to use ultraviolet A/ultraviolet B sunscreens if unavoidable exposure occurred.

Key exclusion criteria

- Female study participant who was breastfeeding, pregnant, or planned to become pregnant during the study or within 20 weeks following the final dose of IMP.
- Study participant had previously participated in a bimekizumab clinical study who received at least 1 dose of the IMP (including placebo).
- Study participant participating in another study of a medication (systemic) under investigation must have been washed out of the medication for 12 weeks or at least 5 half-lives prior to the Baseline Visit, whichever was greater.
- Study participant participating in another study of a topical medication under investigation must have been washed out of the medication for 4 weeks prior to the Baseline Visit.
- Study participant had a known hypersensitivity to any excipients of bimekizumab or adalimumab.
- Study participant had a form of PSO other than chronic plaque-type (e.g., pustular, erythrodermic and guttate PSO, or drug-induced PSO).
- Study participant had an active infection or history of infection(s).
- Study participant had received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline visit (e.g., inactivated influenza and pneumococcal vaccines were allowed but nasal influenza vaccination was not permitted).
- Study participant had received Bacillus Calmette-Guerin vaccinations within 1 year prior to the Baseline Visit.
- Study participant had known tuberculosis (TB) infection, was at high risk of acquiring TB infection, or had current or history of nontuberculous mycobacterium (NTMB) infection.
- Study participant had a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease.
- Study participant had 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 diagnosis of inflammatory conditions other than PSO or PsA, including but not limited to rheumatoid arthritis, sarcoidosis, or systemic lupus erythematosus. Study participants with a diagnosis of Crohn's disease or ulcerative colitis were allowed as long as they had no active symptomatic disease at Screening or Baseline.
- Study participant had any systemic disease considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the study.
- Study participant had laboratory abnormalities at screening
- Study participant had experienced primary failure (no response within 12 weeks) to 1 or more IL-17 biologic response modifier OR more than 1 biologic response modifier other than an IL-17.
- Study participant was taking PsA medications other than stable doses (ie, stable for at least 1 week prior to the Screening Visit) of nonsteroidal anti-inflammatory drugs (NSAIDs) or analgesics

Study PS0009

Key inclusion criteria were the same as for Study PS0008 with the exception of the minor difference reflecting different active comparator:

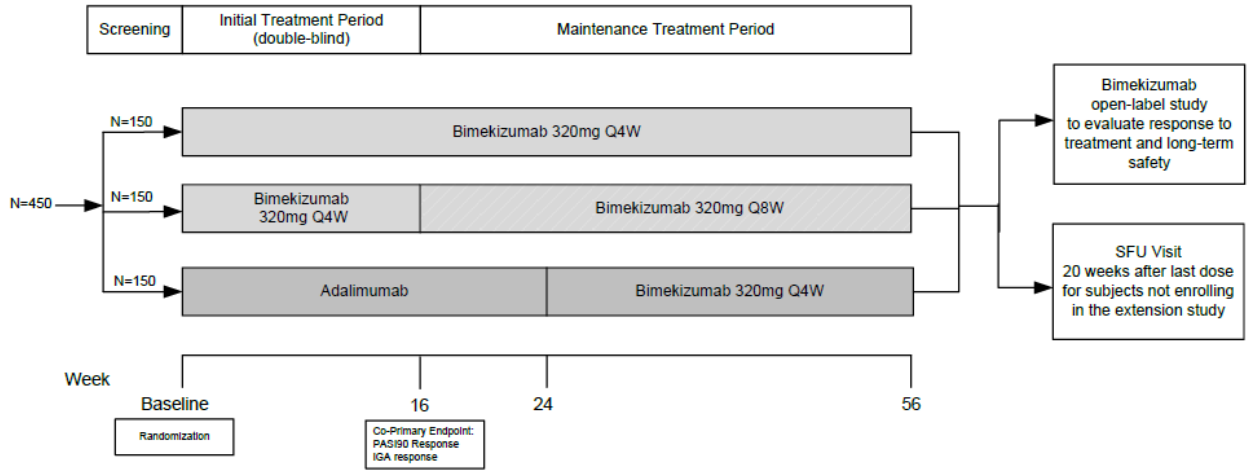
- Study participant must have been considered, in the opinion of the Investigator, to be a suitable candidate for treatment with ustekinumab per regional labeling and had no contraindications to receive ustekinumab as per the local label.

Key exclusion criteria were the same as for Study PS0008 with the exception of the minor differences reflecting different active comparator:

- Study participant had a known hypersensitivity to any excipients of bimekizumab or ustekinumab.
- Study participant had previous exposure to ustekinumab

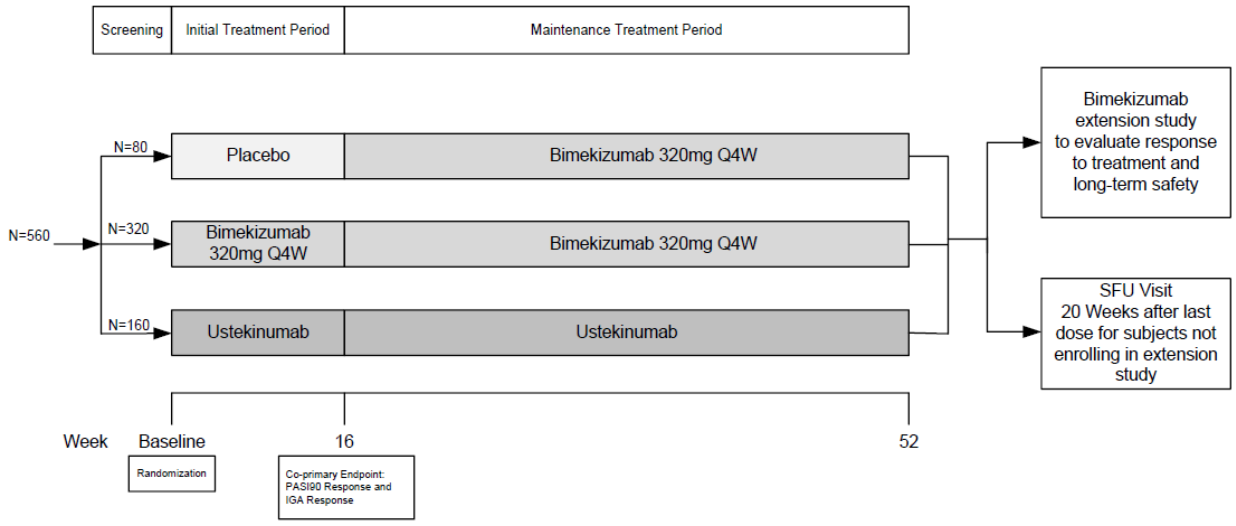
Treatments

Figure 19- Schematic diagram of Study PS0008



IGA=Investigator's Global Assessment; N=number; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks; SFU=Safety Follow-Up

Figure 20- Schematic diagram of Study PS0009



IGA=Investigator's Global Assessment; N=number; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up

Adalimumab and ustekinumab were administered in line with their EU-authorised doses for moderate to severe psoriasis. All IMPs were administered subcutaneously at the trial site.

Prohibited concomitant medicines

The prohibited medicines and the washout periods for PS0008 are listed below.

Drug	Washout period relative to Baseline Visit
Topicals except for those permitted (Section 3.7.5.1.1)	2 weeks
Systemic retinoids	3 months
Systemic treatment (nonbiological): systemic immunosuppressant agents (eg, methotrexate, cyclosporine, azathioprine, thioguanine) fumaric acid esters specifically used for the treatment of PSO systemic corticosteroids phototherapy	1 month
Anti-TNFs: adalimumab (including biosimilar) etanercept (including biosimilar) infliximab (including biosimilar), golimumab, certolizumab pegol	 Any exposure to adalimumab 1 month for etanercept 3 months for infliximab (including biosimilar), golimumab, certolizumab pegol
Other biologics and other systemic therapies, eg: apremilast, tofacitinib alefacept, efalizumab, guselkumab tildrakizumab, risankizumab ustekinumab, briakinumab rituximab	 2 weeks for apremilast and tofacitinib 3 months for alefacept, efalizumab, and guselkumab 5 months for tildrakizumab and risankizumab 6 months for ustekinumab and briakinumab 12 months for rituximab
Anti-IL-17 therapy: brodalumab ixekizumab secukinumab	3 months (bimekizumab was excluded per exclusion criteria)
Any other antipsoriatic agent (systemic) under investigation (or approved after the protocol was approved)	3 months or 5 half-lives, whichever was greater
Any other antipsoriatic agent (topical) under investigation	1 month

IL-17=interleukin 17; PSO=psoriasis; TNF=tumor necrosis factor

The prohibited medicines and the washout periods were similar for PS0009, except that no prior exposure to ustekinumab was allowed and a 3-month washout period was required for adalimumab.

Objectives

Study PS0008

Primary objective

The primary objective of the study was to compare the efficacy of bimekizumab administered s.c. for 16 weeks versus adalimumab in the treatment of study participants with moderate to severe chronic plaque PSO.

Secondary objectives

- Evaluate the efficacy of bimekizumab compared to adalimumab after 4, 16, and 24 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to adalimumab at achieving complete clearance (PASI 100) after 16 weeks and 24 weeks of treatment
- Assess the maintenance of efficacy of bimekizumab dosing Q4W versus Q8W at Week 56
- Assess TEAEs, serious adverse events (SAEs), and treatment-emergent adverse events (TEAEs) leading to withdrawal adjusted by duration of study participant exposure to study treatment

Study PS0009

Primary objective

The primary objective of the study was to compare the efficacy of bimekizumab administered s.c. for 16 weeks versus placebo in the treatment of study participants with moderate to severe chronic plaque PSO.

Secondary objectives

- Evaluate the efficacy of bimekizumab compared to placebo at achieving complete clearance (PASI100) after 16 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to placebo after 4 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to ustekinumab after 4 weeks, 12 weeks, 16 weeks, and 52 weeks of treatment
- Evaluate the change in itch, pain, and scaling of bimekizumab compared to placebo after 16 weeks of treatment as reported by study participants using the Patient Symptom Diary (PSD)
- Assess treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal adjusted by duration of study participant exposure to study treatment

Outcomes/endpoints

Primary efficacy variables

Study PS0008 & PS0009

The co-primary efficacy variables were:

- the PASI 90 response (defined as a study participant that achieved 90% reduction from Baseline in the PASI score) at Week 16 and

- the IGA 0/1 response (defined as Clear [0] or Almost Clear [1] with at least a 2-category improvement relative to Baseline) at Week 16.

Secondary efficacy variable

Study PS0008

- PASI 90 response at Week 24
- IGA 0/1 response (Clear [0] or Almost Clear [1] with at least 2-category improvement relative to Baseline) at Week 24
- PASI 75 response at Week 4
- PASI 100 response at Weeks 16 and 24
- PASI 90 response at Week 56
- IGA 0/1 response (Clear [0] or Almost Clear [1] with at least 2-category improvement relative to Baseline) at Week 56

Study PS0009

- PASI 100 response at Week 16
- IGA response (Clear [0] with at least a 2-category improvement relative to Baseline) at Week 16
- PASI 75 response at Week 4
- PSD responses for pain, itch, and scaling at Week 16
- PASI 90 response at Week 12 and 52
- IGA response (Clear [0] or Almost Clear [1] with at least a 2-category improvement relative to Baseline) at Week 12 and 52

Sample size

Study PS0008

A total of 450 subjects were to be randomly assigned in a 1:1:1 ratio to the following treatment groups:

- Bimekizumab 320mg Q4W throughout the study (150 subjects)
- Bimekizumab 320mg Q4W/Q8W (ie, bimekizumab 320mg Q4W until Week 16, then bimekizumab 320mg Q8W from Week 16 through Week 52 (150 subjects)
- Adalimumab 80mg administered as an initial dose, followed by 40mg Q2W starting 1 week after the initial dose until Week 24, then bimekizumab 320mg Q4W from Week 24 to Week 52 (150 subjects)

Study PS0009

A total of 560 subjects were to be randomly assigned in a 4:2:1 ratio to the following treatment groups:

- Bimekizumab 320mg (320 subjects)
- Ustekinumab (160 subjects)

- Placebo (80 subjects)

Randomisation / Blinding (masking)

An interactive response technology (IRT) was used for assigning eligible study participants to a treatment regimen based on a predetermined production randomization and/or packaging schedule provided by the applicant (or designee). The randomization schedule was produced by the IRT vendor.

Study participant treatment assignment was stratified by region (North America, Western Europe, Central/Eastern Europe and Asia/Australia) and prior biologic exposure (yes/no). The IRT generated individual assignments for study participant kits of IMP, as appropriate, according to the visit schedule.

These studies were double-blinded. Due to differences in presentation between the bimekizumab and the active comparators, special precautions were taken to ensure study blinding and study sites had blinded and unblinded personnel. Study sites were required to have a written blinding plan in place, signed by the Principal Investigator, to ensure that the double-blind nature of the study is maintained. Sites were instructed to keep study subjects blind to the IMP as detailed in the site blinding plan.

Due to obvious differences in schedule of IMPs administration and number of injections received at each visit patients were receiving also PBO injections so the blind could be preserved.

Statistical methods

Statistical Analysis Plan

PS0008

The original SAP, dated 06 June 2018, was amended 2 times. Amendment 1 of the SAP, dated 17 September 2019, was implemented to achieve consistency with other SAPs of the bimekizumab PSO development program. Amendment 2 of the SAP, dated 31 October 2019, was implemented to further align with other SAPs of the program.

The interim CSR is a complete analysis of the first 56 weeks of the study (including the 16-week Initial Treatment Period and 40-week Maintenance Treatment Period) based on a clinical cut-off date of 28 October 2019. The date of database lock and unblinding was 11 November 2019.

The results presented in the PS0008 final CSR provide a complete analysis of data collected through Week 56, including the 16-week Initial Treatment Period and 40-week Maintenance Treatment Period, and the complete 20-week SFU Period. After the data cut-off date for the interim CSR, an additional 13 study participants completed unscheduled or SFU Visits, and these data have been included in the final CSR.

PS0009

The original SAP, dated 24 January 2018, was amended 2 times. Amendment 1 of the SAP, dated 16 August 2018, was implemented to align the SAP with Protocol Amendment 3 and to achieve consistency with other SAPs of the bimekizumab PSO development program. Amendment 2 of the SAP, dated 13 September 2019, was implemented to align the SAP with Protocol Amendment 4 and to achieve consistency with other SAPs of the bimekizumab PsO development program.

The interim CSR is a complete analysis of the first 52 weeks of the study (including the 16-week Initial Treatment Period and 36-week Maintenance Treatment Period) based on a cutoff date of 04 Sep 2019. The date of database lock and unblinding was 19 Sep 2019.

The results presented in the PS0009 final CSR provide a complete analysis of data collected through Week 52, including the 16-week Initial Treatment Period and 36-week Maintenance Treatment Period, and the complete 20-week SFU Period. After the data cutoff date for the interim CSR, an additional 20 study participants completed unscheduled and SFU Visits and these data have been included in this final CSR.

Analysis Populations

PS0008

The **Enrolled Set (ES)** consisted of all subjects who gave informed consent.

The **Randomized Set (RS)** consisted of all randomized subjects.

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

The **Full Analysis Set (FAS)** consisted of all randomized subjects who received at least 1 dose of the IMP and had a valid measurement of each of the co-primary efficacy variables at Baseline.

The **Bimekizumab Set (BKZ Set)** consisted of all subjects who received at least 1 dose of bimekizumab in this study.

The **BKZ Week 24 Set** consisted of all subjects who had received at least 1 dose of BKZ on or after Week 24.

The **Maintenance Set (MS)** consisted of all subjects who received at least 1 dose of active IMP (bimekizumab or adalimumab) in the Maintenance Treatment Period (at Week 16 or later).

The **Per-Protocol Set (PPS)** consisted of all subjects in the RS who had no important protocol deviations affecting the primary efficacy variables. Important protocol deviations were predefined and subjects with important protocol deviations were evaluated during ongoing data cleaning meetings prior to unblinding of the data.

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

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

PS0009

As for PS0008, except the BKZ Set and BKZ Week 24 Set were not defined for this study. The following analysis population was additionally defined for study PS0009:

The **Active Medication Set (AMS)** consisted of all subjects who had received at least 1 dose of active IMP (bimekizumab or ustekinumab). The AMS was to be used for summaries of safety that include all data from the initial Treatment Period and/or Maintenance Treatment Period.

Analysis of co-primary endpoints – PASI 90 & IGA 0/1 at week 16

PS0008

The co-primary efficacy variables for this study were PASI 90 response and IGA response at Week 16, and the corresponding analyses were based on the RS. A subject was classified as a PASI90 responder if the PASI score at Week 16 had improved at least 90% from Baseline. An IGA responder was any subject with a score of 0 or 1 (Clear or Almost Clear) with at least a 2-category improvement from Baseline to Week 16 in IGA score.

The primary analysis used the stratified Cochran-Mantel-Haenszel (CMH) test where region and prior biologic exposure (yes/no) were used as stratification variables.

For the assessment of non-inferiority, a non-inferiority margin of 10% was used and evaluated based on the confidence interval for the stratified Cochran Mantel-Haenszel risk difference between bimekizumab and adalimumab. To calculate the stratified Mantel-Haenszel risk difference, the method of Greenland and Robins (1985) was used. The Wald method was used to calculate the confidence interval. A non-inferiority margin of 10% was selected as this was considered to be a clinically relevant difference that could influence the choice of interventions used to treat chronic plaque PSO.

The evaluation of superiority used pairwise treatment comparisons based on the CMH test using the p-value for the general association. The odds ratio and associated confidence interval (CI) based on the Wald test were presented. If one of the treatment groups has 0 or very low response where CMH can no longer be used, the logit method was to be applied instead.

For the assessment of non-inferiority of bimekizumab to adalimumab, the lower 97.5% confidence limit for the stratified Mantel-Haenszel risk difference was considered. If that value was greater than -10%, then non-inferiority would have been established.

Non-responder imputation was used to account for missing data in the primary analysis. Specifically, any subject who withdrew from IMP prior to Week 16 or who had missing data for the co-primary efficacy variables at the Week 16 time point was considered as a non-responder.

A number of sensitivity analyses for the co-primary efficacy variables were performed to evaluate the assumptions related to the handling of missing data, including:

Sensitivity analysis 1

Missing data were addressed using MI (Markov-Chain Monte Carlo [MCMC] method for intermittent missing data, followed by monotone regression for monotone missing data) to evaluate the effect of the method for handling missing data on the analysis.

The actual PASI/IGA scores were imputed and then dichotomized to obtain the response status. The treatment differences for each imputed data set were subsequently evaluated using the stratified CMH test as used in the primary analysis. The results from each of the imputed data sets were combined for overall inference using Rubin's rules.

This procedure assumes a missing at random (MAR) pattern of missingness and corresponds to an estimand of the difference in outcome improvement if all subjects tolerated or adhered to treatment (Mallinckrodt et al, 2012). This is an estimand of efficacy to evaluate the de jure hypothesis.

Sensitivity analysis 2

This sensitivity analysis was based on observed data at Week 16. Subjects with missing data or who had prematurely discontinued IMP were to be treated as missing. The same stratified CMH test as in the primary efficacy analysis was to be used.

PS0009

As for PS0008, except the active comparator is ustekinumab rather than adalimumab. The following additional sensitivity analysis was conducted:

Deviations from the MAR pattern assumed in sensitivity analysis 1 were evaluated. Intermittent missing data was imputed using MI based on the MCMC method but the remaining monotone missing data was assumed to follow a missing not at random (MNAR) pattern. These data were imputed using reference-based imputation in which the imputation model was based on data from placebo group, thereby assuming that monotone missing data follow a trajectory similar to the placebo group (Mallinckrodt et al, 2012). As in sensitivity analysis 1, actual PASI/IGA scores were imputed and then dichotomized to get the response status. The treatment differences for each imputed data set were subsequently evaluated using the stratified CMH test as used in the primary analysis.

The estimand in this procedure is the difference in outcome improvement in all randomized subjects at the planned endpoint of the study attributable to the initially randomized medication (Mallinckrodt et al, 2012). This is an estimand of effectiveness to evaluate the de facto hypothesis.

Analysis of ranked secondary endpoints

PASI and IGA responses (PS0008 & PS0009)

A stratified CMH test similar to the primary endpoint analysis was implemented. Missing data were imputed using NRI in the primary analysis. Sensitivity analyses 1 and 2 above were conducted.

For the assessment of non-inferiority in PS0009, a non-inferiority margin of 10% was used and evaluated based on the confidence interval for the stratified Mantel-Haenszel risk difference between bimekizumab and ustekinumab.

Scalp IGA response (PS0009)

Scalp IGA response at Week 16 was defined as clear [0] or almost clear [1] with at least a two category improvement from Baseline to Week 16. A stratified CMH test similar to the primary endpoint analysis was applied. Missing data were imputed using NRI in the primary analysis. Sensitivity analysis 1 and 2 above were performed.

Patient Symptom Diary responses (PS0009)

The PSD consists of 14 different items, each measuring an aspect of the psoriasis and its impact on the subject's quality of life. Each item was scored separately on a 0-10 scale with 0 for no symptom and 10 for very severe or worst symptom. Weekly averages were derived for each of the 14 items of the Psoriasis Diary up to Week 16. The weekly average was the sum of the scored item over the course of the study week divided by the number of days on which the item was completed. The weekly average value for each item was set to missing if four or more daily assessments (irrespective of whether these are consecutive or not) of that item were missing. The Baseline value was computed in the same manner.

The PSD was computed based on the responder definition. 3 PSD items were included in the hierarchical testing procedure: itch, pain, and scaling. The response thresholds used for itch, pain, and scaling at week 16 were 2.39, 1.98, and 2.86, respectively. The responder analysis was limited to subjects with a Baseline PSD response score at or above the applicable threshold score. Stratified CMH test, similar to the primary efficacy analysis was applied for each of these responder analyses. Missing data for PSD responder variables were imputed using an MI procedure similar to sensitivity analysis 1 for the co-primary efficacy variables.

Subgroup analyses

For both PS0008 and PS0009

Subgroup analyses were performed on PASI75/90/100 response rates and IGA, using by visit summaries only. The following subgroups for analysis were determined using baseline data:

- Age (<40 years, 40 to <65 years, ≥65 years)
- Gender (male, female)
- Disease duration (<median, ≥median)
- Region (North America, Western Europe, Central/Eastern Europe, Asia/Australia)
- Weight (≤100 kg, >100 kg)
- BMI (<25 kg/m2, 25 to <30 kg/m2, ≥30 kg/m2)
- Prior systemic phototherapy or chemotherapy (yes, no)
- Prior biologic exposure (yes, no)
- Prior systemic therapy of any kind (yes, no)
- Baseline disease severity (PASI<20, PASI≥20)
- Antibody positivity (negative, positive)

Antibody positivity was the only subgroup that is not determined by Baseline data. It was presented in a separate table.

Note: The definition of prior systemic therapy of any kind is that if a subject received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic chemotherapy or phototherapy. Subjects who never received previous biologic therapy, previous systemic therapy (non-biologic), or previous systemic photochemotherapy or phototherapy were classified as not receiving prior systemic treatment for psoriasis.

In addition, in order to assess whether an early response to treatment is predictive of response at later time points, subgroup analyses were performed for the RS on PASI90/100 and IGA over time using the following early response subgroups:

- PASI75 responders (OC) at Week 4 (yes, no) to predict PASI90/100 and IGA (NRI) through initial and maintenance treatment period
- PASI90 responders (OC) at Week 16 (yes, no) to predict PASI100 (NRI) through maintenance treatment period

All summaries were based on imputed data as appropriate and included descriptive statistics only.

Multicentre study

PS0008 and PS0009

The centre-by-treatment interaction was tested by replacing region with centre in the logistic regression model used for the sensitivity analysis and adding a centre-by-treatment interaction term. In the model, centre was based on the original centres prior to pooling. However, if the model was unable to converge due to a low number of subjects at a given centre, a pooling by centre was to be applied in order to allow the model to converge. If convergence still cannot be achieved, this analysis was not to be performed.

Type I error control

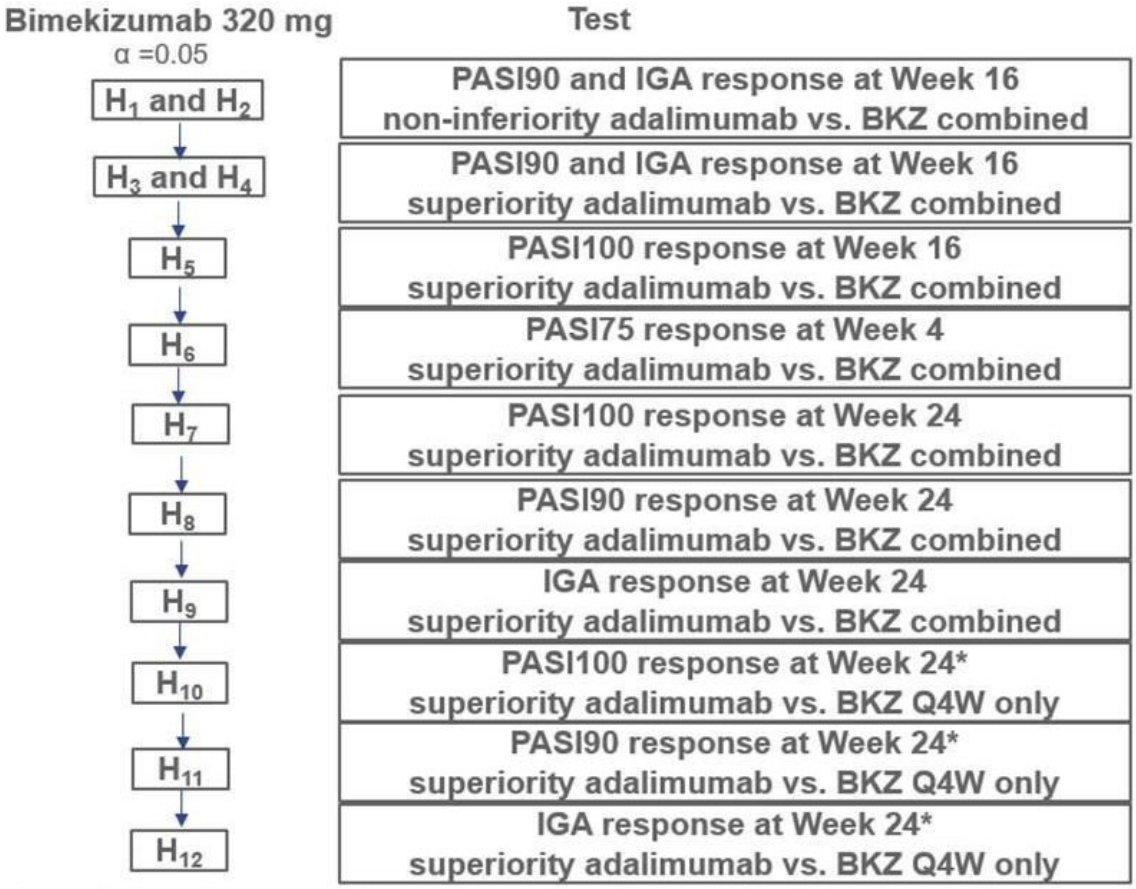
In each of studies PS0008 and PS0009, the statistical analysis of the co-primary efficacy variables and selected secondary efficacy variables accounted for multiplicity and controlled the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure.

PS0008

The hypotheses (H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11 and H12) comparing bimekizumab vs. adalimumab were tested at a 2 -sided alpha level of 0.05.

The first 2 hypotheses (H1 and H2) tested whether bimekizumab is non-inferior to adalimumab for the co-primary efficacy variables, PASI90 response at Week 16 and IGA response at Week 16. This evaluation of non-inferiority was tested at a 1-sided alpha level of 0.025 based on a 1-sided 97.5% CI and a non-inferiority margin of 10%. If non-inferiority was achieved, the alpha was to be passed to the next test in the sequence, allowing the testing procedure to proceed. The co-primary efficacy variables of PASI90 response at Week 16 and IGA response at Week 16 were then to be evaluated for superiority relative to adalimumab at a 2-sided alpha level of 0.05, and testing was to proceed only if superiority was achieved for both endpoints.

The hypotheses associated with the subsequent secondary efficacy endpoints were based on testing for superiority relative to adalimumab.



Note: Calculations for H_1-H_9 are based on the combined Bimekizumab arms with the sample size of 300. * in H_{10}-H_{12} indicated calculations are based on the Bimekizumab Q4W/Q4W arm only with sample size of 150.

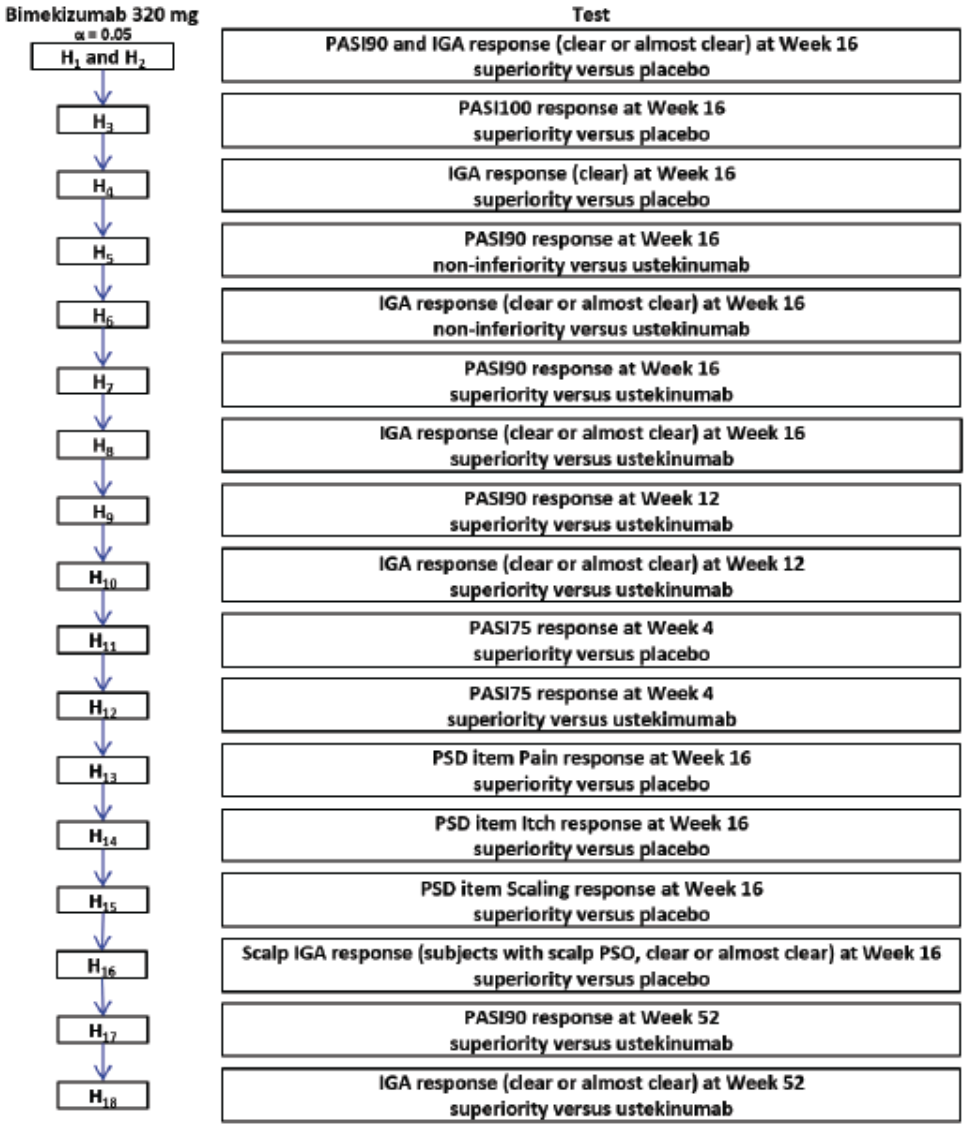
PS0009

The hypotheses (H1, H2, H3, H4, H5, H6, H7, H8, H9, H10, H11, H12, H13, H14, H15, H16, H17 and H18) comparing bimekizumab vs. placebo or bimekizumab vs. ustekinumab were tested at a 2-sided alpha level of 0.05.

The first 2 hypotheses (H1 and H2) were to test whether bimekizumab is superior to placebo for PASI90 response and IGA response at Week 16. These are the hypothesis tests corresponding to the co-primary endpoints. If both were rejected at a 2-sided alpha level of 0.05, that alpha was to be passed to the next test in the sequence, allowing the testing procedure to proceed.

The hypotheses associated with the subsequent secondary efficacy endpoints were based on testing for non-inferiority/superiority relative to ustekinumab or for superiority relative to placebo.

Note that while subjects randomized to ustekinumab may receive either the 45mg or 90mg dose (according to weight at Baseline), all subjects randomized to ustekinumab were analyzed as a single group (and not broken out by dose) since this strategy is consistent with the recommended weight-based dosing for ustekinumab.



BL=Baseline; IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index, PSD=patient symptom diary; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks.

Results

Participant flow

Study PS0008: Disposition and discontinuation reasons – Initial Treatment Period and through Week 24 (RS)

Disposition	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA N=159 n (%)	All study participants N=478 n (%)
Started Initial Treatment Period	161 (100)	158 (100)	319 (100)	159 (100)	478 (100)
Completed Initial Treatment Period	154 (95.7)	153 (96.8)	307 (96.2)	150 (94.3)	457 (95.6)
Discontinued study during Initial Treatment Period	7 (4.3)	5 (3.2)	12 (3.8)	9 (5.7)	21 (4.4)
Primary reason for study discontinuation during Initial Treatment Period					
AE	2 (1.2)	2 (1.3)	4 (1.3)	4 (2.5)	8 (1.7)
Lack of efficacy	0	0	0	1 (0.6)	1 (0.2)
Protocol violation	0	0	0	2 (1.3)	2 (0.4)
Lost to follow up	0	2 (1.3)	2 (0.6)	1 (0.6)	3 (0.6)
Consent withdrawn	4 (2.5)	1 (0.6)	5 (1.6)	1 (0.6)	6 (1.3)
Other	1 (0.6)	0	1 (0.3)	0	1 (0.2)
Completed Week 24	149 (92.5)	152 (96.2)	301 (94.4)	149 (93.7)	450 (94.1)
Discontinued between Week 16 and Week 24	5 (3.1)	1 (0.6)	6 (1.9)	1 (0.6)	7 (1.5)
Primary reason for study discontinuation between Week 16 and Week 24					
AE	3 (1.9)	1 (0.6)	4 (1.3)	0	4 (0.8)
Lack of efficacy	1 (0.6)	0	1 (0.3)	0	1 (0.2)
Protocol violation	0	0	0	0	0
Lost to follow up	0	0	0	1 (0.6)	1 (0.2)
Consent withdrawn	1 (0.6)	0	1 (0.3)	0	1 (0.2)
Other	0	0	0	0	0

ADA=adalimumab; AE=adverse event; BKZ=bimekizumab; Q4W=every 4 weeks; Q8W=every 8 weeks; RS=Randomized Set

Note: Study participants in the BKZ Q4W/Q8W group switched from Q4W to Q8W dosing at Week 16. Study participants in the ADA/BKZ study participants switch from ADA to BKZ at Week 24.

Note: BKZ Total includes study participants randomized to bimekizumab in the Initial Treatment Period.

Study PS0008: Disposition and discontinuation reasons – Week 24 to Week 56 (BKZ Week 24 Set)

Disposition	BKZ 320mg Q4W/Q8W N=149 n (%)	BKZ 320mg Q4W N=152 n (%)	ADA/BKZ 320mg Q4W N=149 n (%)	BKZ Total N=450 n (%)
Started Week 24	149 (100)	152 (100)	149 (100)	450 (100)
Completed Week 56	143 (96.0)	143 (94.1)	133 (89.3)	419 (93.1)
Discontinued between Week 24 and Week 56	6 (4.0)	9 (5.9)	16 (10.7)	31 (6.9)
Primary reason for study discontinuation				
AE	3 (2.0)	4 (2.6)	6 (4.0)	13 (2.9)
Lack of efficacy	0	1 (0.7)	1 (0.7)	2 (0.4)
Protocol violation	0	0	0	0
Lost to follow up	0	2 (1.3)	5 (3.4)	7 (1.6)
Consent withdrawn	3 (2.0)	1 (0.7)	4 (2.7)	8 (1.8)
Other	0	1 (0.7)	0	1 (0.2)

ADA=adalimumab; AE=adverse event; BKZ=bimekizumab; Q4W=every 4 weeks; Q8W=every 8 weeks
Note: Study participants in the BKZ Q4W/Q8W group switched from Q4W to Q8W dosing at Week 16. Study participants in the ADA/BKZ group switched from ADA to BKZ at Week 24.

Study PS0009: Disposition and discontinuation reasons – Initial Treatment Period (RS)

Disposition	PBO N=83 n (%)	BKZ 320mg Q4W N=321 n (%)	Uste N=163 n (%)	All Study participants N=567 n (%)
Started ITP	83 (100)	321 (100)	163 (100)	567 (100)
Completed ITP	74 (89.2)	306 (95.3)	157 (96.3)	537 (94.7)
Discontinued ITP	9 (10.8)	15 (4.7)	6 (3.7)	30 (5.3)
Primary reason for discontinuation				
AE	6 (7.2)	6 (1.9)	3 (1.8)	15 (2.6)
Lack of efficacy	2 (2.4)	1 (0.3)	0	3 (0.5)
Protocol violation	0	0	2 (1.2)	2 (0.4)
Lost to follow up	0	3 (0.9)	0	3 (0.5)
Consent withdrawn	1 (1.2)	2 (0.6)	1 (0.6)	4 (0.7)
Other	0	3 (0.9)	0	3 (0.5)

AE=adverse event; BKZ=bimekizumab; ITP=Initial Treatment Period; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; Uste=ustekinumab
Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Study PS0009: Disposition and discontinuation reasons – Maintenance Treatment Period (MS)

Disposition	PBO/BKZ 320mg Q4W N=74 n (%)	BKZ 320mg Q4W N=306 n (%)	Uste N=157 n (%)	All Study participants N=537 n (%)
Started MTP	74 (100)	306 (100)	157 (100)	537 (100)
Completed MTP	69 (93.2)	283 (92.5)	141 (89.8)	493 (91.8)
Discontinued study MTP	5 (6.8)	23 (7.5)	16 (10.2)	44 (8.2)
Primary reason for discontinuation				
AE	3 (4.1)	12 (3.9)	4 (2.5)	19 (3.5)
Lack of efficacy	0	1 (0.3)	4 (2.5)	5 (0.9)
Protocol violation	1 (1.4)	1 (0.3)	0	2 (0.4)
Lost to follow up	0	4 (1.3)	3 (1.9)	7 (1.3)
Consent withdrawn	1 (1.4)	4 (1.3)	4 (2.5)	9 (1.7)
Other	0	1 (0.3)	1 (0.6)	2 (0.4)

AE=adverse event; BKZ=bimekizumab; MS=Maintenance Set; MTP=Maintenance Treatment Period; PBO=placebo; Q4W=every 4 weeks; Uste=ustekinumab

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period. Placebo study participants switched to BKZ 320mg Q4W at/after Week 16.

Recruitment

Table 16 - Dates defining recruitment and study periods for pivotal Phase 3 Studies PS0008 and PS0009

Study	Recruitment Period	Follow-up Period		
		Study start (Randomization)	Interim CSR data cut-off date	Study completion
PS0008	First study participant signed ICF to last study participant signed ICF: 26 Jan 2018 to 14 Sep 2018	First study participant randomized: 26 Jan 2018	28 Oct 2019	Last study participant completed: 26 Feb 2020
PS0009	First study participant signed ICF to last study participant signed ICF: 06 Dec 2017 to 20 Aug 2018	First study participant randomized: 06 Dec 2017	04 Sep 2019	Last study participant completed: 13 Dec 2019

CSR=clinical study report; ICF=Informed Consent Form

Conduct of the study

Study PS0008

The original PS0008 protocol (dated 15 August 2017) has undergone 2 global protocol amendments.

Protocol Amendment 1 (15 October 2017) was implemented before any study participants were enrolled and included the following key modifications: removed re-randomization at Week 24. Study participants in the bimekizumab groups were allocated to bimekizumab 320mg Q4W throughout the

study or bimekizumab 320mg Q4W through Week 16 and bimekizumab 320mg Q8W thereafter; removed change in dose based on PASI90 response; Updated the study design so study participants in the bimekizumab Q4W/Q8W arm switched at Week 16 instead of Week 24; added a new other efficacy variable (absolute and percent change from Baseline in the product of IGA and BSA [IGAxBSA]); added assessment of the Patient Symptom Diary (daily) to the Screening and Week 16 Visits; added percentage of BSA as an assessment at all visits; removed the criterion that excluded study participants exposed to more than 3 biologic response modifiers (including no more than 1 IL-17); clarified that study participants who experienced primary failure (no response within 12 weeks) to 1 or more IL-17 biologic response modifiers or more than 1 biologic response modifiers other than an IL-17 should have been excluded from the study; removed the withdrawal criterion that study participants who do not achieve a PASI50 response by Week 28 or later be withdrawn from the study; clarified that the same assessor should evaluate the study participant at each efficacy assessment; updated the assessment and management of TB and TB risk factors.

Protocol Amendment 2 (06 April 2018) included the following modifications: updated list of current treatment for PSO to reflect changes in labeling and approved countries; removed references to PD assessments as they were not conducted in this study; updated the schedule of study assessments (Table 3-3) to include a hematology and biochemistry sample at Week 28, and to modify the visits at which the TB questionnaire, body weight, physical examination, and ECG were assessed; clarified that all visits from first dose to Week 24 would have a ±3 day visit window, while all visits from Week 28 to end of study would have a ±7 day window; modified exclusion criteria to exclude use of prohibited PSO medications; modified exclusion criteria pertaining to history of malignancy, systemic disease, and major depression; added new withdrawal criteria for non-responders and for study participants with newly diagnosed inflammatory bowel disease (IBD); clarified withdrawal criteria for study participants with depression or suicidal ideation or behaviour; updated prohibited concomitant medications to include tildrakizumab and risankizumab; updated laboratory measurements to be performed; provided additional details for requirements for IMP rechallenge in the event of PDILI;dDefined a Bimekizumab Set as an analysis population; updated the sequence testing and analysis of secondary efficacy variables.

Study PS0009

The original PS0009 protocol (dated 15 August 2017) has undergone 4 global protocol amendments.

Protocol Amendment 1 (19 September 2017) was implemented to remove the escape arm to allow for a 1-year comparison of bimekizumab versus ustekinumab that was not confounded by an escape arm at Week 16 and to remove the mandatory withdrawal at Week 28 or later.

Protocol Amendment 2 (15 October 2017) added a new other efficacy variable (absolue and percent change from Baseline for IGAxBSA. It also removed the 30% enrolment limit for study participants with prior biologic exposure.

Protocol Amendment 3 (06 April 2018) included the following modifications: updated the schedule of study assessments to include a hematology and biochemistry sample at Week 20, to modify the visits at which the TB questionnaire, body weight, physical examination, and electrocardiogram (ECG) were assessed, and to modify the visits at which photographs were taken; clarified that all visits from first dose to Week 24 were to have a ±3 day visit window, whileall visits from Week 28 to end of study were to have a ±7 day window; added new withdrawal criteria for non-responders and for study participants with newly diagnosed inflammatory bowel disease; provided additional details for requirements for IMP rechallenge in the event of potential drug-induced liver injury (PDILI); updated the sequence testing.

Protocol Amendment 4 (dated 21 May 2019) was to update the secondary and "other" efficacy variables to be consistent with the wording in the statistical analysis plan (SAP).

Baseline data

PS0008

A summary of study participant demographics is presented for the SS in **Table 17**.

Table 17: Demographics (SS)

Variable	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA/BKZ 320mg Q4W N=159 n (%)	All Study Participants N=478 n (%)
Age (years)					
Mean (SD)	44.0 (13.5)	45.3 (13.2)	44.6 (13.3)	45.5 (14.3)	44.9 (13.6)
Median (min, max)	43.0 (18, 83)	45.5 (19, 76)	44.0 (18, 83)	44.0 (18, 72)	44.0 (18, 83)
Age [a], n (%)					
18 to <65 yrs	148 (91.9)	147 (93.0)	295 (92.5)	139 (87.4)	434 (90.8)
65 to <85 yrs	13 (8.1)	11 (7.0)	24 (7.5)	20 (12.6)	44 (9.2)
≥85 years	0	0	0	0	0
Age group, n (%)					
<40 years	65 (40.4)	58 (36.7)	123 (38.6)	59 (37.1)	182 (38.1)
40 to <65 years	83 (51.6)	89 (56.3)	172 (53.9)	80 (50.3)	252 (52.7)
≥65 years	13 (8.1)	11 (7.0)	24 (7.5)	20 (12.6)	44 (9.2)
Gender, n (%)					
Male	112 (69.6)	102 (64.6)	214 (67.1)	114 (71.7)	328 (68.6)
Female	49 (30.4)	56 (35.4)	105 (32.9)	45 (28.3)	150 (31.4)
Weight (kg)					
Mean (SD)	93.155 (24.381)	89.630 (21.363)	91.409 (22.968)	90.508 (22.144)	91.109 (22.678)
Median (min, max)	91.000 (45.00, 237.00)	85.000 (47.60, 152.00)	87.800 (45.00, 237.00)	86.360 (45.60, 181.00)	87.000 (45.00, 237.00)

Variable	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA/BKZ 320mg Q4W N=159 n (%)	All Study Participants N=478 n (%)
Weight, n(%)					
≤100 kg	108 (67.1)	113 (71.5)	221 (69.3)	114 (71.7)	335 (70.1)
>100 kg	53 (32.9)	45 (28.5)	98 (30.7)	45 (28.3)	143 (29.9)
Height (cm)					
Mean (SD)	173.26 (9.32)	172.32 (9.65)	172.79 (9.48)	173.06 (10.07)	172.88 (9.67)
Median (min, max)	174.00 (152.0, 195.0)	173.00 (149.9, 192.0)	174.00 (149.9, 195.0)	175.00 (151.0, 202.0)	174.00 (149.9, 202.0)
BMI (kg/m^2)					
Mean (SD)	31.04 (7.66)	30.18 (6.86)	30.61 (7.28)	30.20 (7.02)	30.47 (7.19)
Median (min, max)	29.85 (18.5, 73.2)	28.99 (17.9, 50.4)	29.54 (17.9, 73.2)	28.73 18.3, 59.5)	29.40 (17.9, 73.2)
Racial group, n (%)					
Asian	13 (8.1)	10 (6.3)	23 (7.2)	11 (6.9)	34 (7.1)
Black	2 (1.2)	2 (1.3)	4 (1.3)	2 (1.3)	6 (1.3)
Native Hawaiian or other Pacific Islander	2 (1.2)	1 (0.6)	3 (0.9)	0	3 (0.6)
White	140 (87.0)	140 (88.6)	280 (87.8)	141 (88.7)	421 (88.1)
Other/mixed	4 (2.5)	5 (3.2)	9 (2.8)	5 (3.1)	14 (2.9)
Ethnicity, n (%)					
Hispanic or Latino	18 (11.2)	12 (7.6)	30 (9.4)	16 (10.1)	46 (9.6)
Not Hispanic or Latino	143 (88.8)	146 (92.4)	289 (90.6)	143 (89.9)	432 (90.4)
Region, n (%)					
Asia/Australia	11 (6.8)	10 (6.3)	21 (6.6)	11 (6.9)	32 (6.7)
Central/Eastern Europe	60 (37.3)	59 (37.3)	119 (37.3)	59 (37.1)	178 (37.2)
North America	74 (46.0)	73 (46.2)	147 (46.1)	71 (44.7)	218 (45.6)
Western Europe	16 (9.9)	16 (10.1)	32 (10.0)	18 (11.3)	50 (10.5)

ADA=adalimumab; BKZ=bimekizumab; BMI=body mass index; EudraCT=European Union Drug Regulating Authorities Clinical Trials; max=maximum; min=minimum; Q4W=every 4 weeks; Q8W=every 8 weeks; SD=standard deviation; SS=Safety Set

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Note: No study participants were younger than 18 years at time of informed consent.

[a] EudraCT age categories

A summary of Baseline disease characteristics is presented for the SS in **Table 18**.

Table 18: Baseline disease characteristics (SS)

Variable	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA/BKZ 320mg Q4W N=159 n (%)	All Study Participants N=478 n (%)
BSA (%)					
n	161	158	319	159	478
Mean (SD)	25.2 (12.4)	26.5 (15.9)	25.9 (14.2)	25.0 (14.4)	25.6 (14.3)
Median	22.0	20.0	20.0	20.0	20.0
Min, max	10, 80	10, 81	10, 81	10, 76	10, 81
PASI score					
n	161	158	319	159	478
Mean (SD)	19.93 (6.08)	20.46 (6.93)	20.19 (6.51)	19.05 (5.94)	19.81 (6.34)
Median	19.00	18.10	18.50	17.40	18.00
Min, max	12.0, 42.6	12.0, 44.1	12.0, 44.1	12.0, 38.0	12.0, 44.1
mNAPSI total score [a]					
n	90	91	181	95	276
Mean (SD)	20.3 (19.9)	23.7 (23.7)	22.0 (21.9)	18.3 (18.1)	20.7 (20.7)
Median	12.5	17.0	14.0	13.0	13.0
Min, max	1, 100	1, 128	1, 128	1, 91	1, 128
PGADA score [b]					
n	161	158	319	159	478
Mean (SD)	24.7 (27.9)	24.6 (28.4)	24.7 (28.1)	27.6 (30.4)	25.6 (28.9)
Median	11.0	13.0	11.0	14.0	12.5
Min, max	0, 100	0, 100	0, 100	0, 100	0, 100
DLQI total score					
n	161	158	319	159	478
Mean (SD)	10.8 (6.2)	11.1 (6.5)	10.9 (6.3)	10.5 (7.4)	10.8 (6.7)
Median	10.0	10.0	10.0	9.0	10.0
Min, max	0, 28	1, 29	0, 29	0, 30	0, 30

Variable	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA/BKZ 320mg Q4W N=159 n (%)	All Study Participants N=478 n (%)
Duration of disease (years)					
n	161	158	319	159	478
Mean (SD)	17.300 (10.862)	20.372 (13.247)	18.821 (12.180)	16.159 (11.942)	17.936 (12.154)
Median	15.640	19.510	16.690	14.320	15.875
Min, max	0.57, 53.53	0.45, 56.70	0.45, 56.70	0.57, 56.55	0.45, 56.70
Duration of disease, n (%)					
<median years	84 (52.2)	68 (43.0)	152 (47.6)	87 (54.7)	239 (50.0)
≥median years	77 (47.8)	90 (57.0)	167 (52.4)	72 (45.3)	239 (50.0)
IGA score, n (%)					
3 (Moderate)	111 (68.9)	102 (64.6)	213 (66.8)	114 (71.7)	327 (68.4)
4 (Severe)	50 (31.1)	56 (35.4)	106 (33.2)	45 (28.3)	151 (31.6)
PASI score, n (%)					
<20	95 (59.0)	94 (59.5)	189 (59.2)	108 (67.9)	297 (62.1)
≥20	66 (41.0)	64 (40.5)	130 (40.8)	51 (32.1)	181 (37.9)
Nail involvement, n (%)					
Yes	90 (55.9)	91 (57.6)	181 (56.7)	95 (59.7)	276 (57.7)
No	71 (44.1)	67 (42.4)	138 (43.3)	64 (40.3)	202 (42.3)
Scalp involvement, n (%)					
Yes	156 (96.9)	148 (93.7)	304 (95.3)	143 (89.9)	447 (93.5)
No	5 (3.1)	10 (6.3)	15 (4.7)	16 (10.1)	31 (6.5)
Palmoplantar involvement, n (%)					
Yes	60 (37.3)	60 (38.0)	120 (37.6)	46 (28.9)	166 (34.7)
No	101 (62.7)	98 (62.0)	199 (62.4)	113 (71.1)	312 (65.3)
Prior biologic therapy, n (%)					
Yes	50 (31.1)	50 (31.6)	100 (31.3)	53 (33.3)	153 (32.0)
No	111 (68.9)	108 (68.4)	219 (68.7)	106 (66.7)	325 (68.0)

Variable	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA/BKZ 320mg Q4W N=159 n (%)	All Study Participants N=478 n (%)
Prior anti-TNF therapy, n (%)					
Yes	10 (6.2)	14 (8.9)	24 (7.5)	14 (8.8)	38 (7.9)
No	151 (93.8)	144 (91.1)	295 (92.5)	145 (91.2)	440 (92.1)
Prior systemic phototherapy or chemophototherapy, n (%)					
Yes	52 (32.3)	59 (37.3)	111 (34.8)	62 (39.0)	173 (36.2)
No	109 (67.7)	99 (62.7)	208 (65.2)	97 (61.0)	305 (63.8)
Any prior systemic therapy, n (%)					
Yes	116 (72.0)	112 (70.9)	228 (71.5)	110 (69.2)	338 (70.7)
No	45 (28.0)	46 (29.1)	91 (28.5)	49 (30.8)	140 (29.3)
PSD: itch					
n	141	130	271	125	396
Mean (SD)	6.894 (2.153)	7.365 (2.039)	7.120 (2.108)	6.628 (2.495)	6.965 (2.246)
Median	7.167	7.536	7.429	7.000	7.286
Min, max	0, 10.00	1.17, 10.00	0, 10.00	0, 10.00	0, 10.00
PSD: pain					
n	141	130	271	125	396
Mean (SD)	6.115 (2.426)	6.445 (2.686)	6.273 (2.555)	5.685 (2.913)	6.088 (2.683)
Median	6.333	7.000	6.500	6.143	6.429
Min, max	0, 10.00	0, 10.00	0, 10.00	0, 10.00	0, 10.00
PSD: scaling					
n	141	130	271	125	396
Mean (SD)	7.087 (2.049)	7.508 (2.080)	7.289 (2.071)	6.696 (2.304)	7.102 (2.162)
Median	7.286	7.657	7.500	7.000	7.286
Min, max	0.80, 10.00	0, 10.00	0, 10.00	0, 10.00	0, 10.00

ADA=adalimumab; BKZ=bimekizumab; BSA=body surface area affected by psoriasis; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; max=maximum; min=minimum; mNAPSI=Modified Nail Psoriasis Severity Index; pp-IGA=palmoplantar Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; PGADA=Patient's Global Assessment of Disease Activity; PSD=Patient Symptom Diary; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks; SD=standard deviation; SS=Safety Set; TNF=tumor

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.
Note: Duration of disease (years)=(Date of randomization - date of onset of plaque PSO)/365.25.
Note: Baseline nail, scalp, and palmoplantar involvement were based on the number of study participants achieving mNAPSI>0, Scalp IGA>0, and pp-IGA>0, respectively.
Note: For PSD, in cases where there was >1 diary record completed on a particular day, all available records within the 7-day window (including any double entries on one day) were used in the calculation of weekly average scores. If this resulted in having >7 available scores to calculate the weekly average, the 7 records closest to the visit were used.
[a] mNAPSI total score for study participants with nail involvement (ie, mNAPSI>0) at Baseline.
[b] PGADA for arthritis visual analogue scale score.

PS0009

Table 19: Demographics (RS)

Variable	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321 n (%)	Uste N=163 n (%)	All Study participants N=567 n (%)
Age (years)				
Mean (SD)	49.7 (13.6)	45.2 (14.0)	46.0 (13.6)	46.1 (13.9)
Median (min, max)	50.0 (19, 78)	43.0 (18, 81)	47.0 (18, 79)	45.0 (18, 81)
Age [a], n (%)				
18 to <65 years	73 (88.0)	287 (89.4)	145 (89.0)	505 (89.1)
65 to <85 years	10 (12.0)	34 (10.6)	18 (11.0)	62 (10.9)
≥85 years	0	0	0	0
Age group				
<40 years	19 (22.9)	123 (38.3)	57 (35.0)	199 (35.1)
40 to <65 years	54 (65.1)	164 (51.1)	88 (54.0)	306 (54.0)
≥65 years	10 (12.0)	34 (10.6)	18 (11.0)	62 (10.9)
Gender, n (%)				
Male	60 (72.3)	229 (71.3)	117 (71.8)	406 (71.6)
Female	23 (27.7)	92 (28.7)	46 (28.2)	161 (28.4)
Weight (kg)				
Mean (SD)	89.059 (26.402)	88.731 (23.059)	87.244 (21.078)	88.352 (23.006)
Median (min, max)	83.400 (44.50, 179.60)	87.300 (42.90, 217.90)	86.300 (42.05, 142.43)	86.400 (42.05, 217.90)
Weight, n (%)				
≤100kg	60 (72.3)	226 (70.4)	122 (74.8)	408 (72.0)
>100kg	23 (27.7)	95 (29.6)	41 (25.2)	159 (28.0)
Height (cm)				
Mean (SD)	171.58 (8.86)	172.91 (9.45)	172.12 (10.57)	172.49 (9.70)

Variable	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321 n (%)	Uste N=163 n (%)	All Study participants N=567 n (%)
Median (min, max)	171.90 (153.7, 194.0)	172.70 (150.0, 202.0)	172.70 (147.5, 196.0)	172.70 (147.5, 202.0)
BMI (kg/m2)				
Mean (SD)	30.01 (7.55)	29.57 (7.00)	29.35 (6.43)	29.57 (6.92)
Median (min, max)	28.27 (17.4, 52.8)	28.50 (17.4, 72.6)	28.36 (15.9, 47.8)	28.37 (15.9, 72.6)
Racial group, n (%)				
American Indian/Alaskan Native	0	1 (0.3)	1 (0.6)	2 (0.4)
Asian	20 (24.1)	71 (22.1)	36 (22.1)	127 (22.4)
Black	0	9 (2.8)	3 (1.8)	12 (2.1)
Native Hawaiian or other Pacific Islander	0	0	0	0
White	63 (75.9)	237 (73.8)	120 (73.6)	420 (74.1)
Other/mixed	0	3 (0.9)	3 (1.8)	6 (1.1)
Ethnicity, n (%)				
Hispanic or Latino	4 (4.8)	20 (6.2)	13 (8.0)	37 (6.5)
Not Hispanic or Latino	79 (95.2)	301 (93.8)	150 (92.0)	530 (93.5)
Region				
Asia/Australia	18 (21.7)	69 (21.5)	35 (21.5)	122 (21.5)
Central/Eastern Europe	27 (32.5)	108 (33.6)	54 (33.1)	189 (33.3)
North America	26 (31.3)	100 (31.2)	51 (31.3)	177 (31.2)
Western Europe	12 (14.5)	44 (13.7)	23 (14.1)	79 (13.9)

BKZ=bimekizumab; BMI=body mass index; EudraCT=European Union Drug Regulating Authorities Clinical Trials; max=maximum; min=minimum; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; Uste=ustekinumab

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Note: No study participants were younger than 18 years at date of informed consent.

[a] EudraCT age categories

A summary of Baseline disease characteristics during the Initial Treatment Period is presented for the RS in table below.

Table 20: Baseline disease characteristics (RS)

Variable	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321	Uste N=163	All Study participants N=567
BSA (%)				
Mean (SD)	27.0 (16.3)	29.0 (17.1)	27.3 (16.7)	28.2 (16.9)
Median	21.0	23.0	22.0	22.0
Min, max	11, 84	10, 88	10, 97	10, 97
PASI score				
Mean (SD)	20.05 (6.81)	22.04 (8.55)	21.32 (8.29)	21.54 (8.26)
Median	17.60	19.40	18.45	19.00
Min, max	12.0, 39.2	11.7, 58.5	12.0, 51.4	11.7, 58.5

Variable	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321	Uste N=163	All Study participants N=567
mNAPSI total score, n [a]	51	194	109	354
Mean (SD)	18.3 (19.5)	20.5 (20.1)	21.0 (21.0)	20.3 (20.2)
Median	12.0	15.0	14.0	14.0
Min, max	1, 102	1, 110	1, 103	1, 110
PGADA score [b]				
Mean (SD)	18.4 (23.9)	20.2 (28.0)	20.6 (28.2)	20.1 (27.5)
Median	7.0	4.0	4.0	5.0
Min, max	0, 88	0, 100	0, 95	0, 100
PGADA score category [b]				
0	22 (26.5)	111 (34.6)	47 (28.8)	180 (31.7)
>0	61 (73.5)	209 (65.1)	115 (70.6)	385 (67.9)
Missing	0	1 (0.3)	1 (0.6)	2 (0.4)
DLQI total score				
Mean (SD)	10.0 (6.8)	9.9 (6.3)	11.0 (6.9)	10.2 (6.6)
Median	8.0	9.0	10.0	9.0
Min, max	1, 27	0, 29	0, 30	0, 30
DLQI score category				
0	0	2 (0.6)	1 (0.6)	3 (0.5)
>0	83 (100)	319 (99.4)	161 (98.8)	563 (99.3)
Missing	0	0	1 (0.6)	1 (0.2)
Duration of disease (years)				
Mean (SD)	19.690 (13.760)	16.015 (11.611)	17.845 (11.597)	17.079 (11.998)
Median	17.520	13.650	15.620	14.660
Min, max	1.20, 58.97	0.62, 57.68	0.48, 56.49	0.48, 58.97
Duration of disease, n (%)				
<median years (14.66 years)	36 (43.4)	172 (53.6)	74 (45.4)	282 (49.7)
≥median years (14.66 years)	47 (56.6)	149 (46.4)	89 (54.6)	285 (50.3)

Variable	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321	Uste N=163	All Study participants N=567
IGA score, n (%)				
2 (Mild)	1 (1.2)	1 (0.3)	1 (0.6)	3 (0.5)
3 (Moderate)	54 (65.1)	201 (62.6)	96 (58.9)	351 (61.9)
4 (Severe)	28 (33.7)	119 (37.1)	66 (40.5)	213 (37.6)
PASI score, n (%)				
<20	54 (65.1)	170 (53.0)	102 (62.6)	326 (57.5)
≥20	29 (34.9)	151 (47.0)	60 (36.8)	240 (42.3)
Missing	0	0	1 (0.6)	1 (0.2)
Nail involvement, n (%)				
Yes	51 (61.4)	194 (60.4)	109 (66.9)	354 (62.4)
No	32 (38.6)	127 (39.6)	54 (33.1)	213 (37.6)
Scalp involvement, n (%)				
Yes	73 (88.0)	302 (94.1)	155 (95.1)	530 (93.5)
No	10 (12.0)	19 (5.9)	8 (4.9)	37 (6.5)
Palmoplantar involvement, n (%)				
Yes	33 (39.8)	129 (40.2)	65 (39.9)	227 (40.0)
No	50 (60.2)	192 (59.8)	98 (60.1)	340 (60.0)
Prior biologic therapy, n (%)				
Yes	33 (39.8)	125 (38.9)	63 (38.7)	221 (39.0)
No	50 (60.2)	196 (61.1)	100 (61.3)	346 (61.0)
Prior anti-TNF therapy, n (%)				
Yes	16 (19.3)	51 (15.9)	24 (14.7)	91 (16.0)
No	67 (80.7)	270 (84.1)	139 (85.3)	476 (84.0)
Prior systemic phototherapy or chemophototherapy, n (%)				
Yes	38 (45.8)	141 (43.9)	73 (44.8)	252 (44.4)
No	45 (54.2)	180 (56.1)	90 (55.2)	315 (55.6)
Any prior systemic therapy, n (%)				
Yes	64 (77.1)	267 (83.2)	132 (81.0)	463 (81.7)
No	19 (22.9)	54 (16.8)	31 (19.0)	104 (18.3)

Variable	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321	Uste N=163	All Study participants N=567
PSD: pain				
N	67	260	124	451
Mean (SD)	5.052 (2.887)	5.682 (2.853)	5.746 (2.929)	5.606 (2.882)
Median	5.333	6.000	6.450	6.000
Min, max	0.00, 10.00	0.00, 10.00	0.00, 10.00	0.00, 10.00
PSD: itch				
N	67	260	124	451
Mean (SD)	6.107 (2.517)	6.584 (2.402)	6.824 (2.387)	6.524 (2.416)
Median	6.000	6.833	7.00	6.833
Min, max	0.00, 10.00	0.00, 10.00	0.71, 10.00	0.00, 10.00
PSD: scaling				
n	67	260	124	451
Mean (SD)	6.570 (2.254)	6.677 (2.264)	6.824 (2.388)	6.702 (2.294)
Median	6.333	6.714	7.310	6.800
Min, max	2.00, 10.00	1.00, 10.00	1.40, 10.00	1.00, 10.00

BKZ=bimekizumab; BSA=body surface area; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; max=maximum; min=minimum; mNAPSI=Modified Nail Psoriasis Severity Index; PASI=Psoriasis Area and Severity Index; PBO=placebo; PGADA=Patient's Global Assessment of Disease Activity; PSD=Patient Symptom Diary; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; TNF=tumor necrosis factor; Uste=ustekinumab

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Note: Duration of disease (years)=(Date of randomization – date of onset of plaque psoriasis)/365.25

Note: Baseline nail, scalp, and palmoplantar involvement were based on the number of study participants achieving mNAPSI>0, Scalp IGA>0, and pp-IGA>0, respectively.

[a] mNAPSI total score for study participants with nail involvement (ie, mNAPSI>0) at Baseline.

[b] PGADA for arthritis visual analog scale score, which was performed on the study population overall at Baseline.

Numbers analysed

Study PS0008

Analysis set	BKZ 320mg Q4W/Q8W N=161 n (%)	BKZ 320mg Q4W N=158 n (%)	BKZ Total N=319 n (%)	ADA/BKZ 320mg Q4W N=159 n (%)	All Study Participants N=478 n (%)
RS	161 (100)	158 (100)	319 (100)	159 (100)	478 (100)
SS	161 (100)	158 (100)	319 (100)	159 (100)	478 (100)
FAS	161 (100)	158 (100)	319 (100)	159 (100)	478 (100)
BKZ Set	161 (100)	158 (100)	319 (100)	149 (93.7)	468 (97.9)
BKZ Week 24 Set	149 (92.5)	152 (96.2)	301 (94.4)	149 (93.7)	450 (94.1)
PPS	156 (96.9)	157 (99.4)	313 (98.1)	156 (98.1)	469 (98.1)
PK-PPS	161 (100)	158 (100)	319 (100)	146 (91.8)	465 (97.3)
MS	154 (95.7)	153 (96.8)	307 (96.2)	149 (93.7)	456 (95.4)

ADA=adalimumab; BKZ=bimekizumab; FAS=Full Analysis Set; MS=Maintenance Set; PPS=Per-Protocol Set; PK-PPS=Pharmacokinetics Per-Protocol Set; RS=Randomized Set; SS=Safety Set
Note: BKZ Total includes study participants randomized to bimekizumab in the Initial Treatment Period.

Study PS0009

Analysis set	PBO/BKZ 320mg Q4W N=83 n (%)	BKZ 320mg Q4W N=321 n (%)	Uste N=163 n (%)	All Study participants N=567 n (%)
RS	83 (100)	321 (100)	163 (100)	567 (100)
SS	83 (100)	321 (100)	163 (100)	567 (100)
FAS	83 (100)	321 (100)	162 (99.4)	566 (99.8)
AMS	74 (89.2)	321 (100)	163 (100)	558 (98.4)
MS	74 (89.2)	306 (95.3)	157 (96.3)	537 (94.7)
PPS	81 (97.6)	312 (97.2)	159 (97.5)	552 (97.4)
PK-PPS	83 (100)	321 (100)	163 (100)	567 (100)

AMS=Active Medication Set; BKZ=bimekizumab; FAS=Full Analysis Set; MS=Maintenance Set; PBO=placebo; PPS=Per-Protocol Set; PK-PPS=Pharmacokinetics Per-Protocol Set; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set; Uste=ustekinumab

Outcomes and estimation

Study PS0008: Co-primary endpoints

The co-primary endpoints were met. The bimekizumab total group was superior compared with the adalimumab group for the co-primary endpoints of PASI90 and IGA 0/1 response rates at Week 16. The differences were statistically significant and clinically meaningful for both co-primary endpoints, with odds ratios versus adalimumab of 7.459 ($p<0.001$) and 4.341 ($p<0.001$), respectively.

Study PS0008: Co-primary endpoints at Week 16: Randomised set (NRI)

	PASI90 response rate		IGA 0/1 response rate	
	BKZ Total N=319	**ADA N=159**	**BKZ Total N=319**	**ADA N=159**
Response rate				
n (%)	275 (86.2)	75 (47.2)	272 (85.3)	91 (57.2)
n/Nsub (%)	275/303 (90.8)	75/148 (50.7)	272/303 (89.8)	91/148 (61.5)
Odds ratio vs ADA [a]	7.459	-	4.341	-
95% CI for odds ratio	4.709, 11.816	-	2.785, 6.765	-
p-value [b]	<0.001	-	<0.001	-
Risk difference[c]	39.3	-	28.2	-
95% CI for risk difference	30.9, 47.7	-	19.7, 36.7	-

ADA=adalimumab; BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; OC=observed case; PASI=Psoriasis Area and Severity Index; RS=Randomized Set

Note: In the n (%) row, study participants with missing data at a given week were counted as nonresponders (NRI).

Note: In the n/Nsub (%) row, Nsub represented the number of study participants with a nonmissing measurement for PASI at the given week, and percentages were calculated accordingly (OC).

Note: The evaluation of noninferiority was tested at a 1-sided alpha level of 0.025 and based on a 1-sided 97.5% CI and a noninferiority margin of 10%.

[a] Odds ratio for BKZ/ADA was calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

[c] Risk difference for BKZ/ADA was calculated using stratified CMH

Study PS0008: Key secondary endpoints

The bimekizumab total group had a higher PASI100 response rate compared with the adalimumab group at Week 16 (60.8% vs 23.9%, respectively; p<0.001) and Week 24 (66.8% vs 29.6%, respectively; p<0.001), a difference that was statistically significant and clinically meaningful at both time points. In addition, the bimekizumab 320mg Q4W group demonstrated a statistically significant and clinically meaningful superior PASI100 response rate compared to the adalimumab group at Week 24 (67.7% vs 29.6%, respectively; p<0.001).

Study PS0008: PASI90 and IGA 0/1 responses at Week 24 and Week 56: (Randomised Set [NRI])

Week Statistic	PASI90 response rate				IGA 0/1 response rate			
	BKZ 320mg Q4W/Q8W N=161	BKZ 320mg Q4W N=158	BKZ Total N=319	ADA N=159	BKZ 320mg Q4W/Q8W N=161	BKZ 320mg Q4W N=158	BKZ Total N=319	ADA N=159
Week 24								
n (%)	137 (85.1)	136 (86.1)	273 (85.6)	82 (51.6)	140 (87.0)	136 (86.1)	276 (86.5)	92 (57.9)
n/Nsub (%)	137/149 (91.9)	136/149 (91.3)	273/298 (91.6)	82/147 (55.8)	140/149 (94.0)	136/149 (91.3)	276/298 (92.6)	92/147 (62.6)
Odds ratio vs ADA [a]	5.284	6.231	5.750	-	4.779	4.724	4.762	-
95% CI for odds ratio	3.084, 9.054	3.515, 11.046	3.657, 9.041	-	2.737, 8.345	2.683, 8.318	3.014, 7.523	-
p-value [b]	<0.001 [c]	<0.001	<0.001	-	<0.001 [c]	<0.001	<0.001	-
Week 56								
n (%)	133 (82.6)	134 (84.8)	267 (83.7)	-[d]	134 (83.2)	130 (82.3)	264 (82.8)	-[d]
n/Nsub (%)	133/143 (93.0)	134/140 (95.7)	267/283 (94.3)	-[d]	134/143 (93.7)	130/140 (92.9)	264/283 (93.3)	-[d]

ADA=adalimumab; BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; OC=observed case; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks; RS=Randomized Set

Note: In the n (%) row, study participants with missing data at a given week were counted as nonresponders (NRI).

Note: In the n/Nsub (%) row, Nsub represented the number of study participants with a nonmissing measurement at the given week, and percentages were calculated accordingly (OC).

[a] Odds ratio for BKZ/ADA was calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

[c] Nominal p-value

[d] Study participants in the ADA/BKZ 320mg Q4W group were excluded from this summary.

Study PS0008: PASI100 response rate at Week 16 and Week 24: Randomised set (NRI)

Visit Statistic	BKZ 320mg Q4W/Q8W N=161	BKZ 320mg Q4W N=158	BKZ Total N=319	ADA N=159
Week 16				
n (%)	-	-	194 (60.8)	38 (23.9)
n/Nsub (%)	-	-	194/303 (64.0)	38/148 (25.7)
Odds ratio vs ADA [a]	-	-	4.974	-
95% CI for odds ratio	-	-	3.230, 7.661	-
p-value [b]	-	-	<0.001	-
Week 24				
n (%)	106 (65.8)	107 (67.7)	213 (66.8)	47 (29.6)
n/Nsub (%)	106/149 (71.1)	107/149 (71.8)	213/298 (71.5)	47/147 (32.0)
Odds ratio vs ADA [a]	4.689	5.249	4.974	-
95% CI for odds ratio	2.904, 7.573	3.207, 8.593	3.257, 7.594	-
p-value [b]	<0.001 [c]	<0.001	<0.001	-

ADA=adalimumab; BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; NRI=nonresponder imputation; OC=observed case; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks; RS=Randomized Set

Note: In the n (%) row, study participants with missing data at a given week were counted as nonresponders (NRI).

Note: In the n/Nsub (%) row, Nsub represented the number of study participants with a nonmissing measurement for PASI at the given week, and percentages were calculated accordingly (OC).

[a] Odds ratio for BKZ/ADA was calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

[c] Nominal p-value

PASI75 at Week 4

The bimekizumab total group had a higher PASI75 response rate compared with the adalimumab group at Week 4 after one dose of bimekizumab (76.5% vs 31.4%, respectively; p<0.001), which was a statistically significant and clinically meaningful difference.

In the BE SURE study at week 24, a significantly higher percentage of patients treated with bimekizumab (Q4W/Q4W and Q4W/Q8W combined dosing arms) achieved PASI 90 and IGA 0/1 responses as compared with adalimumab (85.6% and 86.5% respectively vs 51.6% and 57.9% respectively, p<0.001). At week 56, 70.2% of patients treated with bimekizumab Q8W achieved a PASI 100 response. Among the 65 adalimumab non-responders at week 24 (< PASI 90), 78.5% achieved a PASI 90 response after 16 weeks of treatment with bimekizumab. The safety profile observed in patients who switched from adalimumab to bimekizumab without a wash-out period was similar to patients who initiated bimekizumab after wash out of prior systemic therapies.

Study PS0009: Co-primary endpoints

Treatment with bimekizumab 320mg Q4W demonstrated clinically meaningful and statistically superior response rates for the co-primary efficacy variables (PASI90 and IGA 0/1 response at Week 16), and all secondary efficacy variables in the statistical hierarchy compared with both placebo and ustekinumab.

Co-primary endpoints at Week 16: **PS0009** [Randomised sample (NRI)]

	PASI90 response rate			IGA 0/1 response rate		
	PBO N=83	BKZ 320mg Q4W N=321	Uste N=163	PBO N=83	BKZ 320mg Q4W N=321	Uste N=163
Response rate						
n (%)	4 (4.8)	273 (85.0)	81 (49.7)	4 (4.8)	270 (84.1)	87 (53.4)
n/Nsub (%)	4/76 (5.3)	273/307 (88.9)	81/155 (52.3)	4/76 (5.3)	270/307 (87.9)	87/156 (55.8)
Odds ratio vs PBO [a]	-	99.869	-	-	118.762	-
95% CI for odds ratio	-	34.020, 293.175	-	-	36.701, 384.307	-
p-value [b]	-	<0.001	-	-	<0.001	-
Odds ratio vs Uste [a, c]	-	6.056		-	4.809	-
95% CI for odds ratio	-	3.874, 9.466		-	3.096, 7.470	-
p-value [b]	-	<0.001		-	<0.001	-
Risk difference [d,e]	79.9	-	35.2	78.9	-	30.4
95% CI for risk difference	74.0, 85.9	-	27.0, 43.4	72.9, 84.8	-	22.2, 38.7

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; Uste=ustekinumab

Note: Study participants with missing data at a given week were counted as nonresponders.

Note: Nsub represented the number of study participants with a nonmissing measurement for PASI at the given week, and percentages were calculated accordingly.

[a] Odds ratio was calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

[c] The comparison of bimekizumab to ustekinumab was a secondary endpoint.

[d] Risk difference: BKZ-PBO or BKZ-Uste were calculated based on stratified CMH.

[e] The evaluation of noninferiority was tested at a 1-sided alpha level of 0.025 and based on a 1-sided 97.5% CI and a noninferiority margin of 10%.

Study PS0009: Key secondary endpoints

PASI 100 and IGA 0 at Week 16

Statistic	PASI100 response rate		IGA 0 response rate	
	PBO N=83	BKZ 320mg Q4W N=321	PBO N=83	BKZ 320mg Q4W N=321
n (%)	0	188 (58.6)	0	188 (58.6)
n/Nsub (%)	0/76	188/307 (61.2)	0/76	188/307 (61.2)
Odds ratio vs PBO [a]	-	25.590	-	25.471
95% CI for odds ratio	-	9.063, 72.253	-	9.020, 71.925
p-value [b]	-	<0.001	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: Study participants with missing data at a given week were counted as nonresponders.

Note: Nsub represents the number of study participants with a nonmissing measurement for PASI or IGA at the given week, and percentages were calculated accordingly.

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Note: IGA 0 response was defined as clear (0) with at least a 2-category improvement from Baseline.

[a] Odds ratio: Bimekizumab/PBO calculated using stratified CMH test with region and prior biologic exposure as stratification variables. The logit method was used where CMH test was not possible due to very low response.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

The bimekizumab 320mg Q4W group also had a higher PASI100 response rate compared with the ustekinumab group at Week 16 (58.6% vs 20.9%, respectively; nominal p<0.001) and a higher IGA 0 response rate compared with the ustekinumab group at Week 16 (58.6% vs 22.1%, respectively; nominal p<0.001) which were statistically significant and clinically meaningful differences.

PASI75 at Week 4

The bimekizumab 320mg Q4W group had a higher PASI75 response rate compared with the placebo and ustekinumab groups at Week 4 after only a single dose of bimekizumab (76.9% vs 2.4% and 15.3%, respectively; p<0.001 for both comparisons), differences that were statistically significant and clinically meaningful.

The bimekizumab 320mg Q4W group had higher PSD response rates based on pain, itch, and scaling item scores compared with the placebo group at Week 16, differences that were statistically significant (77.3% vs 16.7%, 76.6% vs 13.1%, and 78.5% vs 12.7% respectively; p<0.001 for all comparisons).

The bimekizumab 320mg Q4W group also had slightly higher PSD response rates based on pain, itch, and scaling item scores compared with the ustekinumab group at Week 16 (77.3% vs 68.2%; nominal p=0.053; 76.6% vs 65.8%; nominal p=0.035, and 78.5% vs 59.5%; nominal p<0.001, respectively)

PASI90 and IGA 0/1 responses at Week 12 and Week 52, **PS0009** [Randomised Set (NRI)]

Visit Statistic	PASI90 response rate			IGA 0/1 response rate		
	PBO N=83	BKZ 320mg Q4W N=321	Uste N=163	PBO N=83	BKZ 320mg Q4W N=321	Uste N=163
Week 12						
n (%)	2 (2.4)	273 (85.0)	71 (43.6)	4 (4.8)	263 (81.9)	85 (52.1)
n/Nsub (%)	2/77 (2.6)	273/314 (86.9)	71/153 (46.4)	4/78 (5.1)	263/314 (83.8)	85/154 (55.2)
Odds ratio vs PBO [a]	-	272.193	-	-	79.717	-
95% CI for odds ratio	-	58.342, 1269.907	-	-	28.383, 223.888	-
Nominal p-value [b]	-	<0.001	-	-	<0.001	-
Odds ratio vs Uste [c]	-	8.047	-	-	4.379	-
95% CI for odds ratio	-	5.107, 12.679	-	-	2.850, 6.730	-
p-value [b]	-	<0.001	-	-	<0.001	-

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; Uste=ustekinumab

Note: Study participants with missing data at a given week were counted as non-responders.

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period. Placebo study participants switched to BKZ 320mg Q4W in the Maintenance Treatment Period.

a Odds ratio: Bimekizumab/PBO calculated using stratified CMH test with region and prior biologic exposure as stratification variables. The logit method was used where CMH test was not possible due to very low response.

b p-values for the comparison of treatment groups were based on the CMH test from the general association.

c Odds ratio: Bimekizumab/ustekinumab calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

Table 21 – PASI90 response at week 52 (RS – NRI)

	PBO/BKZ 320mg Q4W N=83	BKZ 320mg Q4W N=321	Uste N=163
PASI90 response rate			
n (%)	-	263 (81.9)	91 (55.8)
n/Nsub (%)	-	263/277 (94.9)	91/138 (65.9)
Odds ratio vs Uste [a]	-	3.795	-
95% CI for odds ratio	-	2.442, 5.899	-
p-value [b]	-	<0.001	-

BKZ=bimekizumab; CI=Confidence Interval; CMH=Cochran-Mantel-Haenszel; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set; Uste=ustekinumab

Note: Study participants with missing data at a given week were counted as nonresponders. Nsub represents the number of study participants with a non-missing measurement at the given week, and percentages are calculated accordingly.

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period. Placebo study participants switched to BKZ 320mg Q4W in the Maintenance Treatment Period.

[a] Odds ratio: Bimekizumab/ustekinumab calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

Table 22: IGA 0/1 response at week 52 (RS – NRI)

	PBO/BKZ 320mg Q4W N=83	BKZ 320mg Q4W N=321	Uste N=163
IGA 0/1 response rate			
n (%)	-	251 (78.2)	99 (60.7)
n/Nsub (%)	-	251/277 (90.6)	99/139 (71.2)
Odds ratio vs Uste [a]	-	2.412	-
95% CI for odds ratio	-	1.573, 3.699	-
p-value [b]	-	<0.001	-

BKZ=bimekizumab; CI=Confidence Interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; Q4W=every 4 weeks; RS=Randomized Set; Uste=ustekinumab

Note: Study participants with missing data at a given week were counted as nonresponders. Nsub represents the number of study participants with a non-missing measurement at the given week, and percentages are calculated accordingly.

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period. Placebo study participants switched to BKZ 320mg Q4W in the Maintenance Treatment Period.

[a] Odds ratio: Bimekizumab/ustekinumab calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

In the BE VIVID study, at week 52, bimekizumab-treated patients (every 4 weeks) achieved significantly higher response rates than the ustekinumab-treated patients on the endpoints of PASI 100 (64.5% bimekizumab vs 38.0% ustekinumab).

Summary of main studies

The following two tables summarise the efficacy results from the main Phase 3 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 Study PS0008 "BE SURE"

Title: A Phase 3, Multicenter, Randomized, Double-Blind Study With An Active-Controlled Initial Treatment Period Followed By A Dose-Blind Maintenance Treatment Period To Evaluate The Efficacy And Safety Of Bimekizumab In Adult Study Participants With Moderate To Severe Chronic Plaque Psoriasis			
Study identifier	PS0008 EudraCT Number: 2016-003392-22 NCT03412747		
Design	PS0008 is a Phase 3, multicenter study consisting of a 16-week, randomized, double-blind, parallel-group, active-comparator-controlled Initial Treatment Period followed by a 40-week Maintenance Treatment Period to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque psoriasis (PSO)		
	Duration of initial treatment phase: Duration of maintenance phase: Duration of Safety Follow up (SFU):		16 weeks 40 weeks SFU Visit was planned 20 weeks after the final dose of IMP (for study participants not enrolling in open-label study PS0014)
Hypothesis	Superiority to adalimumab		
Treatments groups	Bimekizumab (BKZ) 320mg Q4W		Bimekizumab 320mg administered Q4W throughout the study (56 weeks) 158 randomized
	BKZ 320mg Q4W/Q8W		Bimekizumab 320mg administered Q4W until Week 16 and bimekizumab Q8W from Week 16 thereafter throughout the study (56 weeks) 161 randomized
	Adalimumab (ADA)/BKZ Q4W		Adalimumab 80mg administered as an initial dose, followed by 40mg Q2W starting 1 week after the initial dose and until Week 24. All patients switched to receive bimekizumab 320mg Q4W starting at Week 24 and throughout the study (56 weeks) 159 randomized
Endpoints and definitions	Co-primary endpoints	PASI90 and IGA 0/1 at Week 16	Proportion of participants who achieved a PASI90 response at Week 16 and proportion of participants who achieved an IGA 0/1 response at Week 16 (bimekizumab vs. adalimumab)
	Major Secondary endpoints	PASI90 response at Week 24	Proportion of participants who achieved a PASI90 response at Week 24

		IGA 0/1 at Week 24	Proportion of participants who achieved an IGA 0/1 response at Week 24
		PASI75 response at Week 4	Proportion of participants who achieved a PASI75 response at Week 4
		PASI100 response at Week 16	Proportion of participants who achieved a PASI100 response at Week 16
		PASI100 response at Week 24	Proportion of participants who achieved a PASI100 response at Week 24
		PASI90 response at Week 56	Proportion of participants who achieved a PASI90 response at Week 56
		IGA 0/1 response at Week 56	Proportion of participants who achieved an IGA 0/1 response at Week 56
Database lock	09 Apr 2020		

Results and Analysis

Analysis description	**Primary Analysis**				
Analysis population and time point description	Intent to treat (Randomized Set) Week 16				
Descriptive statistics and estimate variability	Treatment group	BKZ 320mg Q4W		ADA	
	Number of participants	319		159	
	PASI90 Wk 16 n/N (%)	275/319 (86.2%)		75/159 (47.2%)	
	IGA 0/1 Wk 16 n/N (%)	272/319 (85.3%)		91/159 (57.2%)	
Effect estimate per comparison	Co-primary endpoints	Comparison groups		BKZ vs ADA	
		p-value		p<0.001	
Notes	Both co-primary endpoints at Week 16 were highly statistically significant demonstrating superiority over adalimumab with p<0.001				
Analysis description	**Secondary analysis**				
Analysis population and time point description	Intent to treat Week 4, 16, 24, 56				
Descriptive statistics and estimate variability	Treatment group	BKZ 320mg Q4W/Q8W	BKZ 320mg Q4W	BKZ total	ADA
	Number of participants	161	158	319	159

	PASI90 Week 24 n/N (%)	137/161 (85.1%)	136/158 (86.1%)	273/319 (85.6%)	82/159 (51.6%)
	IGA 0/1 Week 24 n/N (%)	140/161 (87.0%)	136/158 (86.1%)	276/319 (86.5%)	92/159 (57.9%)
	PASI75 Week 4 n/N (%)	N/A	N/A	244/319 (76.5%)	50/159 (31.4%)
	PASI100 Week 16 n/N (%)	N/A	N/A	194/319 (60.8%)	38/159 (23.9%)
	PASI100 Week 24 n/N (%)	106/161 (65.8%)	107/158 (67.7%)	213/319 (66.8%)	47/159 (29.6%)
	PASI90 Week 56 n/N (%)	133/161 (82.6%)	134/158 (84.8%)	267/319 (83.7%)	N/A
	IGA 0/1 Week 56 n/N (%)	134/161 (83.2%)	130/158 (82.3%)	264/319 (82.8%)	N/A

Effect estimate per comparison	Secondary endpoints (in pre-defined testing hierarchy)	Comparison groups	BKZ vs ADA at Week 16
		p-value	p<0.001
		Comparison groups	BKZ vs ADA at Week 4
		p-value	p<0.001
		Comparison groups	BKZ vs ADA at Week 24
		p-value	p<0.001
Notes	All secondary endpoints in pre-defined testing hierarchy were highly statistically significant in favor of bimekizumab treatment with p<0.001. Note that endpoints at Week 56 were not part of the pre-defined testing hierarchy.		

Summary of efficacy for Study PS0009 "BE VIVID"

Title: A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled, Parallel-Group Study To Evaluate The Efficacy And Safety Of Bimekizumab In Adult Subjects With Moderate To Severe Chronic Plaque Psoriasis		
Study identifier	PS0009 EudraCT Number: 2016-003425-42 NCT03370133	
Design	PS0009 is a multicenter study consisting of a 16-week, randomized, double-blind placebo- and active comparator controlled Initial Treatment Period followed by a 36-week Maintenance Treatment Period to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque psoriasis.	
	Duration of initial treatment phase: Duration of maintenance phase: Duration of Safety Follow up (SFU):	16 weeks 36 weeks SFU Visit was planned 20 weeks after the final dose of IMP (for study participants not enrolling in open-label study PS0014)

Hypothesis	Superiority to placebo and superiority to ustekinumab		
Treatments groups	Bimekizumab (BKZ) 320mg Q4W		Bimekizumab 320mg administered Q4W throughout the study (52 weeks) 321 randomized
	Placebo (PBO) /BKZ 320mg Q4W		Placebo administered sc Q4W for 16 weeks followed by BKZ 320mg Q4W for 36 weeks 83 randomized
	Ustekinumab (USTE)		Ustekinumab - For study participants weighing ≤100kg at Baseline, 45mg sc initially and 4 weeks later, then Q12W through 52 weeks - For study participants weighing >100kg at Baseline, 90mg sc initially and 4 weeks later, then Q12W through 52 weeks 163 randomized
Endpoints and definitions	Co-Primary endpoints	PASI90 and IGA 0/1 at Week 16	Proportion of participants who achieved a PASI90 response at Week 16 and proportion of participants who achieved an IGA 0/1 response at Week 16 (superiority vs. placebo)
	Secondary endpoints	PASI100 at Week 16	Proportion of participants who achieved a PASI100 response at Week 16 (superiority vs. placebo)
		IGA 0 at Week 16	Proportion of participants who achieved an IGA 0 response at Week 16 (superiority vs. placebo)
		PASI90 at Week 16	Proportion of participants who achieved a PASI90 response at Week 16 (non-inferiority and superiority vs. ustekinumab)
		IGA 0/1 at Week 16	Proportion of participants who achieved a IGA 0/1 response at Week 16 (non-inferiority and superiority vs. ustekinumab)
		PASI75 response at Week 4	Proportion of participants who achieved a PASI75 response at Week 4 (superiority vs. placebo, superiority vs. ustekinumab)
		PSD responses for pain, itch, and scaling at Week 16	Proportion of participants who achieved responder definition threshold for each item at Week 16 (superiority vs. placebo)
		Scalp IGA 0/1 at Week 16	Proportion of participants who achieved a Scalp IGA response 0/1 at Week 16 for study participants with scalp PSO at Baseline ≥2 (superiority vs. placebo)
		PASI90 at Weeks 12 and 52	Proportion of participants who achieved a PASI90 response at Weeks 12 and 52, respectively (superiority vs. ustekinumab)
		IGA 0/1 at Weeks 12 and 52	Proportion of participants who achieved an IGA 0/1 response at Weeks 12 and 52, respectively (superiority vs. ustekinumab)

Database lock	07 Feb 2020			
Results and Analysis				
Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (Randomized Set) Week 16			
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W	USTE
	Number of participant	83	321	163
	PASI90 Week 16 n/N (%)	4/83 (4.8%)	273/321 (85.0%)	81/163 (49.7%)
	IGA 0/1 Week 16 n/N (%)	4/83 (4.8%)	270/321 (84.1%)	87/163 (53.4%)
Effect estimate per comparison	Co-primary endpoints	Comparison groups	Bimekizumab vs. placebo	
		p-value	p<0.001	
Notes	Both co-primary endpoints at Week 16 were highly statistically significant demonstrating superiority over placebo with p<0.001			
Analysis description	**Secondary analysis**			
Analysis population and time point description	Intent to treat Week 4, 12, 16, 52			
Descriptive statistics and estimate variability	Treatment group	PBO/BKZ 320mg Q4W	BKZ 320mg Q4W	USTE
	Number of participants	83	321	163
	PASI100 at Week 16 n/N (%)	0/83	188/321 (58.6%)	34/163 (20.9%)
	IGA 0 at Week 16 n/N (%)	0/83	188/321 (58.6%)	36/163 (22.1%)
	PASI75 response at Week 4 n/N (%)	2/83 (2.4%)	247/321 (76.9%)	25/163 (15.3%)
	PSD responses for pain at Week 16 (participants with Baseline ≥1.98) n/N (%)	9/54 (16.7%)	177/229 (77.3%)	73/107 (68.2%)

	PSD responses for itch at Week 16 (participants with Baseline ≥2.39) n/N (%)	8/61 (13.1%)	187/244 (76.6%)	77/117 (65.8%)
	PSD responses for scaling at Week 16 (participants with Baseline ≥2.86) n/N (%)	8/63 (12.7%)	193/246 (78.5%)	69/116 (59.5%)
	Scalp IGA 0/1 at Week 16 (participants with a Baseline scalp IGA ≥2) n/N (%)	11/72 (15.3%)	240/285 (84.2%)	103/146 (70.5%)
	PASI90 at Week 12 n/N (%)	2/83 (2.4%)	273/321 (85.0%)	71/163 (43.6%)
	PASI90 at Week 52 n/N (%)	N/A	263/321 (81.9%)	91/163 (55.8%)
	IGA 0/1 at Week 12 n/N (%)	4/83 (4.8%)	263/321 (81.9%)	85/163 (52.1%)
	IGA 0/1 at Week 52 n/N (%)	N/A	251/321 (78.2%)	99/163 (60.7%)
Effect estimate per comparison	Secondary endpoints (all)	Comparison groups		BKZ vs PBO BKZ vs USTE
		p-value		p<0.001
Notes	All secondary endpoints were highly statistically significant in favor of bimekizumab treatment with p<0.001			

PS0013

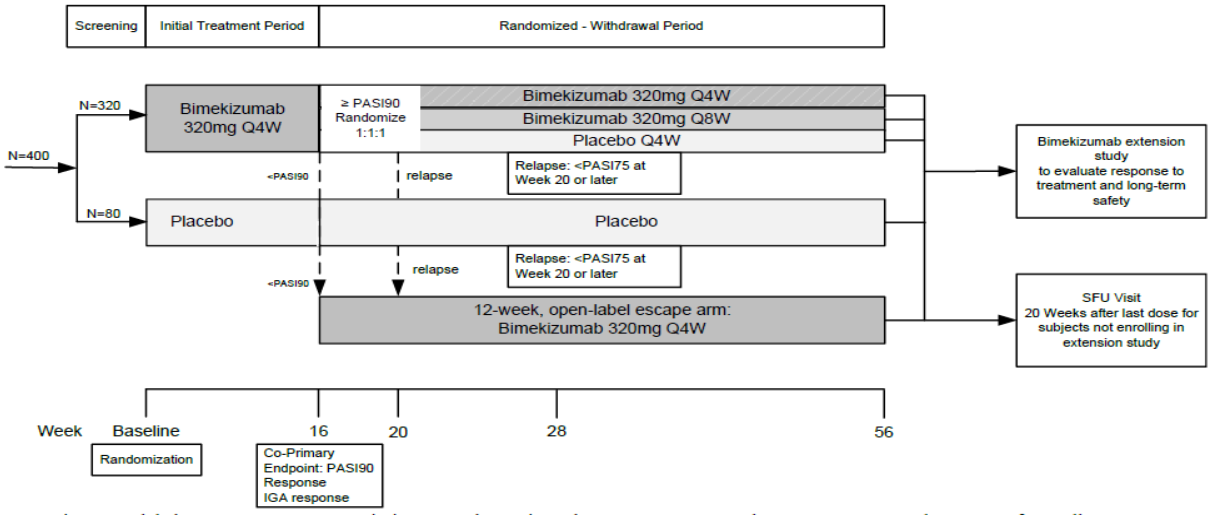
Methods

PS0013 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study consisting of a 16-week Initial Treatment Period followed by a 40-week Randomized-Withdrawal Period to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque PSO.

Study participants initially randomized to bimekizumab 320mg Q4W were re-randomized 1:1:1 to bimekizumab 320mg Q4W, bimekizumab 320mg Q8W, or placebo (ie, treatment withdrawal).

All study participants initially randomized to placebo who achieved a PASI90 response at Week 16 continued to receive placebo (Q4W).

All study participants who relapsed at Week 20 or later during the Randomized-Withdrawal Period (up to Week 56) were allocated to the escape arm. Relapse was defined as not achieving a PASI75 response. Study participants who achieved a PASI50 response at Week 12 of the open-label escape arm were allowed to enroll in PS0014.



Study participants

Main Inclusion criteria

- Male or female ≥18 years of age.
- Chronic plaque PSO for at least 6 months prior to the Screening Visit.
- PASI ≥12 and BSA affected by PSO ≥10% and IGA score ≥3 on a 5-point scale.
- Study participant was a candidate for systemic PSO therapy and/or phototherapy.
- Female study participants must have been: Postmenopausal, permanently sterilized or willing to use a highly effective method of contraception throughout the duration of the study until 20 weeks after last administration of IMP.
- Study participant agreed not to change their usual sun exposure during the course of the study and to use ultraviolet A/ultraviolet B sunscreens if unavoidable exposure occurred.
- Patients were allowed to enrol if they were exposed to 3 biologic response modifiers (including no more than 1 IL-17). (Amendment 1)

Main exclusion criteria

- Study participant previously participated in a bimekizumab clinical study who received at least 1 dose of the IMP (including placebo).
- Study participants who experienced primary failure (no response within 12 weeks) to 1 or more IL-17 biologic response modifiers or more than 1 biologic response modifiers other than an IL-17 were to be excluded from the study. (Amendment 1)
- Study participant participating in another study of a medication (systemic) under investigation was to be washed out of the medication for 12 weeks or at least 5 half-lives prior to the Baseline Visit, whichever was greater.

- Study participant participating in another study of a topical medication under investigation must have been washed out of the medication for 4 weeks prior to the Baseline Visit.
- Study participant had a form of PSO other than chronic plaque-type (eg, pustular, erythrodermic and guttate PSO, or drug-induced PSO).
- Study participant had an active infection or history of infection.
- Study participant had concurrent acute or chronic viral hepatitis B or C or human immunodeficiency virus (HIV) infection.
- Study participant had received any live (includes attenuated) vaccination within the 8 weeks prior to the Baseline visit.
- Study participant had known TB infection, was at high risk of acquiring TB infection, or had current or history of nontuberculous mycobacterium (NTMB) infection.
- Study participant had a history of a lymphoproliferative disorder including lymphoma or current signs and symptoms suggestive of lymphoproliferative disease or any active or history malignancy within 5 years.
- Study participant had a diagnosis of inflammatory conditions other than PSO or PsA,
- Study participant had any systemic disease, psychiatric disease (moderate/severe depression or suicidal ideation) or had laboratory abnormalities at Screening.

Treatment

The IMPs used in this study were bimekizumab and placebo:

- Bimekizumab was supplied in a 1mL prefilled syringe (PFS) at a concentration of 160mg/mL (sodium acetate, glycine, polysorbate 80) for sc injection.
- Placebo was supplied as 0.9% sodium chloride aqueous solution (physiological saline, preservative free) of pharmacopoeia (USP/Ph.Eur.) quality in a 1mL PFS for sc injection.

Double-blind Initial Treatment Period dosing

Study participants randomized to receive bimekizumab 320mg Q4W received 2 bimekizumab 160mg injections sc Q4W.

Study participants randomized to receive placebo received 2 placebo injections sc Q4W.

Randomized-Withdrawal Period dosing

Study participants re-randomized to receive bimekizumab 320mg Q8W alternated between receiving bimekizumab (2 bimekizumab 160mg injections sc) followed 4 weeks later by placebo (2 placebo injections sc). Patients randomised to Q4W or placebo as the same as described above in double blind initial treatment period.

Permitted concomitant treatments (medications and therapies)

Topical medications

Study participants may have continued to use topical moisturizers or emollients, bath oils, or oatmeal bath preparations for skin conditions during the study, as needed. Over-the-counter shampoos for the treatment of PSO of the scalp were also permitted.

Mild and low potency topical steroids were permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medications should not have been used within approximately 24 hours prior to study visits requiring IGA and PASI measures.

Other medications

Study participants who were already receiving an established NSAID regimen for PsA or symptoms of arthritis and had been on a stable dose for ≥1 week prior to the Screening Visit may have continued their use during the study. However, initiation of, or increase in dosage of NSAIDs during the study (especially in study participants with a history of GI intolerance to NSAIDs or a history of GI ulceration) should not have occurred prior to Week 12 and should not have happened within 2 weeks of the Week 56 Visit.

Study participants may have taken mild pain relievers (acetaminophen/paracetamol, mild opiates) as needed for arthritis pain but preferably not within 24 hours of the Baseline and Week 56 Visits.

Intra-articular steroid injections of any joint and hyaluronic acid injections were allowed after Week 12.

The list of prohibited PSO medications was the same as for study PS0008 except that a 3-month washout period was required for adalimumab in PS0013.

Objectives

Primary objective

The primary objective of the study was to compare the efficacy of bimekizumab administered sc for 16 weeks versus placebo in the treatment of study participants with moderate to severe chronic plaque PSO.

Secondary objectives

- Evaluate the efficacy of bimekizumab compared to placebo at achieving complete clearance (PASI100) after 16 weeks of treatment
- Evaluate the efficacy of bimekizumab compared to placebo after 4 weeks of treatment
- Evaluate the change in itch, pain, and scaling of bimekizumab compared to placebo after 16 weeks of treatment as reported by study participants using the Patient Symptom Diary (PSD)
- Evaluate the change in psoriatic scalp disease of bimekizumab compared to placebo after 16 weeks of treatment in study participants with scalp PSO at Baseline
- Evaluate the efficacy of continuous treatment with bimekizumab versus treatment withdrawal (placebo) as defined by PASI90 at Week 56 for study participants who responded to bimekizumab treatment at Week 16
- Assess the maintenance of efficacy of bimekizumab dosing Q4W versus every 8 weeks (Q8W) at Week 56
- Assess treatment-emergent adverse events (TEAEs), serious adverse events (SAEs), and TEAEs leading to withdrawal adjusted by duration of study participant exposure to study treatment

Other objectives

The other objectives of the study were to demonstrate the effects of bimekizumab on aspects of the disease, use of rescue treatment and effects over time.

The Additional objectives also examined for quality of life effects, palmoplantar PSO over time, Psoriatic Arthritis Screening and Evaluation (PASE) questionnaire, PK, immunogenicity, effects on gene and protein expression and safety and tolerability of Bimekizumab.

Outcomes/endpoints

Primary efficacy variables

The co-primary efficacy variables were the PASI90 response (defined as a study participant who achieved 90% reduction from Baseline in the PASI score) at Week 16 and the IGA 0/1 response (defined as Clear [0] or Almost Clear [1] with at least a 2-category improvement relative to Baseline) at Week 16.

The secondary efficacy variables:

- PASI100 response at Week 16
- IGA 0 response (defined as Clear [0] with at least a 2-category improvement relative to Baseline) at Week 16
- PASI75 response at Week 4
- PSD responses for pain, itch, and scaling at Week 16
- Scalp-specific Investigator's Global Assessment (Scalp IGA) 0/1 response (Clear [0] or Almost Clear [1] with at least a 2-category improvement from Baseline) at Week 16 for study participants with scalp PSO at Baseline
- PASI90 response at Week 56 among Week 16 PASI90 responders.

Other efficacy variables:

- PASI50, PASI75, PASI90, and PASI100 response
- Time to PASI50, PASI75, PASI90, and PASI100 response during the Initial Treatment Period.
- Time to relapse during the Randomized-Withdrawal Period
- IGA 0 response (Clear [0] with at least a 2-category improvement from Baseline)
- IGA 0/1 response (Clear [0] or Almost Clear [1] with at least 2-category improvement from Baseline).
- Percentage of study participants achieving a DLQI total score of 0 or 1
- Percentage of study participants achieving a minimally clinically important difference (MCID) (improvement from Baseline of 4 or more) in the DLQI total score.
- Scalp IGA 0/1 response (Clear [0] or Almost Clear [1] with at least a 2-category improvement from Baseline) for study participants with scalp PSO at Baseline
- Change from Baseline in Modified Nail Psoriasis Severity Index (mNAPSI) score for study participants with nail PSO at Baseline.
- mNAPSI75, mNAPSI90 and mNAPSI100 responses.
- Change from Baseline in the PASE questionnaire scores (function score, symptom score, and total score).

- Change from Baseline in Short Form 36-item Health Survey (SF-36) Physical Component Summary (PCS) score, and Mental Component Summary (MCS) score, and individual domain scores
- Responses to Euro-Quality of Life 5-Dimensions, 3 levels (EQ-5D-3L), absolute and changes from Baseline in EQ-5D-3L VAS scores.

Sample size

Approximately 400 study participants were to be randomly assigned in a 4:1 ratio to the following treatment groups:

- Bimekizumab 320mg (approximately 320 study participants)
- Placebo (approximately 80 study participants)

The primary efficacy analysis was based on the comparison of bimekizumab to placebo for the co-primary efficacy variables of PASI90 response and IGA 0/1 response at Week 16. The assumed response rates for PASI90 at Week 16 were 75% and 2% for bimekizumab and placebo, respectively.

Additionally, the assumed response rates for IGA 0/1 response were 85% and 5% for bimekizumab and placebo, respectively. The assumed response rates for bimekizumab were based on the Phase 2b PS0010 data. The power to show statistical superiority of bimekizumab relative to placebo under these assumptions was >99% for the co-primary endpoints.

A total of 435 study participants were randomized and started the study as follows: 349 study participants in the bimekizumab 320mg Q4W group and 86 study participants in the placebo group.

An interim analysis after final week 56 visit was performed, and the final updated CSR was provided once all of the SFU visits were collected.

At the Week 16 study visit, study participants who achieved a PASI90 response entered into the Randomized-Withdrawal Period. Study participants initially randomized to bimekizumab 320mg Q4W were re-randomized 1:1:1 to bimekizumab 320mg Q4W, bimekizumab 320mg Q8W, or placebo (ie, treatment withdrawal). All study participants initially randomized to placebo who achieved a PASI90 response at Week 16 continued to receive placebo Q4W. A total of 312 study participants included in the Week 16 Responder Set (WK16Res) started the Randomized-Withdrawal Period, including 106 study participants in the bimekizumab 320mg

Q4W/Q4W group, 100 study participants in the bimekizumab 320mg Q4W/Q8W group, 105 study participants in the bimekizumab 320mg Q4W/placebo group, and 1 study participant in the placebo/placebo group.

Study participants who did not achieve a PASI90 response at the Week 16 study visit and all study participants who relapsed at Week 20 or later during the Randomized-Withdrawal Period (up to Week 56) were allocated to the escape arm. A total of 182 study participants included in the Escape Study Participant Set (ESS) started the Escape Treatment Period. Three study participants in the Escape Treatment Period were ongoing in the study as of the clinical cutoff date.

Duration of treatment: For each study participant not entering escape treatment, the study was planned to last a maximum of up to 77 weeks, as follows:

-Screening Period: 2 to 5 weeks

-Double-blind, placebo-controlled Initial Treatment Period: 16 weeks

-Double-blind, placebo-controlled Randomized-Withdrawal Period: 40 weeks

-Escape treatment (if required): 12 weeks

Safety Follow-Up Period: an SFU Visit is planned 20 weeks after the final dose of IMP (for study participants not enrolling in the open-label study)

Randomisation

Essentially the same as for studies PS0008 and PS0009

At Week 16, subjects who received bimekizumab Q4W during the Initial Treatment Period may be re-randomized to a new treatment group based on their PASI response.

Blinding (masking)

Essentially identical as for studies PS0008 and PS0009.

Statistical methods:

Statistical Analysis Plan

The original SAP, dated 30 August 2018, was amended once. Amendment 1 of the SAP, dated 16 September 2019, was implemented to align the SAP with both Protocol Amendment 2 (dated 06 April 2018) and Protocol Amendment 3 (dated 21 May 2019), as well as to achieve consistency with other SAPs of the bimekizumab PSO development program. Amendment 1 also clarified the handling of participants who entered the Escape Treatment Period without meeting the escape criteria, or who met the criteria but did not enter the Escape Treatment Period prior to study unblinding.

The interim CSR is a complete analysis of the first 56 weeks of the study (including the 16-week Initial Treatment Period and 40-week Randomized-Withdrawal Period) based on a clinical cut-off date of 18 October 2019. The date of database lock and unblinding was 18 October 2019.

The results presented in the PS0013 final CSR provide a complete analysis of data collected through Week 56 of the study, including the 16-week Initial Treatment Period, the 40-week Randomized-Withdrawal Period, the 12-week Escape Treatment Period, and the complete 20-week SFU Period. After the data cutoff date for the interim CSR, an additional 6 study participants completed unscheduled or SFU visits and 3 study participants were ongoing in the Escape Treatment Period, and these data were included in the final CSR.

Analysis Populations

As for PS0008, except the BKZ Set, BKZ Week 24 Set and MS Set were not defined for this study. The following analysis populations were additionally defined for study PS0013:

The **Escape Subject Set (ESS)** consisted of all subjects who received at least 1 dose of escape bimekizumab 320mg treatment either due to not achieving a PASI90 response at Week 16 or experiencing a relapse after entering the Randomized-Withdrawal Period. Summaries based on the ESS were split between subjects who enter the escape arm: 1) due to PASI90 non-response at Week 16 or 2) due to relapse during the Randomized-Withdrawal Period (after achieving PASI90 response at Week 16).

The **Week 16 Responder Set (WK16ResS)** consisted of all subjects who achieved a PASI90 response at Week 16 and had received at least 1 dose of the IMP during the Randomized-Withdrawal Period at Week 16 or later.

The **Active Medication Set (AMS)** consisted of all subjects who had received at least 1 dose of active IMP (bimekizumab). The AMS was used for summaries of safety that included all data from the Initial Treatment Period and/or Randomized-Withdrawal Period.

Analysis of co-primary endpoints – PASI 90 & IGA 0/1 at week 16

As for PS0008, except there was no active comparator in this study and consequently no testing for non-inferiority.

The additional sensitivity analysis described for PS0009 was also conducted for PS0013.

Analysis of ranked secondary endpoints

As for PS0009.

Subgroup analyses

As for PS0008.

Multicentre study

As for PS0008, except a pooling by region was to be applied if convergence was not achieved when pooling by center.

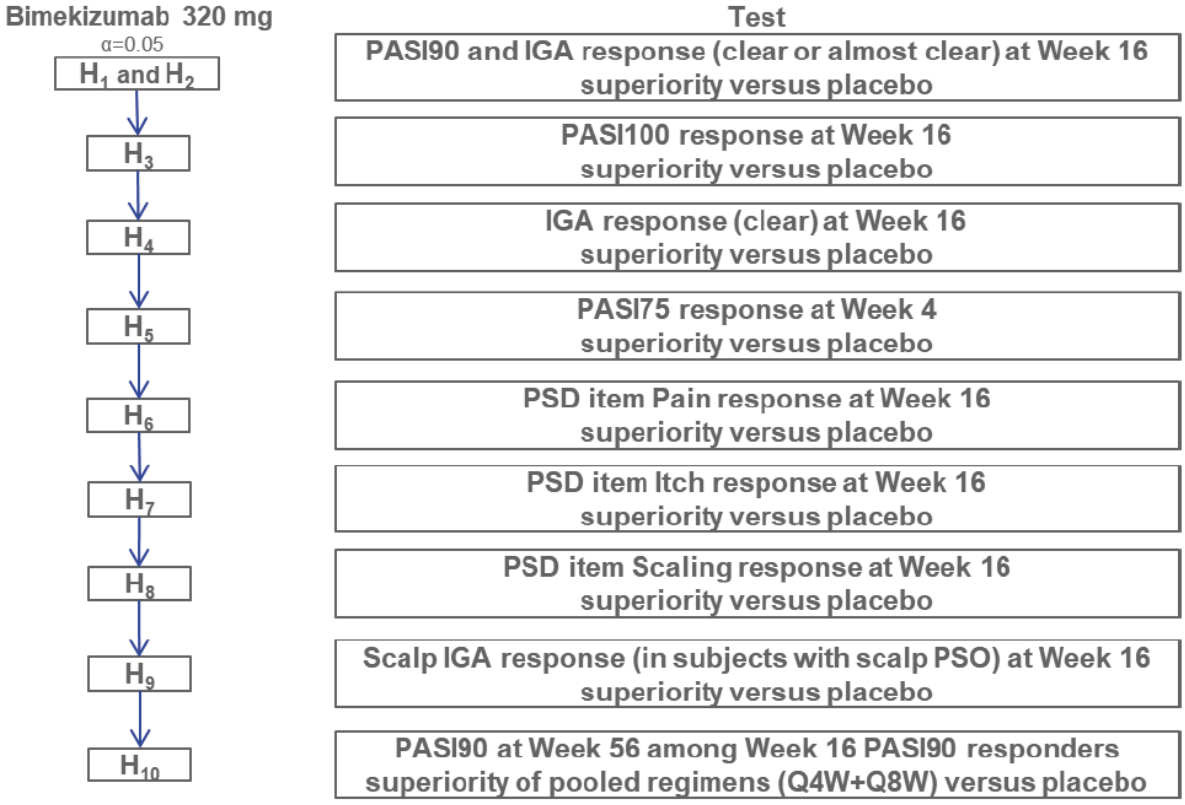
Type I error control

The statistical analysis of the co-primary efficacy variables and selected secondary efficacy variables accounted for multiplicity and controlled the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a fixed sequence testing procedure.

The hypotheses (H1, H2, H3, H4, H5, H6, H7, H8, H9 and H10) comparing bimekizumab vs. placebo were tested at a 2 -sided alpha level of 0.05.

The first 2 hypotheses (H1 and H2) tested whether bimekizumab is superior to placebo for PASI90 response and IGA response at Week 16. These are the hypothesis tests corresponding to the coprimary endpoints. If both were rejected at a 2-sided alpha level of 0.05, that alpha was to be passed to the next test in the sequence, allowing the testing procedure to proceed.

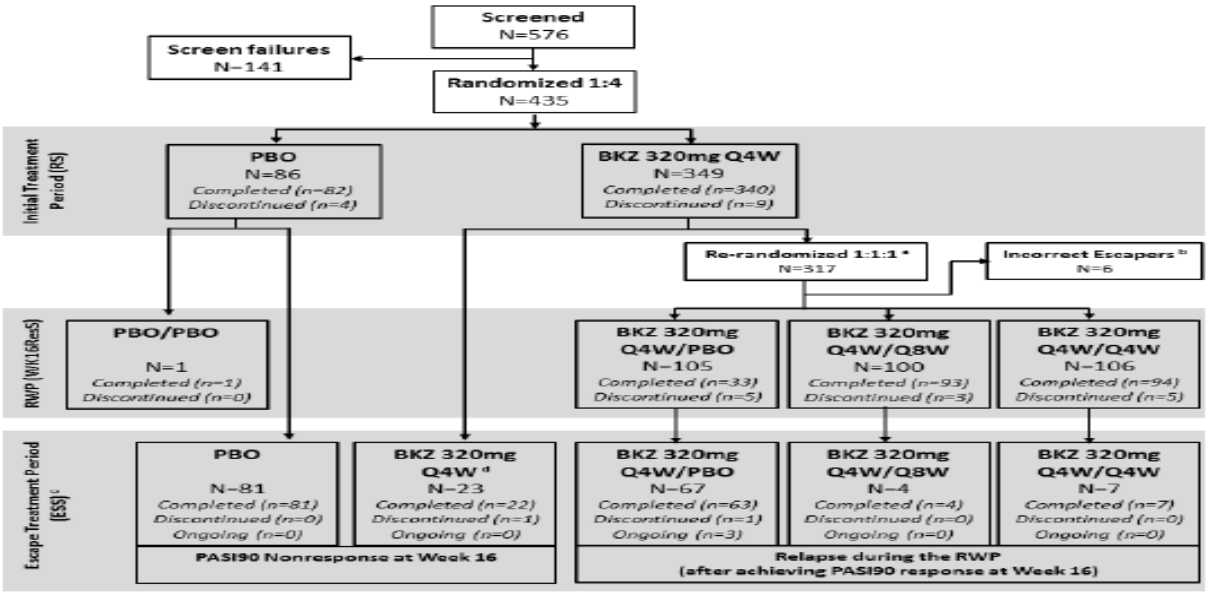
The hypotheses associated with the subsequent secondary efficacy endpoints were based on testing for superiority relative to placebo.



BL=Baseline; IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index, PSD=patient symptom diary; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks.

Results

Study Participant flow



BKZ=bimekizumab; ESS=Escape Study Participant Set; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks; RS=Randomized Set; RWP=Randomized-Withdrawal Period; WK16ResS=Week 16 Responder Set

[a] One study participant was re-randomized at Week 16 in error, but the study participant's last dose of IMP was at Week 8. This study participant was listed as discontinuing the study due to an adverse event with onset during the Initial Treatment Period and was thus not included in the WK16ResS and ESS.

[b] Incorrect escapers entered the RWP but later entered the escape arm without meeting the escape criteria. These study participants were excluded from the WK16ResS and ESS.

[c] All study participants were treated with BKZ 320mg Q4W in the Escape Treatment Period. Study participants were summarized according to randomized treatment in the Initial Treatment Period and assigned treatment in the RWP.

[d] Three study participants met escape criteria at Week 16 but entered the Escape Treatment Period at Week 20 or later. These participants were included in the ESS but were not included in the WK16ResS.

Table 23- Disposition and discontinuation reasons – Initial Treatment Period (RS)

Disposition	PBO N=86 n (%)	BKZ 320mg Q4W N=349 n (%)	All study participants N=435 n (%)
Started Initial Treatment Period	86 (100.0)	349 (100.0)	435 (100.0)
Completed Initial Treatment Period	82 (95.3)	340 (97.4)	422 (97.0)
Discontinued Initial Treatment Period	4 (4.7)	9 (2.6)	13 (3.0)
Primary reason for discontinuation			
AE	0	5 (1.4)	5 (1.1)
Lack of efficacy	2 (2.3)	1 (0.3)	3 (0.7)
Protocol violation	0	0	0
Lost to follow up	1 (1.2)	3 (0.9)	4 (0.9)
Consent withdrawn	1 (1.2)	0	1 (0.2)
Other	0	0	0

AE=adverse event; BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Table 24- Disposition and discontinuation reasons – Randomized-Withdrawal Period (WK16ResS)

Disposition	BKZ 320mg Q4W/PBO N=105 n (%)	BKZ 320mg Q4W/Q8W N=100 n (%)	BKZ 320mg Q4W/Q4W N=106 n (%)	All study participants N=312 n (%)
Started Randomized-Withdrawal Period	105 (100.0)	100 (100.0)	106 (100.0)	312 (100.0)
Completed Randomized-Withdrawal Period	33 (31.4)	93 (93.0)	94 (88.7)	221 (70.8)
Received escape treatment	67 (63.8)	4 (4.0)	7 (6.6)	78 (25.0)
Discontinued study	5 (4.8)	3 (3.0)	5 (4.7)	13 (4.2)
Primary reason for discontinuation				
AE	3 (2.9)	2 (2.0)	0	5 (1.6)
Lack of efficacy	0	0	0	0
Protocol violation	0	0	0	0
Lost to follow up	2 (1.9)	1 (1.0)	2 (1.9)	5 (1.6)
Consent withdrawn	0	0	3 (2.8)	3 (1.0)
Other	0	0	0	0

AE=adverse event; BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks; WK16ResS=Week 16 Responder Set
Note: Study participants were summarized according to randomized treatment in the Initial Treatment Period and assigned treatment in the Randomized-Withdrawal Period.
Note: The All study participants column contains 1 study participant from the PBO/PBO group that is not otherwise shown in the table.

Study participants who did not achieve a PASI90 response at Week 16 of the Initial Treatment Period and all study participants who relapsed at Week 20 or later during the Randomized-Withdrawal Period (up to Week 56) received open-label bimekizumab 320mg Q4W for 12 weeks (ie, escape treatment). A total of 182 study participants started the Escape Treatment Period

Table 25 - Disposition and discontinuation reasons while on BKZ 320mg Q4W by treatment sequence before Escape Treatment Period entry – Escape Treatment Period (ESS)

Disposition	PASI90 Nonresponse at Week 16		Relapse during the Randomized-Withdrawal Period (after achieving PASI90 response at Week 16)			All study participants N=182 n (%)
	PBO N=81 n (%)	BKZ 320mg Q4W N=23 n (%)	BKZ 320mg Q4W/PBO N=67 n (%)	BKZ 320mg Q4W/Q8W N=4 n (%)	BKZ 320mg Q4W/Q4W N=7 n (%)	
Started Escape Treatment Period	81 (100.0)	23 (100.0)	67 (100.0)	4 (100.0)	7 (100.0)	182 (100.0)
Completed Escape Treatment Period	81 (100.0)	22 (95.7)	63 (94.0)	4 (100.0)	7 (100.0)	177 (97.3)
Ongoing in study	0	0	3 (4.5)	0	0	3 (1.6)
Discontinued study	0	1 (4.3)	1 (1.5)	0	0	2 (1.1)
Primary reason for discontinuation						
AE	0	1 (4.3)	0	0	0	1 (0.5)
Lack of efficacy	0	0	0	0	0	0
Protocol violation	0	0	0	0	0	0
Lost to follow up	0	0	0	0	0	0
Consent withdrawn	0	0	1 (1.5)	0	0	1 (0.5)
Other	0	0	0	0	0	0

AE=adverse event; BKZ=bimekizumab; ESS=Escape Study Participant Set; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks
Note: Study participants were summarized according to randomized treatment in the Initial Treatment Period and assigned treatment in the Randomized-Withdrawal Period.

Protocol violations

In the initial treatment period most study participants (97.9%) had no important protocol deviations. The incidence of important protocol deviations during the Initial Treatment Period was low overall and similar between the bimekizumab 320mg Q4W group (2.0%) and the placebo group (2.3%). The most common important protocol deviation was procedural non-compliance (1.1%), and the most common reason for procedural noncompliance was having a Week 16 Visit outside of the ±7-day window.

Overall, few study participants (1.6%) were excluded from the PPS due to protocol deviations during the Initial Treatment Period, and the incidence of study participants excluded from the PPS was similar between treatment groups. Overall, few study participants (0.5%) were excluded from the PK-PPS due to protocol deviations during the Initial Treatment Period, and the incidence of study participants excluded from the PK-PPS was similar between treatment groups.

In the randomised withdrawal period, one study participant in the bimekizumab 320mg Q4W/Q4W group had an important protocol deviation of prohibited concomitant medication use.

There were no important protocol deviations during the Escape Treatment Period.

Recruitment

First study participant enrolled: 05 Feb 2018. Last study participant completed: 18 Oct 2019 (based on the clinical cut-off date for this interim Clinical Study Report [CSR])

Data from the Safety Follow-Up (SFU) Period (20 weeks after the final dose of investigational medicinal product [IMP]) was provided upon request from CHMP (with the clinical cut-off date: 5 March 2020).

As of the clinical cut-off date for this interim CSR, the RS, SS, and FAS each consisted of 435 study participants, including 349 study participants in the bimekizumab 320mg Q4W group and 86 study participants in the placebo group. The majority of study participants were included in the PPS and PK-PPS (98.4% each).

Table 26 - Disposition of analysis sets (RS)

Analysis Set	PBO N=86 n (%)	BKZ 320mg Q4W N=349 n (%)	All study participants N=435 n (%)
RS	86 (100)	349 (100)	435 (100)
SS	86 (100)	349 (100)	435 (100)
FAS	86 (100)	349 (100)	435 (100)
WK16ResS	1 (1.2)	311 (89.1)	312 (71.7)
ESS	81 (94.2)	101 (28.9)	182 (41.8)
AMS	81 (94.2)	349 (100)	430 (98.9)
PPS	84 (97.7)	344 (98.6)	428 (98.4)
PK-PPS	80 (93.0)	348 (99.7)	428 (98.4)

AMS=Active Medication Set; BKZ=bimekizumab; ESS=Escape Study Participant Set; FAS=Full Analysis Set; PBO=placebo; PK-PPS=Pharmacokinetics Per-Protocol Set; PPS=Per-Protocol Set; Q4W=every 4 weeks; RS=Randomized Set; SS=Safety Set; WK16ResS=Week 16 Responder Set

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

Conduct of the study

The original PS0013 protocol (dated 14 August 2017) has undergone 3 global amendments.

Protocol Amendment 1 (dated 15 Oct 2017) was implemented before any study participants were enrolled. The withdrawal criterion that study participants who did not achieve a PASI50 response by Week 28 or later be withdrawn from the study was removed and the same assessor should have evaluated the study participant at each efficacy assessment.

Protocol Amendment 2 (dated 06 Apr 2018) included: Modified exclusion criterion to clarify exclusion of study participants who participated in other studies of bimekizumab, other medications (systemic or topical), or devices; Modified exclusion criteria pertaining to history of malignancy, systemic disease, and major Depression; Added new withdrawal criteria for study participants with newly diagnosed inflammatory bowel disease (IBD), participants with depression or suicidal ideation; Updated prohibited concomitant medications to include tildrakizumab and risankizumab; Provided additional details for requirements for IMP rechallenge in the event of potential drug-induced liver injury (PDILI). Clarified regions for analyses.

Protocol Amendment 3 (dated 21 May 2019): Clarified that IGA 0/1 response was clear or almost clear with at least a 2-category improvement from Baseline; Updated the definition of PSD responder and clarified that the PSD response item scores included in the statistical testing procedure (pain, itch,

and scaling) were to be characterized in terms of the cumulative percent of study participants demonstrating a prespecified point improvement at Week 16.

Baseline data

Demographic and other Baseline characteristics are summarised in below tables.

Table 27 - Baseline disease characteristics (RS)

Variable	PBO N=86	BKZ 320mg Q4W N=349	All study participants N=435
Psoriasis BSA (%)			
Mean (SD)	24.4 (16.0)	24.6 (15.2)	24.5 (15.4)
Median	20.0	18.0	18.0
Min, max	10, 80	10, 86	10, 86
PASI score			
Mean (SD)	20.13 (7.57)	20.36 (7.60)	20.31 (7.59)
Median	17.85	18.00	18.00
Min, max	12.1, 44.8	12.0, 49.5	12.0, 49.5
mNAPSI total score [a]			
n	50	210	260
Mean (SD)	21.1 (21.6)	20.4 (21.4)	20.6 (21.4)
Median	14.0	13.0	13.0
Min, max	1, 118	1, 120	1, 120
PGADA score [b]			
Mean (SD)	28.7 (26.8)	23.7 (27.8)	24.7 (27.7)
Median	23.5	8.0	12.0
Min, max	0, 98	0, 100	0, 100
PGADA score category [a], n (%)			
0	13 (15.1)	66 (18.9)	79 (18.2)
>0	73 (84.9)	283 (81.1)	356 (81.8)
DLQI total score			
Mean (SD)	11.3 (6.9)	10.4 (6.3)	10.6 (6.4)
Median	10.0	9.0	10.0
Min, max	1, 30	0, 29	0, 30
DLQI score category, n (%)			
0	0	3 (0.9)	3 (0.7)
>0	86 (100.0)	346 (99.1)	432 (99.3)

Variable	PBO N=86	BKZ 320mg Q4W N=349	All study participants N=435
Duration of disease (years)			
Mean (SD)	19.09 (12.77)	19.57 (13.25)	19.48 (13.15)
Median	16.44	17.32	17.22
Min, max	1.2, 59.6	0.7, 67.5	0.7, 67.5
Duration of disease, n (%)			
<Median (17.22) years	46 (53.5)	171 (49.0)	217 (49.9)
≥Median (17.22) years	40 (46.5)	178 (51.0)	218 (50.1)
IGA score, n (%)			
3 (Moderate)	62 (72.1)	242 (69.3)	304 (69.9)
4 (Severe)	24 (27.9)	107 (30.7)	131 (30.1)
PASI score, n (%)			
<20	57 (66.3)	217 (62.2)	274 (63.0)
≥20	29 (33.7)	132 (37.8)	161 (37.0)
Nail involvement, n (%)			
Yes	50 (58.1)	210 (60.2)	260 (59.8)
No	36 (41.9)	139 (39.8)	175 (40.2)
Scalp involvement, n (%)			
Yes	78 (90.7)	319 (91.4)	397 (91.3)
No	8 (9.3)	30 (8.6)	38 (8.7)
Palmoplantar involvement, n (%)			
Yes	39 (45.3)	122 (35.0)	161 (37.0)
No	47 (54.7)	227 (65.0)	274 (63.0)
Prior biologic therapy, n (%)			
Yes	37 (43.0)	155 (44.4)	192 (44.1)
No	49 (57.0)	194 (55.6)	243 (55.9)
Prior anti-TNF therapy, n (%)			
Yes	10 (11.6)	57 (16.3)	67 (15.4)
No	76 (88.4)	292 (83.7)	368 (84.6)

Variable	PBO N=86	BKZ 320mg Q4W N=349	All study participants N=435
Prior phototherapy or chemotherapy, n (%)			
Yes	28 (32.6)	129 (37.0)	157 (36.1)
No	58 (67.4)	220 (63.0)	278 (63.9)
Any prior systemic therapy, n (%)			
Yes	71 (82.6)	276 (79.1)	347 (79.8)
No	15 (17.4)	73 (20.9)	88 (20.2)
PSD: pain [c]			
n	74	306	380
Mean (SD)	5.621 (2.901)	5.399 (2.908)	5.443 (2.904)
Median	6.343	5.571	5.714
Min, max	0, 10	0, 10	0, 10
PSD: itch [c]			
n	74	306	380
Mean (SD)	6.424 (2.369)	6.262 (2.519)	6.293 (2.488)
Median	6.714	6.536	6.571
Min, max	1.29, 10	0, 10	0, 10
PSD: scaling [c]			
n	74	306	380
Mean (SD)	6.636 (2.272)	6.569 (2.267)	6.582 (2.265)
Median	6.917	6.845	6.845
Min, max	1.14, 10	0, 10	0, 10

BKZ=bimekizumab; BSA=body surface area; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; max=maximum; Min=minimum; mNAPSI=Modified Nail Psoriasis Severity Index; PASI=Psoriasis Area and Severity Index; PBO=placebo; PGADA=Patient Global Assessment of Disease Activity; PSD=Patient Symptom Diary; Q4W=every 4 weeks; RS=Randomized Set; SD=standard deviation; TNF=tumor necrosis factor; VAS=visual analog scale

Note: Duration of disease (years)=(Date of randomization – date of onset of plaque psoriasis)/365.25

Note: Study participants were summarized according to randomized treatment at Baseline in the Initial Treatment Period.

[a] mNAPSI total score for study participants with nail involvement (ie, mNAPSI>0)

[b] PGADA for arthritis VAS score

[c] Baseline data were only summarized if the study participant had ≥4 nonmissing values.

Data source: Table 3.1.2.1

The baseline characteristics were generally similar for study participants entering the Randomized-Withdrawal Period (WK16ResS) and the Escape Treatment Period (ESS) compared with Baseline disease characteristics for the Initial Treatment Period (RS).

Prior and concomitant diseases

The majority (82.1%) of study participants in the SS reported a previous and ongoing medical condition at Baseline (Table 3.1.3.1). The most frequently reported conditions/diseases at Baseline were in the SOCs of Metabolism and nutrition disorders (32.9%), Vascular disorders (30.8%), and Musculoskeletal and connective tissue disorders (28.0%). The incidences of any previous and ongoing medical history conditions at Baseline by SOC were generally similar between the bimekizumab 320mg Q4W group and the placebo group.

Overall, the most frequently reported medical history conditions at Baseline by PT were hypertension (28.7%), obesity (11.3%), and type 2 diabetes mellitus (9.2%). The incidences of previous or ongoing medical history conditions at Baseline by PT were generally similar between the bimekizumab 320mg Q4W group and the placebo group.

The incidence of prior corticosteroid use was lower in the bimekizumab 320mg Q4W group (23.5%) compared with the placebo group (29.1%).

The use of any past PSO medications and biological treatment was generally similar between the bimekizumab 320mg Q4W group (98.0%) and the placebo group (100%).

Table 28 - Treatment compliance during the Initial Treatment Period (SS)

	PBO N=86	BKZ 320mg Q4W N=349
Treatment compliance, n	86	349
Mean (SD)	99.018 (5.584)	99.729 (2.591)
Min, max	50.00, 100.00	75.00, 100.00
Overall compliance <75%, n (%)	1 (1.2)	0
Overall compliance ≥75%, n (%)	85 (98.8)	349 (100)

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

Treatment compliance during the Randomized-Withdrawal Period and during the escape treatment period was high and similar across treatment groups 2 study participants (1.9%) in the bimekizumab 320mg Q4W/placebo group had <75% compliance and 4 study participants (2.2%) had <75% compliance respectively.

Outcomes and estimation

Table 29 - Summary of co-primary and secondary efficacy analysis results based on the predefined fixed testing sequence (RS) Study PS0013

Ordered Sequential Procedure	Variables	Visit	Response rate		p-value	Significant
			PBO n (%)	BKZ n (%)		
Co-primary						
#1: BKZ 320mg Q4W vs. PBO	PASI90	Week 16	1 (1.2)	317 (90.8)	<0.001	Yes
#2: BKZ 320mg Q4W vs. PBO	IGA 0/1	Week 16	1 (1.2)	323 (92.6)	<0.001	Yes
Secondary						
#3: BKZ 320mg Q4W vs. PBO	PASI100	Week 16	1 (1.2)	238 (68.2)	<0.001	Yes
#4: BKZ 320mg Q4W vs. PBO	IGA 0	Week 16	1 (1.2)	243 (69.6)	<0.001	Yes
#5: BKZ 320mg Q4W vs. PBO	PASI75	Week 4	1 (1.2)	265 (75.9)	<0.001	Yes
#6: BKZ 320mg Q4W vs. PBO	PSD item pain response	Week 16	6 (9.0)	201 (78.8)	<0.001	Yes
#7: BKZ 320mg Q4W vs. PBO	PSD item itch response	Week 16	4 (5.6)	210 (75.5)	<0.001	Yes
#8: BKZ 320mg Q4W vs. PBO	PSD item scaling response	Week 16	4 (5.7)	223 (78.0)	<0.001	Yes
#9: BKZ 320mg Q4W vs. PBO	Scalp IGA 0/1 (in study participants with scalp PSO)	Week 16	5 (6.8)	286 (92.3)	<0.001	Yes
#10: BKZ 320mg Q4W+Q8W vs. PBO	PASI90 [a] (among Week 16 PASI90 responders)	Week 56	17 (16.2)	183 (88.8)	<0.001	Yes

BKZ=bimekizumab; IGA=Investigator's Global Assessment; NRI=non-responder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; PSD=Patient Symptom Diary; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks; RS=Randomized Set. Note: All tests were performed at a 2-sided alpha level of 0.05. PASI90/100/75=responses were based on at least 90%/100%/75% improvement from Baseline in PASI score, IGA 0/1=response was defined as Clear (0) or Almost Clear (1) with at least a 2-category improvement relative to Baseline, IGA 0=response was defined as Clear (0) with at least a 2-category improvement relative to Baseline, Scalp IGA 0/1=response was defined as Clear (0) or Almost Clear (1) with at least a 2-category improvement relative to Baseline. Patient Symptom Diary pain/itch/scaling responses were based on item scores less than

thresholds of 1.98/2.39/2.86 respectively. The responder analysis was limited to the study participants with a Baseline PSD score at or above the applicable threshold score. For binary variables, p-values were based on using a stratified Cochran-Mantel-Haenszel test, where region and prior biologic exposure (yes/no) were used as stratification variables. Study participants with missing data at a given week were counted as non-responders (NRI). (a) Study participants who met the criterion for relapse were also counted as non-responders (NRI).

Co-primary efficacy variables

Primary analysis of the co-primary efficacy variables

PASI90 response at Week 16

The bimekizumab 320mg Q4W group was superior compared with the placebo group for the co-primary endpoint of PASI90 response rate at Week 16 (90.8% vs 1.2%, respectively). This difference was statistically significant and clinically meaningful, with an odds ratio of 496.318 (p<0.001).

A summary of the co-primary analysis of PASI90 response at Week 16 is presented for the RS (NRI) in table below.

Table 30 - PASI90 response rates at Week 16 (RS [NRI]) Study PS0013

	PBO N=86	BKZ 320mg Q4W N=349
PASI90 response rate		
n (%)	1 (1.2)	317 (90.8)
n/Nsub (%)	1/83 (1.2)	317/340 (93.2)
Odds ratio vs PBO [a]	-	496.318
95% CI for odds ratio	-	82.798, 2975.086
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; NRI=non-responder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set. Note: In the n (%) row, study participants with missing data at Week 16 were counted as non-responders (NRI). In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for PASI or IGA at the given week, and percentages were calculated accordingly. (a) Odds ratio (BKZ/PBO) calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

IGA 0/1 response rate at Week 16

The bimekizumab 320mg Q4W group was superior compared with the placebo group for the co-primary endpoint of IGA 0/1 response rate at Week 16 (92.6% vs 1.2%, respectively). This difference was statistically significant and clinically meaningful, with an odds ratio of 657.255 (p<0.001)

A summary of the co-primary analysis of IGA 0/1 response at Week 16 is presented for the RS (NRI) in table below.

Table 31 - IGA 0/1 response rates at Week 16 (RS [NRI]) Study PA0013

	PBO N=86	BKZ 320mg Q4W N=349
IGA 0/1 response rate		
n (%)	1 (1.2)	323 (92.6)
n/Nsub (%)	1/83 (1.2)	323/340 (95.0)
Odds ratio vs PBO [a]	-	657.255
95% CI for odds ratio	-	105.792, 4083.333
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA= Investigator's Global Assessment; NRI=non-responder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set Note: In the n (%) row, study participants with missing data at Week 16 were counted as non-responders (NRI). Note: In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for IGA at the given week, and percentages were calculated accordingly. IGA 0/1 response was defined as Clear (0) or Almost Clear (1) with at least a 2-category improvement from Baseline. (a) Odds ratio (BKZ/PBO) calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

Sensitivity analyses of the co-primary efficacy variables

The results of the sensitivity analyses of the co-primary efficacy variables were supportive of the co-primary efficacy results. When PASI90 and IGA 0/1 response rates were analyzed with alternative missing data assumptions (MI using MCMC monotone or reference-based regression, OC, or LOCF), with additional analysis sets (FAS or PPS), and an additional analysis method (logistic regression), the bimekizumab 320mg Q4W group maintained higher PASI90 and IGA 0/1 response rates compared with the placebo group (nominal p<0.001 for all comparisons).

Additionally, there was no evidence that specific sites or regions were contributing disproportionately to the co-primary efficacy results.

Secondary efficacy analyses

Primary analysis of the secondary efficacy variables

PASI100 response at Week 16

The bimekizumab 320mg Q4W group had a higher PASI100 response rate compared with the placebo group at Week 16, a difference that was statistically significant and clinically meaningful (68.2% vs 1.2%, respectively; p<0.001).

A summary of PASI100 response at Week 16 is presented for the RS (NRI) in table below.

Table 32 - PASI 100 response rates at Week 16 (RS [NRI]) Study PS0013

	PBO N=86	BKZ 320mg Q4W N=349
PASI100 response rate		
n (%)	1 (1.2)	238 (68.2)
n/Nsub (%)	1/83 (1.2)	238/340 (70.0)
Odds ratio vs PBO [a]	-	220.038
95% CI for odds ratio	-	28.757, 1683.639
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; NRI=non-responder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set. Note: In the n (%) row, study participants with missing data at Week 16 were counted as non-responders (NRI). In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for PASI at the given week, and percentages were calculated accordingly. (a) Odds ratio (BKZ/PBO) calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

IGA 0 response at Week 16

The bimekizumab 320mg Q4W group had a higher IGA 0 response rate compared with the placebo group at Week 16, a difference that was statistically significant and clinically meaningful (69.6% vs 1.2%, respectively; p<0.001).

A summary of IGA 0 response at Week 16 is presented for the RS (NRI) in table below.

Table 33 - IGA 0 response rates at Week 16 (RS [NRI]) Study PS0013

	PBO N=86	BKZ 320mg Q4W N=349
IGA 0 response rate		
n (%)	1 (1.2)	243 (69.6)
n/Nsub (%)	1/83 (1.2)	243/340 (71.5)
Odds ratio vs PBO [a]	-	224.744
95% CI for odds ratio	-	30.130, 1676.425
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=non-responder imputation; PBO=placebo; Q4W=every 4 weeks; RS=Randomized Set Note: In the n (%) row, study participants with missing data at Week 16 were counted as non-responders (NRI). Note: In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for IGA at the given week, and percentages were calculated accordingly. IGA 0 response was defined as Clear (0) with at least a 2-category improvement from Baseline. (a) Odds ratio (BKZ/PBO) calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

PASI75 response at Week 4

The bimekizumab 320mg Q4W group had a higher PASI75 response rate compared with the placebo group at Week 4 after only a single dose of bimekizumab, a difference that was statistically significant and clinically meaningful (75.9% vs 1.2%, respectively; p<0.001).

A summary of PASI75 response at Week 4 is presented for the RS (NRI) in table below.

Table 34 - PASI75 response rates at Week 4 (RS [NRI]) Study PS0013

	PBO N=86	BKZ 320mg Q4W N=349
PASI75 response rate		
n (%)	1 (1.2)	265 (75.9)
n/Nsub (%)	1/85 (1.2)	265/348 (76.1)
Odds ratio vs PBO [a]	-	316.641
95% CI for odds ratio	-	39.423, 2543.254
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; NRI=non-responder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; RS=Randomized Set Note: In the n (%) row, study participants with missing data at a given week were counted as non-responders. In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for PASI at the given week, and percentages were calculated accordingly. (a) Odds ratio (BKZ/PBO) calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

PSD response at Week 16

The bimekizumab 320mg Q4W group had higher PSD response rates based on pain, itch, and scaling item scores compared with the placebo group at Week 16, differences that were statistically significant (78.8% vs 9.0%, 75.5% vs 5.6%, and 78.0% vs 5.7%, respectively; p<0.001 for all comparisons).

A summary of PSD response rates based on pain, itch, and scaling item scores at Week 16 is presented for the RS (NRI) in table below.

Table 35 - PSD response rates based on pain, itch, and scaling item scores at Week 16 (RS [NRI]) Study PS0013

	PBO N=86	BKZ 320mg Q4W N=349
Pain (# of study participants with Baseline ≥1.98)		
Baseline, n	67	255
n (%)	6 (9.0)	201 (78.8)
n/Nsub (%)	6/53 (11.3)	201/210 (95.7)
Odds ratio vs PBO [a]	-	34.325
95% CI for odds ratio	-	14.220, 82.856
p-value [b]	-	<0.001
Itch (# of study participants with Baseline ≥2.39)		
Baseline, n	72	278
n (%)	4 (5.6)	210 (75.5)
n/Nsub (%)	4/56 (7.1)	210/230 (91.3)
Odds ratio vs PBO [a]	-	43.497
95% CI for odds ratio	-	15.728, 120.295
p-value [b]	-	<0.001
Scaling (# of study participants with Baseline ≥2.86)		
Baseline, n	70	286
n (%)	4 (5.7)	223 (78.0)
n/Nsub (%)	4/54 (7.4)	223/237 (94.1)
Odds ratio vs PBO [a]	-	60.946
95% CI for odds ratio	-	20.560, 180.669
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; NRI=non-responder imputation; PBO=placebo; PSD=Patient Symptom Diary; Q4W=every 4 weeks; RS=Randomized Set Note: In the n (%) row, study participants with missing data at a given week were counted as non-responders. The denominator was the number of study participants with Baseline value greater than or equal to the responder threshold. In the Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for PSD, and percentages were calculated accordingly. (a) Odds ratio calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

Scalp IGA 0/1 response at Week 16 for study participants with scalp PSO at Baseline

A scalp IGA 0/1 response was defined as Clear (0) or Almost Clear (1) with at least a 2-category improvement from Baseline. Only study participants with a Baseline score of ≥2 were included in the responder analysis.

The bimekizumab 320mg Q4W group had a higher scalp IGA 0/1 response rate compared with the placebo group at Week 16, a difference that was statistically significant and clinically meaningful (92.3% vs 6.8%, respectively; p<0.001).

A summary of scalp IGA 0/1 response at Week 16 is presented for the RS (NRI) in table below.

Table 36 - Scalp IGA 0/1 response (for study participants with scalp PSO at Baseline) at Week 16 (RS [NRI]) Study PS0013

	PBO N=74	BKZ 320mg Q4W N=310
Scalp IGA 0/1 response rate		
n (%)	5 (6.8)	286 (92.3)
n/Nsub (%)	5/71 (7.0)	286/303 (94.4)
Odds ratio vs PBO [a]	-	158.000
95% CI for odds ratio	-	49.263, 506.745
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=non-responder imputation; PBO=placebo; PSO=psoriasis; Q4W=every 4 weeks; RS=Randomized Set. Note: In the n (%) row, study participants with missing data at a given week were counted as non-responders (NRI). In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement at the given week, and percentages were calculated accordingly (observed case). Only study participants with a scalp IGA of ≥2 at Baseline were included. A scalp IGA 0/1 response was defined as Clear (0) or Almost Clear (1) with ≥2 category improvement from Baseline. (a) Odds ratio: BKZ/PBO calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

PASI90 response at Week 56 among Week 16 PASI90 responders

Among Week 16 PASI90 responders, the bimekizumab 320mg Q4W/Q4W + Q8W group had a higher PASI90 response rate compared with the bimekizumab 320mg Q4W/placebo group at Week 56, a difference that was statistically significant and clinically meaningful (88.8% vs 16.2%, respectively; p<0.001).

A summary of PASI90 response at Week 56 is presented for the WK16ResS (NRI) in table below.

Table 37 - PASI90 response at Week 56 among Week 16 PASI90 responders (WK16ResS [NRI]) Study PS0013

	BKZ 320mg Q4W/PBO N=105	BKZ 320mg Q4W/Q4W + Q8W N=206
PASI90 response rate		
n (%)	17 (16.2)	183 (88.8)
n/Nsub (%)	17/33 (51.5)	183/186 (98.4)
Odds ratio vs PBO [a]	-	47.406
95% CI for odds ratio	-	22.087, 101.750
p-value [b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; NRI=non-responder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks; WK16ResS=Week 16 Responder Set. In the n (%) row, study participants with missing data at Week 56 or who met the criterion for relapse were counted as non-responders (NRI). In the n/Nsub (%) row, Nsub represents the number of study participants with a non-missing measurement for PASI at the given week, and percentages were calculated accordingly. (a) Odds ratio: BKZ/PBO calculated using stratified CMH test with region and prior biologic exposure as stratification variables. (b) P-values for the comparison of treatment groups were based on the CMH test from the general association.

When compared by individual treatment groups, a clinically meaningful difference in the PASI90 response rate was observed in study participants in the bimekizumab 320mg Q4W/Q4W and bimekizumab 320mg Q4W/Q8W groups compared with study participants in bimekizumab 320mg Q4W/placebo group at Week 56 (86.8% and 91.0% vs 16.2%, respectively; nominal p<0.001 for both comparisons).

Sensitivity analyses of the secondary efficacy variables

The results of the sensitivity analyses of the secondary efficacy variables were supportive of the secondary efficacy results. When secondary efficacy variables were analyzed with alternative missing data assumptions (MI using MCMC monotone regression or OC), the bimekizumab group had higher response rates for all secondary variables compared with the placebo group (nominal p<0.001 for all comparisons).

Other efficacy analyses – Randomized-Withdrawal Period

Across the spectrum of other efficacy endpoints measuring disease symptoms and severity

(PASI, IGA, scalp IGA, BSA affected by PSO, IGAxBSA, pp-IGA, mNAPSI), study participants who remained on bimekizumab 320mg Q4W or Q8W maintained clinically meaningful improvements from Week 16 to Week 56 compared with study participants who were re-randomized to withdrawal from bimekizumab. Loss of clinical improvements generally became evident after 12 weeks of withdrawal from bimekizumab treatment (ie, after Week 24).

Few study participants receiving bimekizumab relapsed during the study. Overall, there were no notable, consistent differences in the efficacy profile of maintenance treatment (ie, from Week 16 through Week 56) with bimekizumab 320mg administered Q4W versus Q8W.

No study participants experienced a rebound (defined as when a study participant experienced a $\geqslant$ 25% increase from Initial Treatment Period Baseline in PASI score occurring within 2 months [60 days] of stopping therapy [ie, being re-randomized to placebo]).

At Week 56, all subgroups had a clinically meaningful difference in the bimekizumab groups compared with the placebo group in PASI90 and IGA 0/1 response rates. It should be noted that the sample sizes for many of the subgroup categories in the subgroup analyses were relatively small; therefore, interpretation of these data should be made with caution.

Patient-reported outcomes

Consistent with treatment effect on clinical disease manifestations, at Week 16 of the Initial Treatment Period, the DLQI 0 or 1 rate was higher in the bimekizumab 320mg Q4W group compared with the placebo group (75.6% vs 5.8%, respectively; nominal p<0.001).

During the Randomized-Withdrawal Period, the DLQI 0 or 1 rates were maintained from Week 16 to Week 56 in the bimekizumab 320mg Q4W/Q4W (83.0% to 76.4%, respectively) and bimekizumab 320mg Q4W/Q8W groups (73.0% to 86.0%, respectively) but declined from Week 16 to Week 56 in the bimekizumab 320mg Q4W/placebo group (79.0% to 19.0%, respectively).

Immunologic conclusions

During the Combined Initial and Randomized-Withdrawal Period, the incidence of study participants who were ADAb positive at 1 visit or more was similar between the bimekizumab 320mg Q4W/Q4W and bimekizumab 320mg Q4W/Q8W groups (52.1% vs 49.5%, respectively).

In the bimekizumab 320 mg Q4W/Q4W and bimekizumab 320 mg Q4W/Q8W groups, the incidence of Baseline ADAb was low (3.2% each [3/94 and 3/93 study participants in the bimekizumab 320 mg Q4W/Q4W and bimekizumab 320 mg Q4W/Q8W groups, respectively]).

One study participant (1.1%) in the bimekizumab 320 mg Q4W/Q4W group and 2 study participants (2.2%) in the bimekizumab 320mg Q4W/Q8W group had boosted ADAb titers during the Combined Initial and Randomized-Withdrawal Period.

The plasma concentration levels of bimekizumab 320mg Q4W and Q8W were reduced slightly at Week 16 through Week 56 in study participants who were ADAb positive compared with those who were ADAb negative.

Overall, ADAb status had no clear impact on efficacy in the bimekizumab 320mg Q4W group at Week 16, or the bimekizumab 320mg Q4W/Q4W and bimekizumab 320mg Q4W/Q8W groups at Week 56, as measured by PASI90, and IGA 0/1, and PASI100 response rates.

Subgroup analyses

Subgroup analyses were conducted for PASI90 response, IGA 0/1 response, and PASI100 response across the following subgroups: age (<40 years, 40 to <65 years, ≥65 years); gender (male, female); duration of disease (<median [17.22] years, ≥ median [17.22] years); geographic region (North America, Western Europe, Central/Eastern Europe, Asia/Australia); body weight (≤100kg, >100kg), BMI (<25kg/m2, ≥25 to <30kg/m2, ≥30kg/m2); prior systemic phototherapy or chemophototherapy (yes, no); prior systemic therapy (yes, no); prior biologic therapy (yes, no); Baseline PASI score (<20, ≥20) and ADAb status (negative, positive).

Due to the small sample size of some subgroups, results should be interpreted with caution.

Consistent, clinically meaningful improvements in PASI90 response were observed for the bimekizumab 320mg Q4W group compared with the placebo group at Week 16 across all subgroups.

PASI90 response rates at Week 16 were generally similar across subgroups. Response rates in the bimekizumab 320mg Q4W group were higher in Central/Eastern Europe (98.1%) compared with the remaining regions (range: 84.3% to 85.7%).

Response rates in the bimekizumab 320mg Q4W group were higher in study participants weighing ≤ 100kg (93.5%) compared with study participants weighing >100kg (83.0%).

Summary of efficacy for study PS0013

Title: A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study with an Initial Treatment Period Followed by a Randomized-Withdrawal Period to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis	
Study identifier	PS0013 EudraCT Number: 2016-003426-16 NCT03410992

Design	PS0013 is a randomized, double-blind placebo-controlled study consisting of a 16-week Initial Treatment Period followed by a 40-week Randomized-Withdrawal Period to evaluate the efficacy and safety of bimekizumab administered subcutaneously in adult study participants with moderate to severe chronic plaque psoriasis. Study participants who did not achieve a PASI90 response at Week 16 of the Initial Treatment Period or who relapsed after Week 20 were allocated to bimekizumab escape treatment		
	Duration of initial treatment phase: Duration of randomized-withdrawal phase: Duration of Safety Follow up (SFU):		16 weeks 40 weeks SFU Visit was planned 20 weeks after the final dose of IMP (for study participants not enrolling in open-label study PS0014)
Hypothesis	Superiority to placebo		
Treatment groups	**Initial Treatment Period**: Placebo (PBO)		Placebo 16 weeks 86 randomized
	Initial Treatment Period: Bimekizumab (BKZ) 320mg Q4W		Bimekizumab 320mg Q4W 16 weeks 349 randomized All participants who achieved PASI90 response at Week 16 were re-randomized to double-blind placebo, BKZ Q4W, or BKZ Q8W in 1:1:1 ratio in the Randomized-
	Randomized-Withdrawal Period: Re-randomized to placebo (BKZ 320mg Q4W/PBO)		Placebo from Week 16 to Week 56 105 responders were re-randomized to placebo
	Randomized-Withdrawal Period: Re-randomized to BKZ Q4W or Q8W (BKZ 320mg Q4W/Q4W or Q4W/Q8W)		BKZ Q4W or Q8W from Week 16 to Week 56: • 100 responders were re-randomized to BKZ 320mg Q8W • 106 responders were re-randomized to BKZ 320mg Q4W
Endpoints and definitions	Co-primary endpoints	PASI90 and IGA 0/1 at Week 16	Proportion of participants who achieved a PASI90 response at Week 16 and proportion of participants who achieved an IGA 0/1 response at Week 16 (superiority vs. placebo)
	Secondary endpoints	PASI100 at Week 16	Proportion of participants who achieved a PASI100 response at Week 16 (superiority vs. placebo)
		IGA 0 at Week 16	Proportion of participants who achieved an IGA 0 response at Week 16 (superiority vs. placebo)
		PASI75 response at Week 4	Proportion of participants who achieved a PASI75 response at Week 4 (superiority vs. placebo)

		PSD responses for pain, itch, and scaling at Week 16	Proportion of participants who achieved responder definition threshold for each item at Week 16 (superiority vs. placebo)
		Scalp IGA 0/1 at Week 16	Proportion of participants who achieved a Scalp IGA response 0/1 at Week 16 for study participants with scalp PSO at Baseline ≥2 (superiority vs. placebo)
		PASI90 at Week 56 among Week 16 PASI90 responders	Proportion of participants who achieved a PASI90 response at Week 56 among Week 16 PASI90 responders (superiority vs. placebo) during Randomized-Withdrawal Period
Database lock	05 Mar 2020		

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Intent to treat (Randomized Set) Week 16		
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W
	Number of participan	86	349
	PASI90 Week 16 n/N (%)	1/86 (1.2%)	317/349 (90.8%)
	IGA 0/1 Week 16 n/N (%)	1/86 (1.2%)	323/349 (92.6%)
Effect estimate per comparison	Co-primary endpoints	Comparison groups	Bimekizumab vs. placebo
		p-value	p<0.001
Notes	Both co-primary endpoints at week 16 were highly statistically significant demonstrating superiority over placebo with p<0.001		
Analysis description	**Secondary analysis**		
Analysis population and time point description	Intent to treat (Week 4, Week 16)		
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg Q4W
	Number of participants	86	349
	PASI100 at Week 16 n/N (%)	1/86 (1.2%)	238/349 (68.2%)
	IGA 0 at Week 16 n/N (%)	1/86 (1.2%)	243/349 (69.6%)

	PASI75 at Week 4 n/N (%)	1/86 (1.2%)	265/349 (75.9%)
	PSD responses for pain at Week 16 (in participants with Baseline ≥1.98) n/N (%)	6/67 (9.0%)	201/255 (78.8%)
	PSD responses for itch at Week 16 (participants with Baseline ≥2.39)) n/N (%)	4/72 (5.6%)	210/278 (75.5%)
	PSD responses for scaling at Week 16 (participants with Baseline ≥2.86)	4/70 (5.7%)	223/286 (78.0%)
	Scalp IGA 0/1 at Week 16 (participants with a Baseline scalp IGA ≥2) n/N (%)	5/74 (6.8%)	286/310 (92.3%)
Analysis description	**Secondary analysis**		
Analysis population and time point	Week 16 Responder Set (Week 56)		
Descriptive statistics and estimate variability	Treatment group	PBO	BKZ 320mg total (BKZ 320mg Q4W/Q4W and Q4W/Q8W)
	Number of PASI90 responders at Week 16	105	206
	PASI90 at Week 56 among Week 16 PASI90 responders n/N (%)	17/105 (16.2%)	183/206 (88.8%)
Effect estimate per comparison	Secondary endpoints (all)	Comparison groups	Bimekizumab vs. placebo
		p-value	p<0.001
Notes	All secondary endpoints were highly statistically significant in favor of bimekizumab treatment with p<0.001		

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

Integrated efficacy analyses were conducted for the efficacy pools described below.

Description of efficacy pools

Pool name	Studies included in pool	Treatment groups included in pool	Treatment Periods included in pool	Purpose of pool
E1	PS0009 PS0013	Study participants randomized to: BKZ 320mg Q4W PBO	Initial Treatment Period (Weeks 0 to 16)	Investigate subgroups; add precision to treatment effect (BKZ vs PBO) through Week 16 in applicable Phase 3 studies
E2	PS0008 PS0009 PS0013	Maintenance dose regimens: BKZ 320mg Q4W BKZ 320mg Q8W	Maintenance Treatment Period (Weeks 16 to 52)	Assess maintenance of response through Week 52 on 2 BKZ dose regimens among study participants with an initial response at Week 16
E3	PS0008 PS0009	Study participants randomized to: BKZ 320mg Q4W (PS0009) BKZ 320mg Q4W/Q4W (PS0008)[a]	Initial and Maintenance Treatment Periods (Weeks 0 to 52)	Obtain pooled estimates of efficacy after 1 year on BKZ 320mg Q4W based on the ITT principle

BKZ=bimekizumab; ITT=intent-to-treat; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks

[a] BKZ 320mg Q4W/Q4W refers to study participants that maintain BKZ Q4W (and do not switch to Q8W) after Week 16

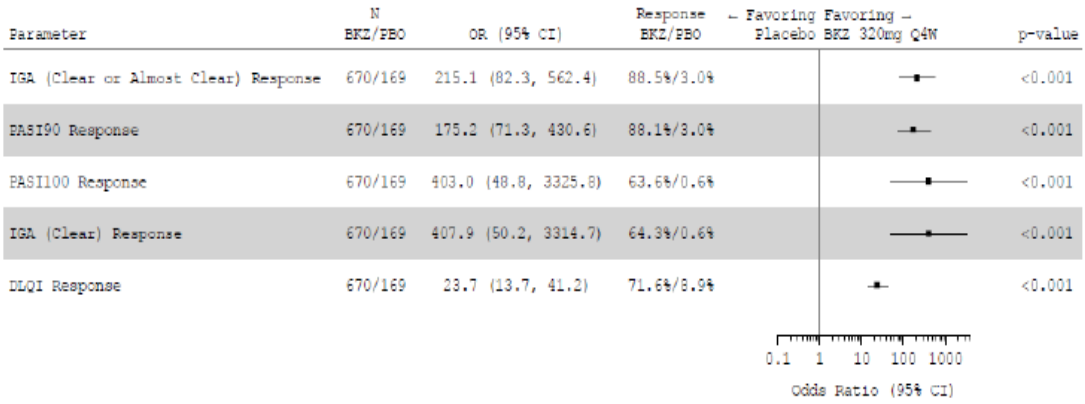
Pooled efficacy results

Pool E1 (Placebo controlled)

Pool E1 (placebo-controlled) combined efficacy data from PS0009 and PS0013 to assess the response through Week 16. Results demonstrated that:

- Bimekizumab 320mg Q4W demonstrated superior response rates compared with placebo for PASI90, IGA 0/1, PASI100, and IGA 0 at Week 16. Similar results were observed for all other efficacy outcome measures analyzed.
- PASI90, IGA 0/1, and PASI100 response rates in the bimekizumab group at Week 16 were generally similar across subgroups. There were no notable differences in PASI90 or IGA 0/1 responder rates in the key subgroups of disease severity (baseline PASI<20, PASI≥20) or weight, and no notable difference in PASI100 responder rates with disease severity (PASI<20, PASI≥20). The neutralizing antibody (NAb) status showed some differences at Week 16; however, no impact on efficacy was observed after longer exposure.

Efficacy Pool E1 (Placebo controlled data to Week 16): IGA 0/1, PASI90, PASI100, IGA and DLQI



BKZ=bimekizumab; CI=confidence interval; DLQI=Dermatology Life Quality Index; IGA=Investigator's Global Assessment; OR=odds ratio; PASI=Psoriasis Area and Severity Index; PBO=placebo; PSO=psoriasis; Q4W=every 4 weeks
Note: Nominal p-values

Pool E1 (Placebo controlled data to Week 16: Primary endpoints (NRI)

	PASI90 response rate		IGA 0/1 response rate	
Statistic	Placebo N=169	BKZ 320mg Q4W N=670	Placebo N=169	BKZ 320mg Q4W N=670
n (%)	5 (3.0)	590 (88.1)	5 (3.0)	593 (88.5)
n/Nsub (%)	5/159 (3.1)	590/647 (91.2)	5/159 (3.1)	593/647 (91.7)
Odds ratio vs PBO [a]	-	175.176	-	215.134
95% CI for odds ratio	-	71.262, 430.616	-	82.290, 562.436
Nominal p-value [b]	-	<0.001	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks
[a] Odds ratio calculated using stratified CMH test with region and prior biologic exposure as stratification variables.
[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.
Note: Study participants with missing data at a given week were counted as nonresponders.
Note: In the n/Nsub (%) row, Nsub represents the number of study participants with a nonmissing measurement, and percentages were calculated accordingly.

Pool E1 (Placebo controlled data to Week 16: Secondary endpoints (NRI)

Statistic	PASI100 response rate		IGA 0 response rate	
	Placebo N=169	BKZ 320mg Q4W N=670	Placebo N=169	BKZ 320mg Q4W N=670
n (%)	1 (0.6)	426 (63.6)	1 (0.6)	431 (64.3)
n/Nsub (%)	1/159 (0.6)	426/647 (65.8)	1/159 (0.6)	431/647 (66.6)
Odds ratio vs PBO [a]	-	402.978[a]	-	407.921
95% CI for odds ratio	-	48.828, 3325.797	-	50.201, 3314.650
Nominal p-value [b]	-	<0.001[b]	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; PBO=placebo; Q4W=every 4 weeks

Note: Study participants with missing data at a given week were counted as nonresponders.

Note: Nsub represents the number of study participants with a non-missing measurement for PASI or IGA, and percentages were calculated accordingly.

[a] Odds ratio calculated using stratified CMH test with region and prior biologic exposure as stratification variables.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

Bimekizumab 320mg Q4W demonstrated higher response rates compared with placebo for PASI75 response rate at Week 4 (76.4% versus 1.8%, respectively; nominal p<0.001. A clinically meaningful difference in PASI75 response rate was observed as early as Week 2.

Treatment with bimekizumab 320mg Q4W resulted in higher PSD response rates at Week 16 (nominal p<0.001) for pain, itch and scaling compared to placebo, based on the pre-specified response thresholds (pain ≥1.98, itch ≥2.39, and scaling ≥2.86. Results were consistent with data for the underlying individual studies (PS0009 and PS0013.

A supportive sensitivity analysis for PSD response using a more stringent threshold of ≥4 in the 3 PSD items performed for Pool E1 confirmed the results of the prespecified main analysis (nominal p<0.001 for all comparisons). Of note: PSD compliance was slightly higher in the bimekizumab 320mg Q4W group.

The bimekizumab 320mg Q4W group had a higher scalp IGA 0/1 response rate compared with the placebo group at Week 16 (88.4% versus 11.0%, nominal p<0.001), differences that were clinically meaningful. A clinically meaningful difference in scalp IGA 0/1 response rate was observed as early as Week 1

Pool E1 (Study PS0009 & PS0013): Sensitivity analysis PSD results at Week 16 (NRI)

	Pain (study participants with Baseline ≥4)		Itch (study participants with Baseline ≥4)		Scaling (study participants with Baseline ≥4)	
	PBO N=97	BKZ 320mg Q4W N=399	PBO N=113	BKZ 320mg Q4W N=466	PBO N=121	BKZ 320mg Q4W N=487
n (%)	5 (5.2)	288 (72.2)	6 (5.3)	312 (67.0)	7 (5.8)	369 (75.8)
n/Nsub (%)	5/73 (6.8)	288/325 (88.6)	6/86 (7.0)	312/387 (80.6)	7/91 (7.7)	369/406 (90.9)
Odds ratio vs PBO [a]	-	47.469	-	38.053	-	43.509
95% CI for odds ratio	-	17.988, 125.270	-	15.869, 91.252	-	19.498, 97.090
p-value [b]	-	<0.001	-	<0.001	-	<0.001

BKZ=bimekizumab; CI=confidence interval; CMH=Cochran-Mantel-Haenszel; NRI=nonresponder imputation; PBO=placebo; PSD=Patient Symptom Diary; Q4W=every 4 weeks

Note: Study participants with missing data at a given week were counted as nonresponders in the n (%) row.

Note: In the n/Nsub(%) row, Nsub represents the number of study participants with a non-missing measurement, and percentages were calculated accordingly.

Note: PSD score for each item was an average value of the week prior to the visit.

Note: The threshold criteria are improvement from Baseline. Analysis was limited to study participants with a Baseline score at or above the applicable threshold score.

[a] Odds ratio calculated using stratified CMH test with study, region, and prior biologic exposure as stratification variables. Logit method was used where CMH test not possible due to very low response.

[b] p-values for the comparison of treatment groups were based on the CMH test from the general association.

In Pool E1, in the bimekizumab 320mg Q4W group, the DLQI 0 or 1 rate increased rapidly through Week 8 and continued to increase steadily through Week 16. The DLQI 0 or 1 rate was higher in the bimekizumab 320mg Q4W group compared with the placebo group at Week 1 through Week 16; with a clinically meaningful difference at Week 16 (nominal p<0.001).

Mean Baseline PSD scores for pain, itch, and scaling were similar between the treatment groups. In the bimekizumab 320mg Q4W group, consistent improvements in the PSD item scores of pain, itch, and scaling were observed from Week 1 to Week 16, while no change was observed in the placebo group.

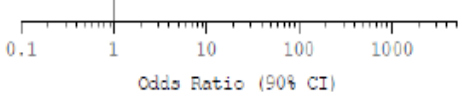
In both Phase 3 studies that comprise Pool E1 (PS0009 and PS0013), treatment with bimekizumab 320mg Q4W demonstrated marked improvements for both physician-assessed and patient-assessed signs and symptoms of PSO, which were rapid and sustained over time for the other efficacy variables.

In Pool E1, bimekizumab 320mg Q4W demonstrated superior response rates compared with placebo for the efficacy endpoint of BSA ≤1 response rate at Week 16 (76.4% versus 0.6%, respectively; nominal p<0.001). A difference in the BSA response rate began as early as Week 2 (6.1% versus 0.6% for bimekizumab 320mg Q4W and placebo, respectively; nominal p=0.003) and a clinically meaningful difference was observed as early as Week 4 (25.7% versus 1.2% for bimekizumab 320mg Q4W and placebo, respectively; nominal p<0.001), consistent with other efficacy endpoints.

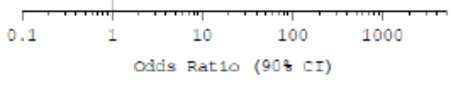
Comparison of results in Pool E1 Subgroups

Pool E1 PS0009 & PS0013 Placebo-controlled data: PASI90 responder rate at Week 16 (NRI)

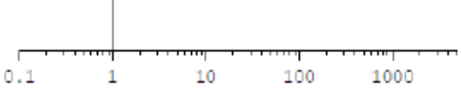
Subgroup	N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
Age (years)				
<40 yrs	303	53.8 (24.9, 116.6)	90.8%/0.0%	
40 - <65 yrs	467	125.8 (54.6, 289.8)	87.7%/5.0%	
>=65 yrs	69	15.0 (4.3, 52.5)	78.2%/0.0%	>0.999
Gender				
Male	602	118.7 (54.4, 258.7)	88.0%/4.2%	
Female	237	45.6 (20.4, 101.7)	89.2%/0.0%	0.981
Race				
White	703	182.1 (77.6, 427.2)	88.8%/2.8%	
Non-White	136	150.7 (24.2, 938.3)	84.4%/3.7%	0.373
PSO disease duration (years)				
<Median [15.58]	418	133.0 (49.7, 356.0)	88.0%/3.9%	
>=Median [15.58]	421	287.1 (81.0, 1017.3)	88.1%/2.2%	0.524

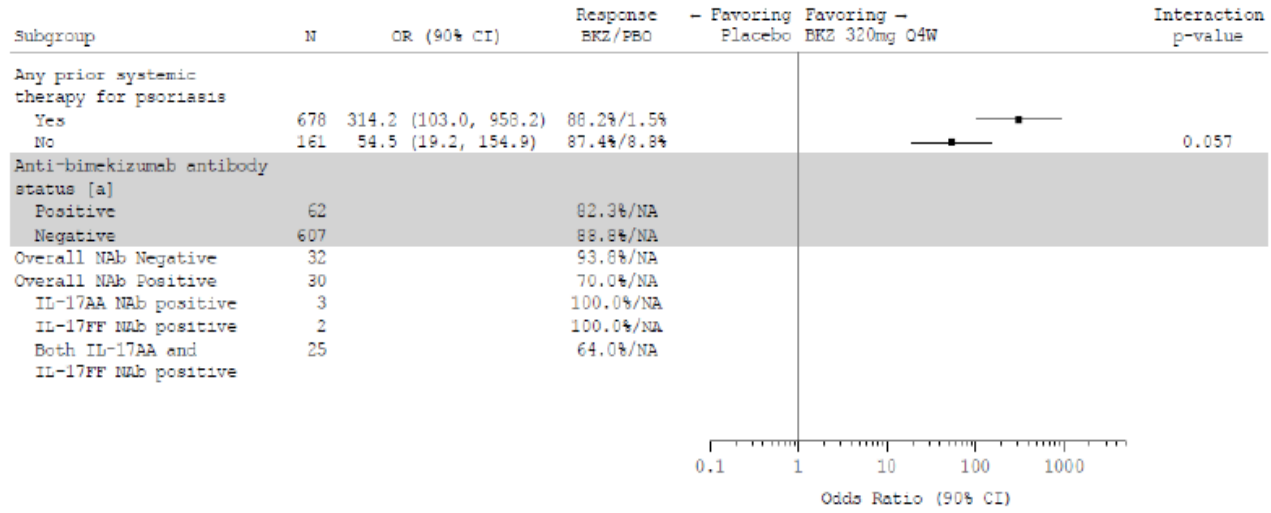


Subgroup	N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
Geographical region				
North America	300	77.5 (28.7, 209.4)	92.9%/5.0%	
Western Europe	100	44.0 (12.0, 161.5)	81.0%/0.0%	
Central/Eastern Europe	335	946.3 (183.9, 4868.9)	95.5%/1.5%	
Asia/Australia	104	118.3 (19.7, 708.9)	85.5%/4.8%	0.159
Baseline BMI (kg/m2)				
<25	227	47.8 (20.8, 109.8)	92.0%/0.0%	
25-<30	261	115.3 (37.2, 357.4)	88.6%/3.3%	
>=30	351	123.1 (41.9, 361.7)	85.1%/4.3%	0.802
Baseline weight (kg)				
<=100	605	131.8 (58.9, 294.7)	89.9%/3.4%	
>100	234	280.6 (44.0, 1790.8)	83.1%/2.0%	0.968
Baseline disease severity				
PASI<20	498	105.1 (43.7, 252.7)	84.2%/3.6%	
PASI>=20	341	464.5 (91.6, 2357.2)	93.3%/1.7%	0.111



Subgroup	N	OR (90% CI)	Response BKZ/PBO	Interaction p-value
Prior biologic exposure				
Yes	350	114.3 (43.4, 300.9)	88.6%/0.0%	
No	489	100.5 (46.5, 217.4)	87.7%/5.1%	0.985
Prior anti-TNF exposure				
Yes	134	50.4 (15.7, 161.2)	86.1%/0.0%	
No	705	147.9 (69.8, 313.3)	88.4%/3.5%	0.987
Prior phototherapy or chemotherapy				
Yes	336	254.0 (63.5, 1016.7)	88.5%/3.0%	
No	503	145.3 (56.4, 374.2)	87.8%/2.9%	0.984
Prior anti-IL-17 exposure				
Yes	197	63.5 (22.9, 176.7)	88.8%/0.0%	
No	642	133.7 (62.7, 284.8)	87.8%/3.8%	0.984





BKZ=bimekizumab; CI=confidence interval; NA=not applicable; NRI=nonresponder imputation; OR=odds ratio; PASI=Psoriasis Area and Severity Index; PBO=placebo; PSO=psoriasis; Q4W=every 4 weeks

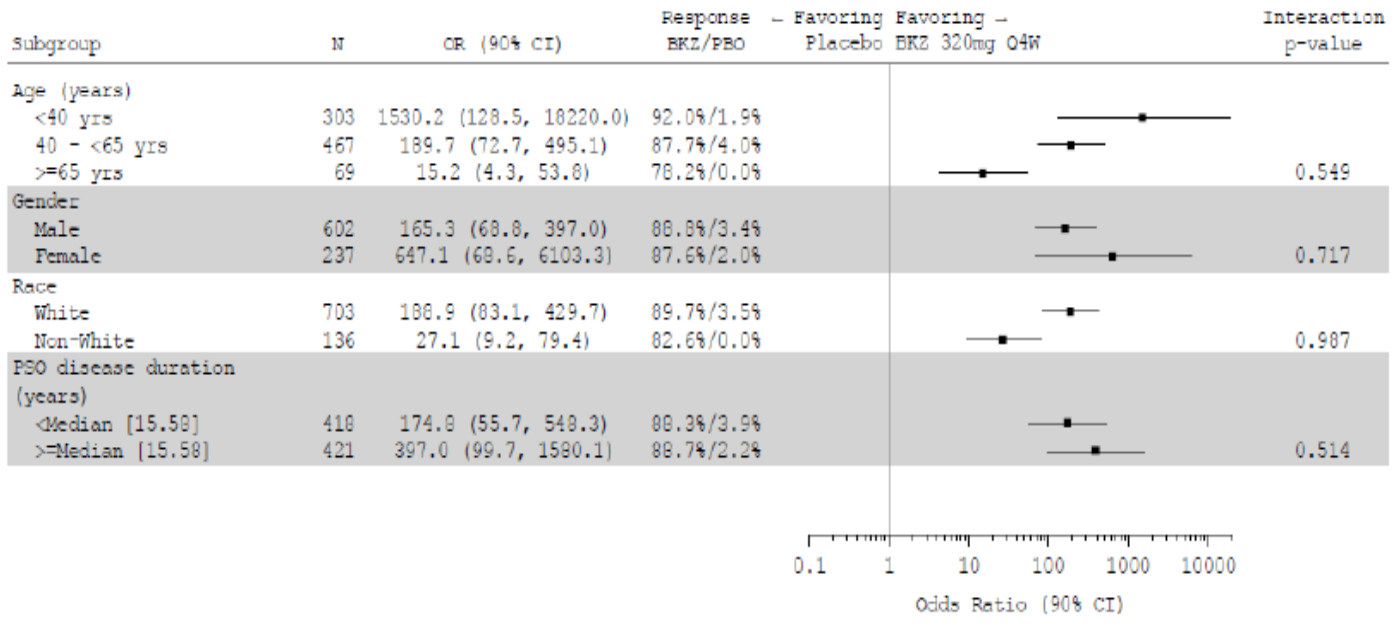
Note: Treatment by subgroup interaction p-values are from a logistic regression model with strata for study, region, and biologics exposure, and with fixed effects for treatment, subgroup, and treatment*subgroup interaction.

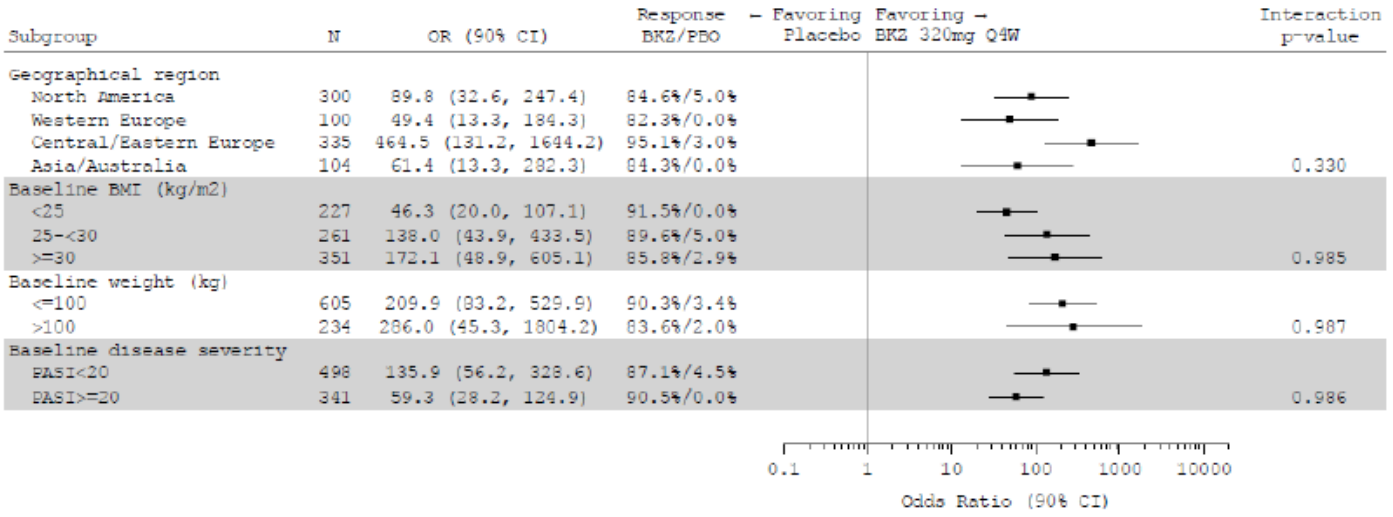
Note: Overall NAb status was summarized for anti-bimekizumab antibody positive study participants.

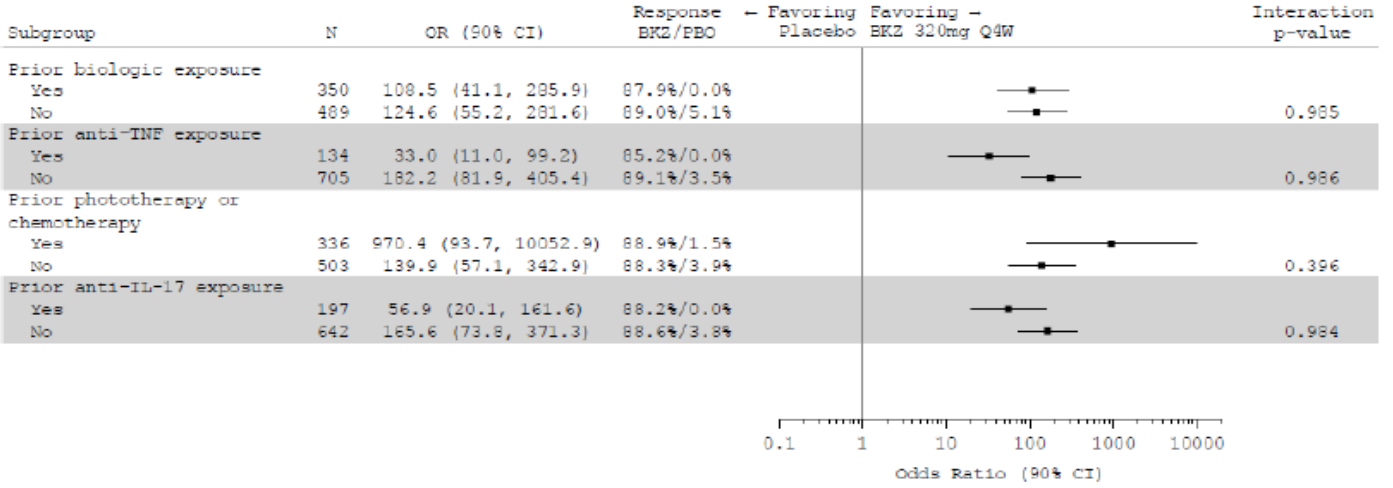
[a] Positive was defined as having at least 2 values that were confirmed positive during the treatment period. Treatment period did not include Baseline/pre-treatment samples or SFU.

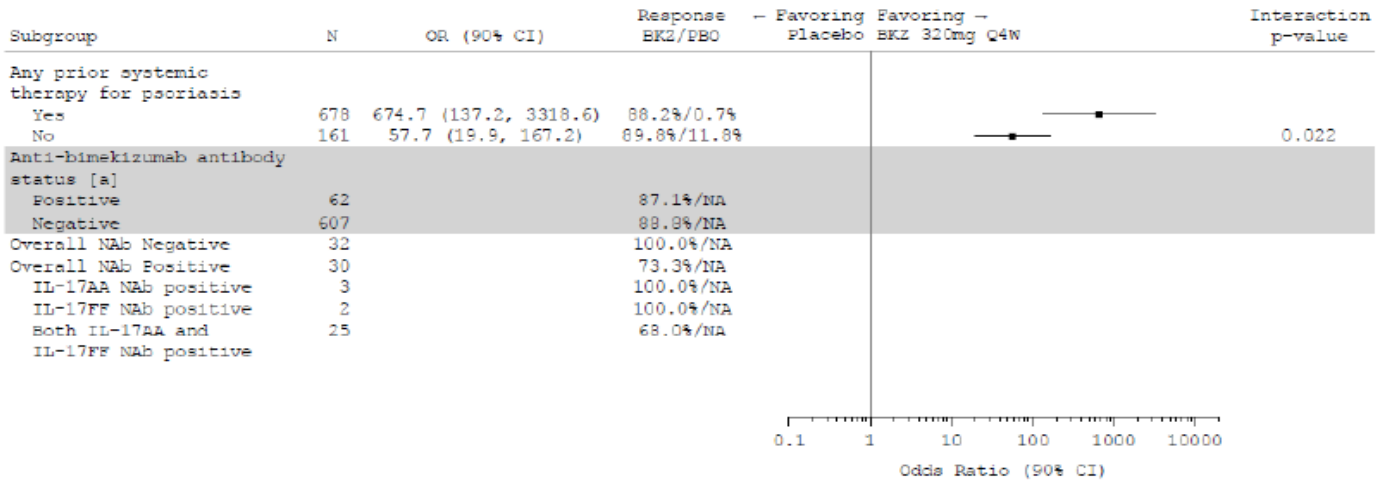
The applicant presented similar subgroup analyses for IGA 0/1 (the other element of the co-primary endpoint) response as follows.

Pool E1 PS0009 & PS0013 Placebo-controlled data: IGA 0/1 response rate at Week 16 (NRI)









ADAb=antidrug antibody; BKZ=bimekizumab; CI=confidence interval; IL=interleukin; NA=not applicable; NAb=neutralizing antibody; NRI=nonresponder imputation; OR=odds ratio; PASI=Psoriasis Area and Severity Index; PBO=placebo; PSO=psoriasis; Q4W=every 4 weeks; SFU=Safety Follow-Up
Note: Treatment by subgroup interaction p-values are from a logistic regression model with strata for study, region, and biologics exposure, and with fixed effects for treatment, subgroup, and treatment*subgroup interaction.
Note: Overall NAb status was summarized for anti-bimekizumab antibody-positive study participants.
[a] Positive was defined as having at least 2 values that were confirmed positive during the treatment period. Treatment period did not include Baseline/pretreatment samples or SFU.

Pool E2: Maintenance treatment period

Pool E2 combined efficacy data from the three pivotal studies, PS0008, PS0009, and PS0013 to assess maintenance of response. Maintenance of response to bimekizumab treatment was evaluated for 2

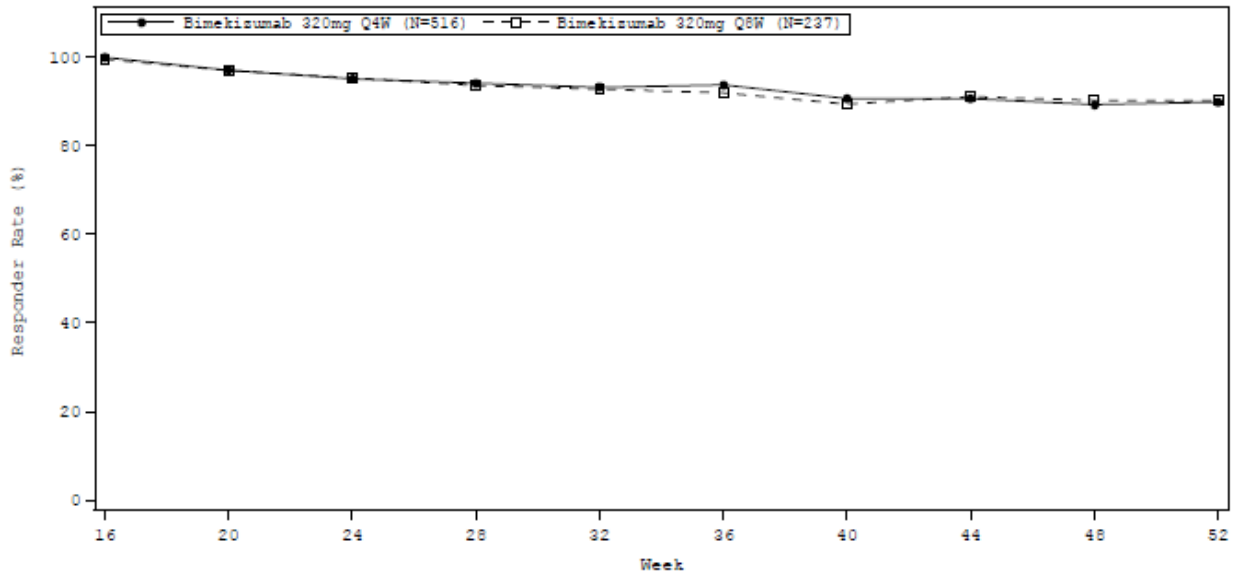
bimekizumab maintenance treatment regimens (bimekizumab 320mg Q4W and bimekizumab 320mg Q8W), which included study participants with initial response at Week 16 after having received bimekizumab 320mg Q4W in the Initial Treatment Periods of PS0008, PS0009 or PS00013.

Maintenance of response in study participants who received bimekizumab and were PASI90, IGA 0/1, PASI100, and IGA 0 responders at Week 16 (NRI; Pool E2)

Time point	PASI90		IGA 0/1		PASI100		IGA 0	
	BKZ Q4W N=516 n (%)	BKZ Q8W N=237 n (%)	BKZ Q4W N=511 n (%)	BKZ Q8W N=234 n (%)	BKZ Q4W N=355 n (%)	BKZ Q8W N=182 n (%)	BKZ Q4W N=361 n (%)	BKZ Q8W N=182 n (%)
Week 28	486 (94.2)	222 (93.7)	471 (92.2)	218 (93.2)	310 (87.3)	161 (88.5)	315 (87.3)	162 (89.0)
Week 40	468 (90.7)	212 (89.5)	456 (89.2)	214 (91.5)	302 (85.1)	155 (85.2)	307 (85.0)	156 (85.7)
Week 52	464 (89.9)	214 (90.3)	447 (87.5)	214 (91.5)	295 (83.1)	161 (88.5)	298 (82.5)	161 (88.5)

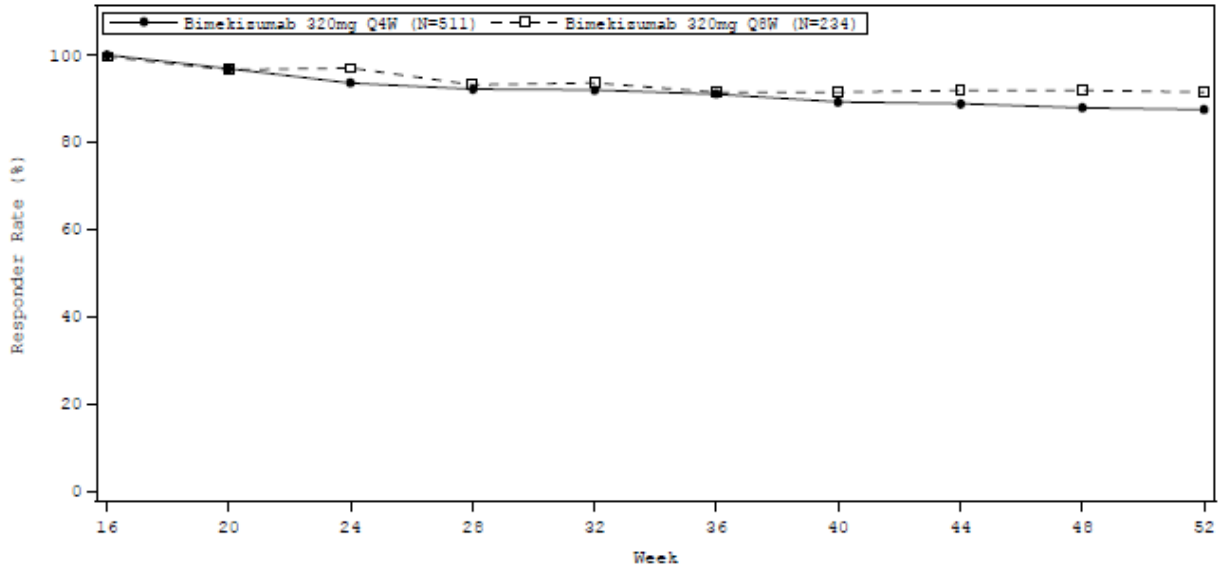
BKZ Q4W=bimekizumab 320mg every 4 weeks; BKZ Q8W=bimekizumab 320mg every 8 weeks; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index
Note: Subjects with missing data at a given week were counted as nonresponders in the n (%).
Note: An IGA 0/1 response was defined as 0 (clear) or 1 (almost clear) with ≥2-category improvement from Baseline. An IGA 0 response was defined as 0 (clear) with ≥2-category improvement from Baseline. Only study participants with a Baseline IGA score of ≥2 were included in the analyses.

PASI90 response rate in Week 16 PASI90 responders by visit during the Maintenance Treatment Period (NRI; Pool E2)



NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks

IGA 0/1 response rate among Week 16 IGA 0/1 responders by visit during the Maintenance Treatment Period (NRI; Pool E2)



IGA=Investigator's Global Assessment; NRI=nonresponder imputation; Q4W=every 4 weeks; Q8W=every 8 weeks
Note: An IGA 0/1 response was defined as 0 (clear) or 1 (almost clear) with ≥2-category improvement from Baseline. Only study participants with a Baseline score of ≥2 were included in the analysis.

Comparison of results in Pool E2 Subgroups

Pool E2 (All Phase 3 studies: Summary of subgroup analyses among Week 16 responders at Week 52 (NRI)

	PASI90		IGA 0/1		PASI100	
Subgroup	**BKZ Q4W N=516 n/Nsub (%)**	**BKZ Q8W N=237 n/Nsub (%)**	**BKZ Q4W N=511 n/Nsub (%)**	**BKZ Q8W N=234 n/Nsub (%)**	**BKZ Q4W N=355 n/Nsub (%)**	**BKZ Q8W N=182 n/Nsub (%)**
Age (years)						
<40	179/202 (88.6)	77/88 (87.5)	177/201 (88.1)	77/87 (88.5)	119/137 (86.9)	57/66 (86.4)
40 to <65	249/277 (89.9)	116/127 (91.3)	238/274 (86.9)	118/125 (94.4)	156/194 (80.4)	91/100 (91.0)
≥65	36/37 (97.3)	21/22 (95.5)	32/36 (88.9)	19/22 (86.4)	20/24 (83.3)	13/16 (81.3)
Race						
White	382/422 (90.5)	199/218 (91.3)	374/422 (88.6)	201/216 (93.1)	253/298 (84.9)	152/169 (89.9)
Nonwhite	82/94 (87.2)	15/19 (78.9)	73/89 (82.0)	13/18 (72.2)	42/57 (73.7)	9/13 (69.2)
Geographical region						
North America	150/177 (84.7)	82/97 (84.5)	149/180 (82.8)	84/99 (84.8)	96/123 (78.0)	62/75 (82.7)

Subgroup	PASI90		IGA 0/1		PASI100	
	BKZ Q4W N=516 n/Nsub (%)	**BKZ Q8W N=237 n/Nsub (%)**	**BKZ Q4W N=511 n/Nsub (%)**	**BKZ Q8W N=234 n/Nsub (%)**	**BKZ Q4W N=355 n/Nsub (%)**	**BKZ Q8W N=182 n/Nsub (%)**
Western Europe	47/54 (87.0)	24/27 (88.9)	46/54 (85.2)	25/26 (96.2)	23/31 (74.2)	13/15 (86.7)
Central/Eastern Europe	204/212 (96.2)	100/104 (96.2)	198/209 (94.7)	98/102 (96.1)	148/159 (93.1)	82/88 (93.2)
Asia/Australia	63/73 (86.3)	8/9 (88.9)	54/68 (79.4)	7/7 (100)	28/42 (66.7)	4/4 (100)
Baseline weight						
≤120kg	435/482 (90.2)	194/215 (90.2)	418/477 (87.6)	196/214 (91.6)	284/342 (83.0)	149/168 (88.7)
>120kg	29/34 (85.3)	20/22 (90.9)	29/34 (85.3)	18/20 (90.0)	11/13 (84.6)	12/14 (85.7)
Baseline disease severity						
PASI<20	239/267 (89.5)	127/143 (88.8)	232/270 (85.9)	129/144 (89.6)	159/185 (85.9)	96/111 (86.5)
PASI≥20	225/249 (90.4)	87/94 (92.6)	215/241 (89.2)	85/90 (94.4)	136/170 (80.0)	65/71 (91.5)
Prior PSO systemic therapy						
Yes	376/413 (91.0)	169/183 (92.3)	359/406 (88.4)	167/180 (92.8)	247/289 (85.5)	131/148 (88.5)
No	88/103 (85.4)	45/54 (83.3)	88/105 (83.8)	47/54 (87.0)	48/66 (72.7)	30/34 (88.2)

BKZ=bimekizumab; IGA=Investigator's Global Assessment; NRI=nonresponder imputation; PASI=Psoriasis Area Severity Index; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks

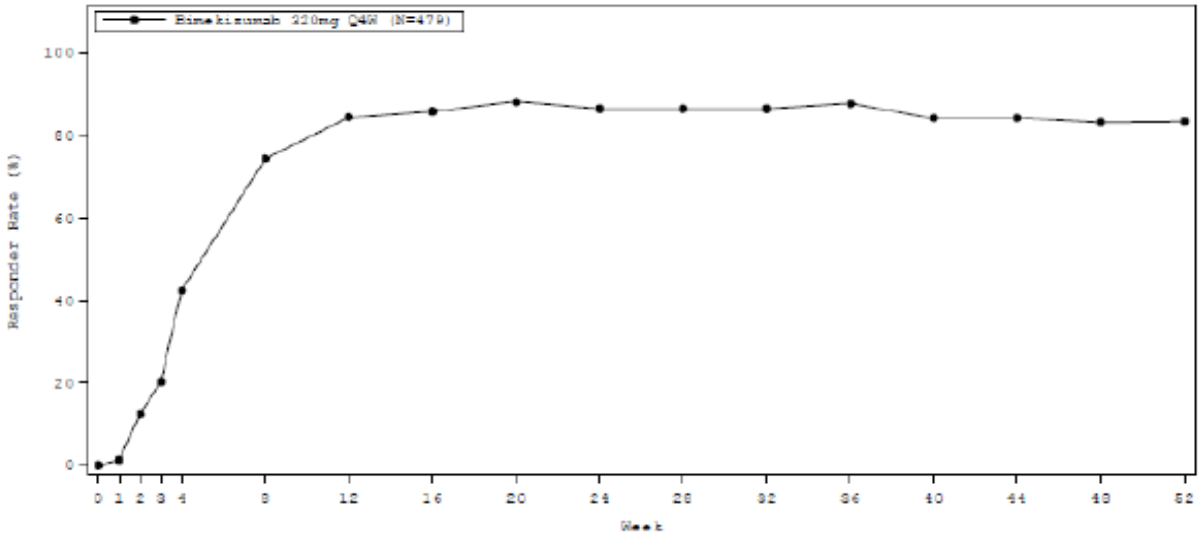
Note: Nsub includes all study participants in each subgroup under a given treatment regardless of whether or not a study participant had missing data at Week 52.

Pool E3 (Efficacy through Week 52 of Q4W bimekizumab dosing)

Pool E3 combined data for study participants in PS0008 and PS0009 to investigate the efficacy of over 1 year of continuous treatment with bimekizumab 320mg Q4W. In Pool E3, there were 479 study participants. Overall, the Baseline characteristics in Pool E3 were similar to Pool E1 and Pool E2. The majority of study participants (88.9%) in Pool E3 completed Week 52 of the Maintenance Treatment Period. The primary reason for discontinuation was adverse event (5.2%).

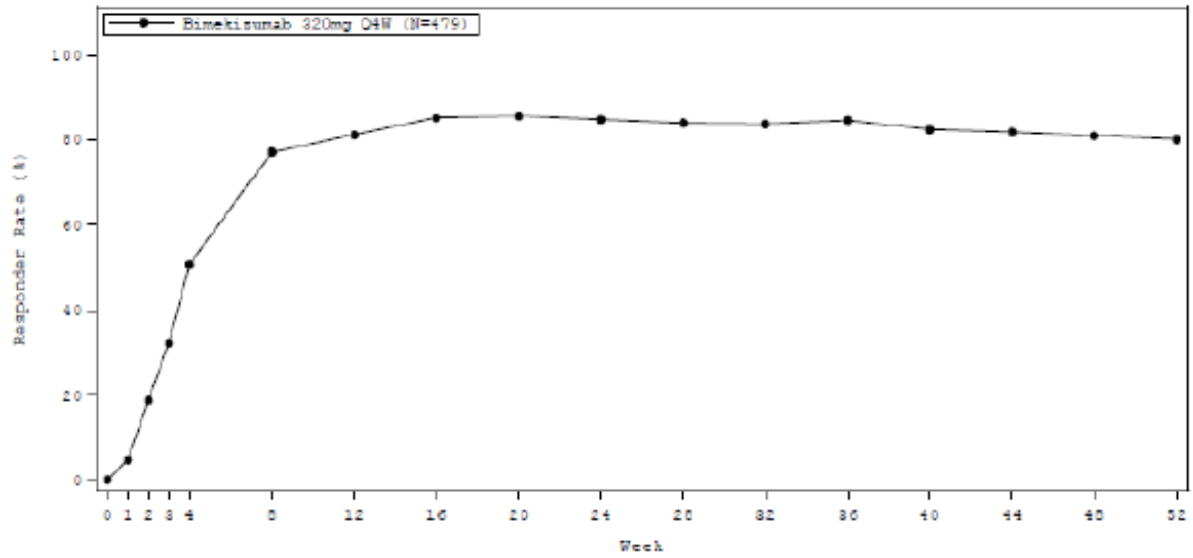
– Study participants rapidly achieved response for all primary (PASI90 and IGA 0/1) and secondary outcomes, and the response was sustained through Week 52.

Efficacy Pool E3: PASI90 response rate during the Initial and Maintenance Treatment Periods



NRI=nonresponder imputation; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks
Note: Not all visits include all individual study data due to different assessment schedules across studies.

Efficacy Pool E3: IGA 0/1 response rate during the Initial and Maintenance Treatment Periods



IGA=Investigator's Global Assessment; NRI=nonresponder imputation; Q4W=every 4 weeks
Note: An IGA 0/1 response was defined as 0 (clear) or 1 (almost clear) with ≥2-category improvement from Baseline. Only study participants with a Baseline score of ≥2 were included in the analysis.
Note: Not all visits include all individual study data due to different assessment schedule across studies.

In Pool E3, DLQI 0 or 1 response rate increased quickly through Week 8 (57.0%) and continued to increase through Week 16 (65.6%). At Week 28 the response rate reached 74.8% and response was sustained at Week 52 (74.5%).

Comparison of results in Pool E3 Subgroups

Notable differences between subgroups included:

- PASI90, IGA 0/1, and PASI100 response rates were higher in Central/Eastern Europe compared with the other regions.

- PASI90 response rates were higher for study participants with prior exposure to systemic therapy for PSO compared with no prior exposure.

Bimekizumab effects in areas of high impact

Improvements were observed in psoriasis involving the scalp, nails, palms and soles in patients treated with bimekizumab at week 16.

Table 38 - Scalp, palmoplantar and nail responses in BE VIVID, BE READY and BE SURE at week 16

	BE VIVID			BE READY		BE SURE	
	Placebo	**Bimekizumab 320 mg Q4W**	**Ustekinumab**	**Placebo**	**Bimekizumab 320 mg Q4W**	**Bimekizumab 320 mg Q4W**	**Adalimumab**
Scalp IGA (N)[a] Scalp IGA 0/1, n (%)	(72) 11 (15.3)	(285) 240 (84.2)[b]	(146) 103 (70.5)	(74) 5 (6.8)	(310) 286 (92.3)[b]	(296) 256 (86.5)	(138) 93 (67.4)
pp-IGA (N)[a] pp-IGA 0/1, n (%)	(29) 7 (24.1)	(105) 85 (81.0)	(47) 39 (83.0)	(31) 10 (32.3)	(97) 91 (93.8)	(90) 75 (83.3)	(34) 24 (70.6)
mNAPSI 100 (N)[a] mNAPSI 100, n (%)	(51) 4 (7.8)	(194) 57 (29.4)	(109) 15 (13.8)	(50) 3 (6.0)	(210) 73 (34.8)	(181) 54 (29.8)	(95) 21 (22.1)

Bimekizumab 320 mg Q4W= bimekizumab every 4 weeks. Non responder imputation (NRI) is used. Scalp IGA 0/1 and pp-IGA 0/1 responses were defined as Clear (0) or Almost Clear (1) with ≥2 category improvement relative to Baseline.
[a)] Include only patients with a scalp Investigator Global Assessment (IGA) of 2 or greater, a palmoplantar IGA of 2 or greater and a modified Nail Psoriasis and Severity Index (mNAPSI) score > 0 at baseline.
[b)] p<0.001 *versus* placebo, adjusted for multiplicity

Scalp IGA and palmoplantar IGA responses in bimekizumab-treated patients were maintained through week 52 / 56. Nail psoriasis continued to improve beyond week 16. In BE VIVID, at week 52, 60.3% of patients treated with bimekizumab 320 mg every 4 weeks achieved complete nail clearance (mNAPSI 100). In BE READY, at week 56, 67.7% and 69.8% of week 16 PASI 90 responders achieved complete nail clearance with bimekizumab 320 mg every 8 weeks and bimekizumab 320 mg every 4 weeks respectively.

Clinical studies in special populations

The following table presents age range of patients studied in controlled and non-controlled studies.

	Phase 2/3 Bimekizumab Total n/N (%)			
Study type	<65 Years	65 to ≤74 Years	75 to ≤84 Years	≥85 Years
Controlled studies	1574/1723 (91.4)	132/1723 (7.7)	17/1723 (1.0)	0
Noncontrolled studies	62/66 (93.9)	3/66 (4.5)	1/66 (1.5)	0

Supportive studies

Study PS0011

A Multicenter, 48-Week, Double-Blind, Placebo-Controlled, Parallel-Group Extension Study to Assess the Long-Term Safety, Tolerability, and Efficacy of Bimekizumab in Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis.

The PS0011 Extension Study to Assess the Long-Term Safety and enrolled patients who completed study PS0010 i.e. dose-response study. The primary objective of PS0011 study was to assess the long-term safety and tolerability of bimekizumab. The assessment of efficacy was secondary and included investigation of changes in the PASI and IGA response over time.

Subjects who were randomized to receive placebo or bimekizumab 64mg, 160mg, or 320mg loading dose + 160mg Q4W in PS0010 must have achieved PASI90 response at Week 12 in PS0010 to enter the PS0011 extension study on the same treatment dose. Subjects who did not achieve PASI90 response at Week 12 in PS0010 while on these treatments were assigned to receive bimekizumab 160 or 320mg Q4W at Baseline in PS0011 as follows:

- Subjects who were randomized to receive placebo and bimekizumab 64mg Q4W in PS001 were assigned to bimekizumab 160mg Q4W in PS0011.
- Subjects who were randomized to receive bimekizumab 160mg Q4W and 320mg loading dose + 160mg Q4W in PS0010 were assigned to bimekizumab 320mg Q4W in PS0011.

Subjects who were randomized to receive bimekizumab 320 or 480mg Q4W in PS0010 were assigned to receive bimekizumab 320mg Q4W on entering PS0011, regardless of their PASI90 response at Week 12 in PS0010.

217 patients were enrolled to this study. As discussed above, PS0010 Week 12 non-responders were transferred to the higher dose of bimekizumab in this study. Subsequently the majority of these patients responded to treatment. The response was also seen in the initial non-responders who continue to receive the same dose in the extension study (320mg) or who were transferred from 480 mg to 320 mg.

It is noted that the majority of PS0010 Week 12 responses maintained their response throughout PS0011 study. It is noted however, that a small percentage of patients with the initial response to treatment lose this response later in the study.

PS0014

Upon request from CHMP, the applicant provided a summary of the efficacy maintenance data available for PASI90 and IGA 0/1, including further data regarding effects on psoriatic nail disease, palmoplantar PSO, and effects on psoriatic scalp disease over time for the entire PS0014 study population as well as the subset of study participants previously treated with ustekinumab. In addition, a summary of antidrug antibody data over time was also provided. Those are presented below.

PS0014 is an ongoing multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in eligible adult participants with moderate to severe chronic plaque PSO who completed one of the Phase 3 pivotal studies (PS0008, PS0009 or PS0013).

The primary objective is to assess the long-term safety and tolerability of bimekizumab in study participants with moderate to severe plaque PSO. Secondary efficacy objectives included assessment of PASI 90 and IGA 0/1 responses over time.

As of the 01 June 2020 data cut-off, a total of 1286 participants were enrolled in study PS0014 and received bimekizumab treatment through Week 24 during the Treatment Period as follows: 903 participants in the bimekizumab 320mg Q4W group and 383 participants in the bimekizumab 320mg Q8W group.

At Week 24, for participants receiving bimekizumab 320mg Q4W, if PASI90 was achieved, the Investigator was able to change the participant's dosing interval from 320mg Q4W to 320mg Q8W (optional). A total of 131 participants in the bimekizumab 320mg Q4W group switched to bimekizumab 320mg Q8W treatment at Week 24.

As of the data cut-off, a total of 386 participants (30.0%) completed Week 48. The majority of participants remained ongoing in the study between Week 24 and Week 48 in the bimekizumab 320mg Q4W/Q4W group (60.8%), the bimekizumab 320mg Q4W/Q8W group (67.2%), and the bimekizumab 320mg Q8W/Q8W group (70.8%).

Across the spectrum of efficacy endpoints, efficacy responses in participants treated with bimekizumab 320mg Q4W reached similar levels to those treated with bimekizumab 320mg Q8W at approximately Week 12. These clinically relevant improvements from pivotal study Baseline and high levels of response were sustained on bimekizumab 320mg Q4W and bimekizumab 320mg Q8W treatment through Week 24 of PS0014.

PASI90 response rate over time

At PS0014 Baseline, the proportion of participants who had achieved PASI90 in the pivotal studies was lower in the bimekizumab 320mg Q4W group (86.0%) compared with the bimekizumab 320mg Q8W group (99.2%) as a result of the study enrolment scheme.

In the bimekizumab 320mg Q4W group, PASI90 response rates increased up to Week 12 (91.2%) and were sustained through Week 24 (89.2%). In the bimekizumab 320mg Q8W group, the high level of PS0014 Baseline PASI90 response rate was sustained at Week 12 (91.4%) and Week 24 (90.1%).

IGA 0/1 response rate over time

At PS0014 Baseline, the proportion of participants who achieved IGA 0/1 compared to pivotal study baseline was lower in the bimekizumab 320mg Q4W group (87.5%) compared with the bimekizumab 320mg Q8W group (96.9%). In the bimekizumab 320mg Q4W group, IGA 0/1 response rates were sustained from PS0014 Baseline up to Week 12 (89.1%) and were sustained at high levels through Week 24 (87.5%). In the bimekizumab 320mg Q8W group, the high level of PS0014 Baseline IGA 0/1 response rate was sustained at Week 12 (90.6%) and Week 24 (88.3%).

Other efficacy endpoints

mNAPSI90 response rate over time

Across all pivotal study / PS0014 treatment groups, the mNAPSI90 response rate at PS0014 Baseline (range: 23.1% to 78.2%) was either increased or sustained through Week 24 (range: 64.3% to 89.5%).

pp-IGA 0/1 response rate over time

Across all pivotal study / PS0014 treatment groups, the pp-IGA 0/1 response rate at PS0014 Baseline (range: 66.7% to 100%) was either increased or sustained through Week 24 (range: 80.0% to 100%).

Scalp-IGA 0/1 response rate over time

Across all pivotal study / PS0014 treatment groups, the scalp-IGA 0/1 response rate at PS0014 Baseline (range: 66.7% to 97.6%) was either increased or sustained through Week 24 (range: 72.0% to 96.0%).

Across the spectrum of physician-assessed signs, symptoms, and impact of PSO efficacy endpoints, bimekizumab 320mg Q4W and Q8W treatment resulted in maintenance of clinically meaningful response rates up to Week 24 and Week 48.

Efficacy in study participants previously treated with ustekinumab

Study participants who received ustekinumab in the feeder study PS0009 were switched to bimekizumab treatment in PS0014; treatment allocation was based on PASI response as follows:

- Study participants who did not achieve PASI90 at the end of the feeder study received bimekizumab 320mg Q4W in PS0014
- Study participants who achieved PASI90 at the end of the feeder study were randomized 1:1 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W

There were 136 study participants treated with ustekinumab that completed study PS0009 and switched to bimekizumab treatment in PS0014. Of these, 39 study participants were allocated to receive bimekizumab 320mg Q8W and 97 study participants received bimekizumab 320mg Q4W

Secondary efficacy endpoints

PASI90 response rate over time

In the ustekinumab/bimekizumab 320mg Q4W group (n=96), the PASI90 response rate increased from PS0014 Baseline (55.2%) up to Week 12 (94.8%) and was sustained through Week 24 (90.6%).

In the ustekinumab/bimekizumab 320mg Q8W group (n=39), the PASI90 response rate was sustained from PS0014 Baseline (94.9%) up to Week 12 (97.4%) and through Week 24 (94.9%).

IGA 0/1 response rate over time

In the ustekinumab/bimekizumab 320mg Q4W group (n=96), the IGA 0/1 response rate increased from PS0014 Baseline (64.6%) to Week 12 (93.8%) and was sustained through Week 24 (87.5%).

In the ustekinumab/bimekizumab 320mg Q8W group (n=39), the high level of PS0014 Baseline IGA 0/1 response rate (92.3%) was sustained at Week 12 (97.4%) and Week 24 (89.7%).

Other efficacy endpoints

mNAPSI90 response rate over time

In the ustekinumab/bimekizumab 320mg Q4W group (n=63), the mNAPSI90 response rate increased from PS0014 Baseline (42.9%) through Week 24 (76.2%).

In the ustekinumab/bimekizumab 320mg Q8W group (n=19), the mNAPSI90 response rate increased from PS0014 Baseline (73.7%) through Week 24 (89.5%)

pp-IGA 0/1 response rate over time

In the ustekinumab/bimekizumab 320mg Q4W group (n=20), the pp-IGA 0/1 response rate was sustained from PS0014 Baseline (85.0%) through Week 24 (80.0%).

In the ustekinumab/bimekizumab 320mg Q8W group (n=11), the pp-IGA 0/1 response rate was sustained from PS0014 Baseline (100%) through Week 24 (100%).

Scalp-IGA 0/1 response rate over time

In the ustekinumab/bimekizumab 320mg Q4W group (n=76), the scalp-IGA 0/1 response rate increased from PS0014 Baseline (77.6%) to Week 24 (89.5%).

In the ustekinumab/bimekizumab 320mg Q8W group (n=29), the scalp-IGA 0/1 response rate was sustained from PS0014 Baseline (89.7%) through Week 24 (86.2%).

Study participants who switched from ustekinumab to bimekizumab 320mg Q4W showed rapid improvement as early as the next assessment after PS0014 Baseline. Sustained responses were observed up to Week 24 at similar levels and over similar time courses compared with participants randomized to bimekizumab 320mg Q4W at Baseline.

Self-administration of bimekizumab – Studies DV0002 and DV0006

DV0002 and DV0006 are clinical use (study participant self-injection) studies conducted as part of the overall device presentation program to provide patients with flexible dosing options for bimekizumab.

In DV0002 and DV0006, the safe and effective use of the bimekizumab-SS-1mL and bimekizumab-AI-1mL device presentations by study participants was evaluated at Baseline and at Week 8. Safe and effective self-injection was evaluated by the study personnel and was defined as complete dose delivery (confirmed by a visual inspection of the investigational device presentation), and no adverse device effects that precluded continued use of the investigational device presentation for self-injection (ie, no serious adverse device effects and/or adverse device effects [ADEs] that led to withdrawal).

Both DV0002 and DV0006 met the primary and secondary objectives, and demonstrated that after the initial training at Baseline, study participants with moderate to severe plaque PSO could continue to safely and effectively self-inject bimekizumab using the bimekizumab SS 1mL or the bimekizumab AI 1mL 8 weeks after training in the self-injection technique.

Study participants reported positive self-injection experiences with the investigational device presentations, as assessed by the Self-Injection Assessment Questionnaire and scores on the visual analog scale for injection-site related pain were low following injection at Baseline and Week 8 with either the bimekizumab SS 1mL or bimekizumab AI 1mL device presentation.

In both substudies, the structural and functional integrity of the bimekizumab SS 1mL and the bimekizumab-AI-1mL was maintained post-injection and both device presentations performed as intended.

2.5.3. Discussion on clinical efficacy

Bimekizumab is a humanized monoclonal antibody of the immunoglobulin G1 subclass with 2 identical antigen binding regions that bind and neutralize interleukin (IL)-17A, IL-17F, and IL-17AF cytokines.

The applicant developed bimekizumab for the treatment of adults with moderate to severe plaque PSO. The indication being sought is "*Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy*."

In support of the efficacy data for this application, the applicant presented data from three pivotal Phase 3 studies of bimekizumab use in adults who have plaque psoriasis (PS0008, PS0009 and PS0013).

The development programme for bimekizumab in the treatment of moderate to severe plaque PSO was discussed with CHMP in two Scientific Advice procedures in May 2016 (EMEA/H/SA/3306/1/2016/III) and in September 2017 (EMEA/H/SA/3306/1/FU/1/2017/III).

Design and conduct of clinical studies

The pivotal phase 3 studies recruited adult subjects who had a diagnosis of moderate to severe plaque PSO for at least 6 months. Subjects were required to be candidates for systemic therapy with a PASI score of ≥12 and an affected body surface area (BSA) of ≥10%. Subjects with other chronic inflammatory conditions (with the exception of psoriatic arthritis) were excluded.

1480 subjects comprise the pooled Phase 3 randomised data set. The median age of subjects overall was 45 years (18 years, 83 years), 70.7% were male and 84.1% were white. 12.1% of subjects were Asian and 1.6% were black. The median weight was 87 kg (40.10 kg, 237.00 kg). 129 subjects (8.7%) weighed >120 kg. The median BMI was 28.730 (15.92, 73.15). The Median PSO disease duration was 15.64 years (0.45, 67.45). 77.6% of subjects had a prior systemic treatment. 38.2% of subjects had a previous biological treatment exposure and 23% had a previous anti-IL-17 exposure. Just 0.3% had a prior primary failure to a biologic. 50% of subjects were recruited in Europe. The median BSA affected was 20% (10, 97). The median baseline PASI was 18.40 (11.7, 58.5). 66.4% of subjects were documented as having moderate PSO and 33.4% of subjects documented as having severe disease.

Review of the baseline demographics revealed that the pivotal studies enrolled mostly male white subjects who were of higher weights. The patient demographic and baseline disease characteristics were, however, generally well-balanced across the various arms of trial. Approximately one third of the subjects were classified as having severe psoriasis and two thirds as having moderate psoriasis. The majority of patients were <65 years of age. Much lower numbers were between 65 to 84 years. The pivotal studies did not recruit any children or elderly (≥85 years) subjects. This is consistent with the disease profile and other similar PSO centralised applications.

The bimekizumab dose and dosing regimens tested in the Phase 3 studies were selected based on safety, efficacy, and PK data from the 2 Phase 2 studies (PS0010 and PS0016) in participants with plaque PSO, as well as PK/PD analyses performed at the end of Phase 2. Based on this combination of clinical data and PK/PD analysis, a bimekizumab 320mg Q4W regimen was selected as the dose in the Initial Treatment Period up to Week 16 in all three Phase 3 pivotal studies.

Both bimekizumab 320mg Q4W (all 3 pivotal studies) and bimekizumab 320mg Q8W (Studies PS0008 & PS0013 only) were selected as the maintenance treatment regimens during the Maintenance Treatment Period/Randomized Withdrawal Period (Week 16 to Week 52/56).

Study PS0008 was not placebo-controlled and adalimumab (a TNF inhibitor) was the active comparator however both Study PS0009 and Study PS0013 were placebo controlled. Study PS0009 also had an active comparator, ustekinumab (IL-23 inhibitor). The active comparators were administered according to their EU-authorised posologies in moderate-severe psoriasis. Study participants could have continued to use topical moisturizers or emollients, bath oils, or oatmeal bath preparations for skin conditions during the study, as needed. Mild and low potency topical steroids were permitted for use limited to the face, axilla, and/or genitalia, as needed. These topical medicines should not have been used within approximately 24 hours prior to study visits requiring IGA and PASI measures.

All of the Phase 3 studies had the same co-primary efficacy endpoints, i.e. the proportion of participants who achieved a PASI90 response at Week 16 and the proportion of participants who achieved an IGA 0/1 response at Week 16. The Initial Treatment Phase for all 3 Phase 3 studies was 16 weeks with a follow-up Maintenance Treatment Period to Week 56/52, respectively (Studies PS0008 and PS0009) or a Randomized Withdrawal Period to Week 56 (Study PS0013). There were minor differences between the three pivotal studies with respect to secondary and other endpoints but all were considered appropriate.

The sample size calculations for the pivotal studies were based on the co-primary efficacy endpoints measured at week 16. The underlying assumptions of the sample size calculation is reasonable. The planned enrolment targets were achieved for the three pivotal studies.

Upon request by the CHMP, the applicant provided further details on GCP findings. FDA inspections took place at two sites in studies PS0008 and PS0013. No findings were issued according to the Applicant. Health Canada conducted an inspection of PS0008; 12 findings were issued and corrective actions were implemented. Therefore, the CHMP concluded unlikely that the GCP findings would have had any significant impact on the efficacy or safety results submitted.

The pivotal studies had a high completion rate, 95.6% of subjects completed the primary endpoint assessment of Study PS0008 with 0.2% discontinuing due to lack of efficacy. 94.7% of subjects completed the primary endpoint assessment of Study PS0009 with 0.5% discontinuing due to lack of efficacy. In Study PS0013, 97.0% of subjects completed Week 16 with 0.7% of subjects discontinuing due to lack of efficacy. 93.1% and 91.8% of subjects completed the Maintenance Treatment Period in Studies PS0008 and PS0009 respectively. In the Randomised Withdrawal Study (PS0013), 4.2% of subjects discontinued the study during the withdrawal period, none of these discontinuations were due to lack of efficacy.

The Patient Symptom Diary (PSD), investigating symptoms of pain, itch and scaling as reported by patients, was developed by the applicant and discussed in a CHMP SA. The PSD consists of 14 items, which are scored on a 0 to 10 scale, with a higher score meaning greater severity or impact and with verbal anchors at the extreme responses and has a recall period of the last 24 hours. It was not submitted yet for regulatory acceptance but, according to the applicant, has undergone thorough development and psychometric validation. The PSD was assessed as an 'other endpoint' in study PS0008 and as a secondary endpoint in studies PS0009 and PS0013, and results are presented in the SmPC. Upon request by the CHMP, the applicant submitted an extensive PRO dossier detailing the progressive development of the PSD starting in phase 2 studies through phase 3 studies. Based on the information provided by the applicant, the CHMP agrees that PSD is a relevant patient reported outcome measure in the context of the assessment of bimekizumab effects in PSO patients on specific PSO symptoms of pain, itch and scaling affecting the quality of life of most patients. Although not a general assessment of health related quality of life in treated patients, it is less generic than the DLQI and in accordance with the EMA PSO guideline, the assessment of HRQL scales specific for PSO, in conjunction with the investigator's assessed efficacy measures, is considered to represent an added value for a new medicine in comparative clinical trials. In follow up analyses on phase 3 trial data using a more conservative approach and mainly based on anchor based methods (different from the anchors used for the phase 2 study data), a more stringent responder definition of 4 points for all PSD items (on a 10 point scale) was selected to represent marked clinically meaningful improvement. Based on the totality of data presented by the applicant, the more stringent 4 point responder definition is agreed by the CHMP and found clinically meaningful to patients and healthcare providers.

Overall, the design of the studies and endpoints chosen are in line with EMA guidelines and previous centralised authorisations for biological therapies for use in plaque psoriasis. Overall, the design of the Phase 3 studies is adequate and in line with the CHMP scientific advices received.

Efficacy data and additional analyses

All three pivotal studies met their co-primary endpoints at Week 16. Integrated efficacy analyses were conducted for 3 distinct efficacy pools.

Study PS0008 was designed to demonstrate superiority over Adalimumab.

PASI 90 at week 16 was 39% higher compared to Adalimumab and IGA 0/1 at week 16 was 28.1% higher versus Adalimumab. Both co-primary endpoints at Week 16 were highly statistically significant demonstrating superiority over adalimumab with p<0.001. Additionally, superiority was demonstrated on all secondary endpoints at week 24 (PASI 90, IGA0/1, PASI 75, PASI 100) and at week 56 for PASI 90 and IGA 0/1, p<0.001.

Study PSO009 was designed to demonstrate superiority over Placebo and Ustekinumab.

PASI 90 response at week 16 for Bimekizumab was superior to both placebo (80.2% difference) and versus Ustekinumab (35.3% difference). Also, for IGA 0/1 response superiority was demonstrated 79.3% better than placebo and 30.7% better than Ustekinumab.

Similar to **Study PS0008** both co-primary endpoints at Week 16 were highly statistically significantly better p<0.001. Additionally, superiority was demonstrated on all secondary endpoints at week 16 (PASI 100, IGA 0, PSD responses for pain, Itch and scaling, Scalp IGA 0/1) and at week 52 for PASI 90 and IGA 0/1, p<0.001.

Study PS0013 was designed to demonstrate superiority over Placebo.

PASI 90 at week 16 was 89.6 % better and IGA 0/1 was 91.4% better versus placebo.

Similar to previous studies **PS0008 and PSO009** both co-primary endpoints at Week 16 were highly statistically significantly better (p<0.001).

Additionally, superiority was demonstrated on all secondary endpoints at week 16 (PASI 100, IGA 0, PSD responses for pain, Itch and scaling, Scalp IGA 0/1) and at week 52 for PASI 90 and IGA 0/1, p<0.001.

Maintenance of efficacy was demonstrated at week 56, PASI 90 was 88.8% at week 56, (90.1% at week 16). Difference from placebo was 72.6% p<0.001.

Regarding anti-drug antibody positivity following retreatment, within the range of dose regimens studied, retreatment did not appear to impact efficacy. For multiple retreatments, the only data available are from PS0016 and PS0018, which suggest that efficacy is not impacted if bimekizumab treatment is interrupted more than once.

In addition, a post-hoc analysis of PS0013 data showed that only 4 study participants became ADAb positive for the first-time following retreatment with bimekizumab, out of the 67 who were retreated. The applicant considered that these data demonstrate a very low increase in observed ADAb positive study participants following retreatment with no observed impact on efficacy. Nevertheless, it cannot be excluded that lower efficacy may become an issue over time if a higher number of patients became anti-drug antibody (ADAb) positive. Thus, this will be followed up in the post marketing setting as part of ongoing study PS0014 where their impact on safety will be further investigated.

Overall the studies showed a consistent effect in IGA0/1 response and PASI 90, 100 response with treatment. Also, superiority was demonstrated over both Adalimumab and Ustekinumab.

The applicant pooled the efficacy results in 3 separate pooled analyses.

Pool E1 reflected a placebo-controlled Initial Treatment Period to Week 16 (Studies PS0009 & PS0013). Pool E2 reflected the Maintenance Treatment Period (Studies PS0008, PS0009 & PS0013). Pool E3 reflected the Initial & Maintenance Treatment Periods for a Q4W regime (ITT) and included data from Studies PS0008 & PS0009.

Results from these studies/pools demonstrated that:

- Treatment with bimekizumab demonstrated clinically meaningful and statistically superior response rates compared with placebo, adalimumab, and ustekinumab for the co-primary efficacy variables, 90% or greater improvement from Baseline in the PASI score (PASI90) and IGA of clear or almost clear (IGA 0/1) response at Week 16.
- Bimekizumab treatment was superior to placebo or comparator across all ranked secondary endpoints. Following treatment with bimekizumab, improvements for both physician-assessed and patient-assessed signs, symptoms, and impact of PSO were rapid and sustained over time.
- Initial bimekizumab 320mg every 4 weeks (Q4W) treatment effects were rapid (75% or greater improvement from Baseline in the PASI score [PASI75] achieved after a single dose) and profound (complete PSO clearance demonstrated by PASI100 and IGA 0).
- Initial treatment responses achieved at Week 16 were well maintained in the bimekizumab groups across all efficacy outcome measures compared with placebo and ustekinumab through 1 year.
- In the Maintenance Treatment Period, efficacy results through Week 56 were similar for both the bimekizumab 320mg Q4W and bimekizumab 320mg every 8 weeks (Q8W) treatment groups following initial treatment with bimekizumab 320mg Q4W for 16 weeks.
- Statistically significant differences in symptom relief were observed by subjects (PSD responses based on pain, itch, and scaling item scores at Week 16).
- Study participants who switched from placebo to bimekizumab 320mg Q4W at Week 16 showed rapid improvement as early as the next assessment after Week 16 across the spectrum of other efficacy endpoints. Sustained responses were observed up to Week 52 at similar levels and over similar time courses compared with study participants randomized to bimekizumab 320mg Q4W at Baseline.
- Consistency of treatment effect for the primary efficacy variables across the three studies was seen.
- Some geographical differences in response to bimekizumab were noted but these relate to differences in clinical practice, rather than reflecting a true difference in efficacy.
- Placebo responses in Studies PS0009 and PS0013 were consistent with other psoriasis trials.

Pooled efficacy data - Subgroup analyses

E1 pool subgroup analyses - (placebo-controlled data to Week 16)

In the E1 subgroup analyses presented, some inconsistency in certain subgroups (age, gender and baseline PASI ≥20) when PASI90 and IGA 0/1 responses are compared were noted. The applicant considered the subgroups of age, gender and Baseline PASI ≥20 to be consistent when PASI90 and IGA Clear (0) or almost clear (1) (IGA 0/1) response rates are compared. When comparing the PASI90 and IGA0/1 response rates across the categories within each subgroup, no differences >3% were observed. Thus, CHMP agreed that the responses across the identified sub-groups are generally consistent. No subgroup analysis has been presented for subjects weighing <120 kg or ≥120 kg for the Initial Treatment Phase (placebo-controlled data to Week 16). The posology in patients ≥120 kg is discussed below.

Further, CHMP considers that it is difficult to form any concrete conclusions regarding the "previous PSO treatment" subgroup data presented by the applicant. Previous treatment with phototherapy or chemotherapy may imply a more favourable response to bimekizumab, whereas previous treatment with an anti-TNF agent may not. However, examination of the "prior biologic exposure" subgroup

suggested no difference in response to bimekizumab. Efficacy would be expected in patients who were not previously treated with a therapy which have a similar mechanism of action.

Upon request by CHMP, the applicant presented a post-hoc subgroup analysis with regards to prior biologic failure. Across the key endpoints (PASI90, IGA 0/1, and PASI100), similar Week 16 responses were observed in study participants with or without prior biologic failure. Although similar results are seen, it is noted that the information is limited with a small number of subjects in the "Prior biologic failure" sub-group of the combined pool and is derived from a post-hoc analysis. Nevertheless, this issue was no longer pursued by CHMP. The following information has been added in SmPC section 5.1: *Efficacy in patients with primary failure to anti-IL17 has not been investigated.*

The subgroup analyses also suggested that subjects from Western Europe had less favourable results than those from Central and Eastern Europe, however, it is unclear if this is a true effect or reflects differences in regional medical practice. This is acknowledged however it was considered that it is unlikely that different effect would be expected and therefore was not further pursued.

Analysis of pool E1 data at week 16 showed a lower treatment response in the NAb+ population (n=30) compared to the overall ADAb- population (n=607) for PASI90, IGA 0/1 and PASI100 responses (e.g. PASI90; 70% vs 89%). Upon request by CHMP, post-hoc analysis of treatment response at Week 52 was performed on the 30 study participants from Pool E1 who were positive for neutralizing antibodies (NAb-positive) at Week 16, compared to the anti-drug antibody (ADAb)-negative population in Pool E1 for the PASI90, IGA0/1, PASI100 and IGA0 endpoints. Overall, the analysis indicated that NAb-positive study participants do not lose response over time.

E2 pool subgroup analyses - (Maintenance Treatment Group, all 3 pivotal studies)

In the E2 pooled analysis group, maintenance of response through Week 52 was similar for the bimekizumab 320mg Q4W and bimekizumab 320mg Q8W maintenance treatment groups, with better results obtained using the Q8W regimen in many subgroups. These findings support the proposed Q8W maintenance regime. Overall, there were no notable differences in maintenance of effect seen in the key subgroups of Baseline disease severity (PASI<20, PASI≥20) or age. For race, geographical region, and prior systemic therapy for PSO, some differences were noted, either between subgroup categories within the maintenance treatment regimen or between maintenance treatment regimens. The subgroup findings in the Maintenance Treatment Group support the use of bimekizumab in patients who require systemic treatment.

In Pool E2 Week 16 responders, NAb status had no impact on efficacy. Higher PASI90 and IGA 0/1 response rates at Week 52 were noted in NAb-positive study participants compared to NAb-negative participants in the bimekizumab 320mg Q4W group, whereas a smaller opposite trend was observed in the bimekizumab 320mg Q8W group. There were no notable differences noted in the PASI100 NAb subgroup analyses.

An additional analysis of week 16 responders of pool E2, who were type ADAb-negative or NAb+ at week 16, showed that treatment response for the PASI90, PASI100 and IGA0/1 endpoints was maintained up to week 52 at levels that were highly similar between groups, suggesting that NAb antibody status at week 16 does not impact maintenance of response in treatment responders.

Overall, antibody positivity did not appear to have an impact on efficacy in the pivotal trials, however numbers of subjects in the antibody positive subgroups were small. It is also noted that neutralizing antibodies were not assessed as a covariate in the population PK and PKPD analyses.

A post-hoc analysis of the impact of NAb status on the efficacy of bimekizumab was performed for all study participants who were anti-drug antibody (ADAb)-positive at 2 timepoints and received bimekizumab in the Initial and Maintenance Treatment Periods in the Phase 3 studies. Both at week 16

and week 52, the efficacy response was lower in the NAb+ group compared to the ADAb negative population but limited to about 10% difference at most. The reported numbers for the NAb+ group have to be interpreted with caution as the number of subjects in this group is limited (n=34). Altogether, this analysis does not indicate a long-term negative impact of NAb-positive antibody status on efficacy outcomes. Appropriate information has been added to SmPC – section 4.8.

In the Maintenance Treatment Phase Subgroup analysis (Pool E2), results suggested that a bimekizumab Q8W treatment schedule in subjects weighing >120 kg may be preferable, however total numbers of subjects in the >120 kg subgroup were low overall. Population PK simulations indicated that there may be lower bimekizumab exposure in persons of higher weights. Similarly, persons of lower weights may have higher exposures (See PK section of AR for further discussion). The applicant presented additional data in patients weighing 120 kg or more from ongoing study PS0015 to complement the limited patient numbers that were considered previously. In the phase 3 clinical program, 116 patients have now been identified with a body weight of minimum 120 kg at baseline.

In the initial treatment period, the efficacy outcomes reported at week 16 for the subgroup of patients weighing 120 kg or more (n=116) are consistent with those reported previously in this patient group (n=86). Especially for the more stringent endpoints PASI100 and IGA 0, there remains a significant lower response compared to patients that weigh less than 120 kg.

For the maintenance treatment period, the applicant conducted post-hoc subgroup analyses (<120kg vs ≥120kg) for the key efficacy endpoints PASI90, IGA 0/1, PASI100, and IGA 0 for the pooled data across studies PS0008, PS0009, and PS0015. Study participants in the ≥120kg group (N=88 [Q4W/Q8W=37; Q4W=51]) on the Q4W maintenance regimen showed greater improvement in PASI100 between Week 16 (39.2%) and Week 48 (68.6%), compared with those on the Q8W maintenance regimen (Week 16: 45.9% vs Week 48: 51.4%). As such, Q4W maintenance appears more effective at week 48 compared to Q8W maintenance therapy in patients weighing 120 kg or more in the most stringent endpoints, with the new data set on the expanded patient group confirming the previously reported outcomes.

A posology recommendation of bimekizumab Q4W in the Maintenance Phase has been made in the SmPC for patients weighing ≥120 kg who did not achieve complete skin clearance at week 16, this has been accepted by CHMP.

E3 pool subgroup analyses (Study PS0008 & PS0009 Q4W dosing data from Screening onwards)

Notable differences between subgroups included the finding that PASI90, IGA 0/1, and PASI100 response rates were higher in Central/Eastern Europe compared with the other regions. PASI90 response rates were also higher for study participants with prior exposure to systemic therapy for PSO compared with no prior exposure. A general Q4W bimekizumab dose in plaque psoriasis is not being pursued by the applicant. However, the applicant proposes a Q4W maintenance treatment dose in patients weighing ≥120 kg and this has been accepted by the CHMP.

PS0014 study with patients previously treated with ustekinumab

The applicant provided updated results from the ongoing PS0014 study. The high-level results show that IGA0/1 and PASI 90 over time was consistent with the pivotal studies and also demonstrated efficacy on nail, scalp psoriasis as well as on patients switched from Ustekinumab.

Studies DV0002 and DV0006

The applicant demonstrated that patients were able to self-administer safe and effective injections 8 weeks after training in self-injection technique or immediately after training in self-injection technique using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL.

Upon request from CHMP, the applicant added a statement in the SmPC – section 4.2 regarding non-responders after 16 weeks of treatment as follows:

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

2.5.4. Conclusions on the clinical efficacy

The efficacy data demonstrated superiority of bimekizumab 320 mg s.c. compared to placebo, adalimumab and ustekinumab in the treatment of moderate to severe plaque psoriasis. The study population included both systemic treatment naïve patients as well as those previously exposed to systemic therapies including biologic therapies. The efficacy of bimekizumab 320 mg s.c. is clinically highly relevant, with fast onset of action and a maintenance of effect was demonstrated. Therefore, the CHMP considers that the available efficacy data support the following therapeutic indication: *Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.*

2.6. Clinical safety

Patient exposure

In the initial application, safety data from 8 phase 2, phase 3 and OLE studies, in patients with moderate to severe plaque psoriasis (PS0010, PS0011, PS0016, PS0018, PS0008, PS0009, PS0013, and PS0014) were pooled to summarize the safety of bimekizumab. In these 8 studies, 1789 patients were treated with bimekizumab with a total time at risk of 1830.4 participant-years. This included exposure up to the data cut-off for the PS0014 study (01 November 2019) which was ongoing. A total of 1495 study participants (1461.5 participant-years) were treated with bimekizumab in the pivotal phase 3 studies (PS0008, PS0009 and PS0013). A total of 1399 study participants (78.2%) and 1073 participants (60.0%) were exposed to bimekizumab in Phase 2 and 3 studies for at least 8 months and 12 months, respectively. A total 237 (13.2%) were exposed for >16 months with no patients treated for greater than 2 years.

The Applicant issued on 19 October 2020 a 120-Day Safety Update report, complementing the initial Summary of Clinical Safety with 5.5 months of additional safety data. The update primarily consisted of additional long-term safety data from the open-label extension (OLE) study (PS0014). As of the 120-Day Safety Update clinical cut-off date (15 April 2020), the total time at risk was 2055.7 participant-years in the Phase 3 bimekizumab Total group compared with 1461.5 participant-years in the initial submission. A total of 1172 study participants were exposed to bimekizumab for ≥12 months during the phase 3 studies, out of which 214 study participants were treated with the maintenance dose of bimekizumab 320mg Q8W for ≥12 months.

In addition, two device presentation studies DV0002 and DV0006 evaluating self-injection technique and 3 formative human factors evaluations were conducted during the development of the bimekizumab-AI-1mL and bimekizumab-SS-1mL. In addition, Study UP0033 a phase I study conducted in healthy subjects demonstrated the bioequivalence of the drug substance formulation administered in the PFS (with true north secondary packaging) utilised in phase III studies in the PSO population, relative to the (commercial scale) drug substance to be administered in a safety syringe (SS) device and auto-injector (AI) (i.e. pre-filled pen) presentations proposed for marketing.

Table 39 - Study medication duration and participant-years of time at risk (Pool S2)

	Data in original BLA submission (as of the clinical cut dates for the respective Phase 3 studies)				Data in Safety Update (15 Apr 2020)			
	Phase 3 BKZ 320mg Q4W N=1456	Phase 3 BKZ 320mg Q8W N=510	Phase 3 BKZ Total N=1495	Phase 2/3 BKZ Total N=1789	Phase 3 BKZ 320mg Q4W N=1456	Phase 3 BKZ 320mg Q8W N=640	Phase 3 BKZ Total N=1495	Phase 2/3 BKZ Total N=1789
Study medication duration (days)								
n	1456	510	1495	1789	1456	640	1495	1789
Mean (SD)	287.0 (150.98)	208.9 (129.41)	351.3 (140.07)	351.4 (139.28)	379.0 (200.85)	288.7 (170.62)	493.5 (165.64)	470.2 (169.41)
Median	305.5	225.0	395.0	398.0	392.0	277.0	559.0	502.0
Min, Max	23, 670	1, 503	23, 670	1, 670	23, 847	1, 621	23, 847	1, 847
Duration of exposure (months)								
>0	1456 (100)	510 (100)	1495 (100)	1789 (100)	1456 (100)	640 (100)	1495 (100)	1789 (100)
≥4	1048 (72.0)	324 (63.5)	1346 (90.0)	1603 (89.6)	1127 (77.4)	505 (78.9)	1437 (96.1)	1694 (94.7)
≥8	850 (58.4)	247 (48.4)	1154 (77.2)	1399 (78.2)	1002 (68.8)	364 (56.9)	1346 (90.0)	1591 (88.9)
≥12	608 (41.8)	59 (11.6)	874 (58.5)	1073 (60.0)	841 (57.8)	214 (33.4)	1172 (78.4)	1371 (76.6)
≥16	138 (9.5)	1 (0.2)	224 (15.0)	237 (13.2)	549 (37.7)	117 (18.3)	915 (61.2)	928 (51.9)
≥20	2 (0.1)	0	6 (0.4)	14 (0.8)	236 (16.2)	10 (1.6)	468 (31.3)	476 (26.6)
≥24	0	0	0	0	15 (1.0)	0	34 (2.3)	34 (1.9)
≥28	NA	NA	NA	NA	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Total time at risk (participant-years)	1167.0	295.9	1461.5	1830.4	1544.9	512.6	2055.7	2424.7

BKZ=bimekizumab; BLA=Biologics License Application; ISS=Integrated Summary of Safety; Max=maximum; Min=minimum; NA=not applicable; NC=not calculated; Q4W=every 4 weeks; Q8W=every 8 weeks; SD=standard deviation; SU=Safety Update

Note: For duration of exposure, 1 month is defined as 30 days.

Note: Study participants who received both bimekizumab 320mg Q4W and bimekizumab 320mg Q8W are included in the population count of both treatment groups, but only once in the Phase 3 bimekizumab Total and Phase 2/3 bimekizumab Total groups.

The full safety analysis for the bimekizumab PSO program included a review of safety data from 5 integrated safety pools (S1, S2, S3, S4, and S5).

Pool S1 included **670** study participants who received bimekizumab 320mg Q4W compared with placebo, in Studies PS0009 and PS0013, of which 646 study participants (96.4%) completed these studies. This was the Primary safety pool and was used to summarize safety of bimekizumab versus PBO through Week 16 and to investigate subgroups.

In response to concerns regarding the completeness of Pool S1 (including only Week 16 data from placebo-controlled periods of studies PS0009 and PS0013), the applicant included additional exposure and safety data from the 16-week Treatment Period of PS0008 (active-comparator-controlled study with adalimumab) and from the 12-week Treatment Period of PS0010 (placebo and bimekizumab 320mg every 4 weeks [Q4W] treatment arms) to create a new post hoc Pool S1C.

Pool S1C included 211 study participants in the placebo group (original Pool S1: N=169) and 1032 participants in the bimekizumab 320mg Q4W group (original Pool S1: N=670) and contained comparative data with adalimumab (N=159) and ustekinumab (N=163).

Pool S2, including all Phase 2 and Phase 3 data from studies in PSO, included **1789** study participants. Safety data from the Initial Treatment Period, Maintenance Treatment Period, and OLE data were combined. Four safety treatment groups were included in this analysis defined as "Phase 3 BKZ 320mg Q4W", "Phase 3 BKZ 320mg Q8W", "Phase 3 BKZ Total", and "Phase 2/3 BKZ Total", reflecting the several different doses administered across these studies. The "Phase 2/3 BKZ Total" summary combined all bimekizumab doses. A total of **841** patients with PSO have been exposed to the highest dose (bimekizumab 320mg Q4W) for a period of ≥ 1 year. 214 study subjects have been treated with the maintenance dose of (bimekizumab 320mg Q8W) treatment for ≥12 months.

Data for active comparators (ustekinumab N=163, adalimumab N=159) were only included in a subset of outputs (Adverse Events of Special Interest and Deaths) produced for Pool S2.

Pool S2 had 4 additional sub pools: S2A (data collected while on blinded bimekizumab); S2B (Data from PS0009 and PS0013 during the Maintenance Period only to evaluate whether the AE profile changes with prolonged exposure); S2C (Data from PS0008 and PS0013 during the Initial and Maintenance Period comparing the safety of both maintenance treatment regimens tested bimekizumab 320mg Q4W or Q8W) after an Initial Treatment Period of 320mg Q4W for 16 weeks.); and S2D (Pool S2 data in which study participants with ≤4 weeks of bimekizumab 320mg Q8W dosing after treatment switched in PS0014 had their Q8W data excluded.)

Safety Pool S3 and Pool S4 summarized plasma concentrations and ADAb, and NAb data including data from device sub studies DV0002 and DV0006 to allow for pooled assessment by dose regimen and device type (autoinjector and safety syringe).

Bimekizumab has also been studied in clinical trials of psoriasis and other indications). Safety Pool S5 combines PSO data with data from other indications in the bimekizumab program. A total of **2178** patients were exposed to bimekizumab in this analysis.

Pool 5 did not include exposure from ongoing studies in these indications. Two complete studies were not included in the analysis on the basis that the applicant was no longer developing bimekizumab for these indications and the dosing regimens and patient populations studied differ substantially from those in the PSO program.

Adverse events

The overall risk of treatment emergent adverse events (TEAEs) decreased with longer exposure to bimekizumab based on a comparison of exposure-adjusted safety data derived from Pool S1 and Pool S2. The incidence of TEAEs leading to discontinuation, severe TEAEs, and serious adverse events (SAEs) in Pool S1 and Pool S2 was low. The majority of TEAEs were mild or moderate in severity (>90%). There was a trend towards increased severe TEAEs and SAEs in pool S2 compared to Pool S1. When adjusting for exposure, exposure-adjusted incidence rate (EAIRs) of severe TEAEs in the Phase 3 bimekizumab Total group were slightly higher in Pool S2 (5.8/100 PYs) compared with the bimekizumab 320mg Q4W group in Pool S1 (3.9/100 PYs); however EAIRs were still lower compared to the placebo group in Pool S1 (7.8/100 PYs). Similarly, for SAES, in Pool S1, EAIR was 5.3/100 PYs in the bimekizumab 320mg Q4W group and EAIR was 7.8/100 PYs in the placebo group. For Pool S2, EAIR was 6.8/100 PYs for SAEs.

In the new Pool S1C, 42.2% of placebo treated patients (n=89/211) and 60% (n=619/1032) of bimekizumab Q4W treated patients reported TEAEs.

Table 40 - Overview of TEAEs (Pool S1 and Pool S2)

	Pool S1			Pool S2	
	Placebo N=169 100 participant-yrs (PYs)=0.52	BKZ 320mg Q4W N=670 100 participant-yrs=2.08		Phase 3 BKZ Total N=1495 100 participant-yrs(PYs)=14.61	Phase 2/3 BKZ Total N=1789 100 participant-yrs(PYs)=18.30

	n (%) EAIR	n (%) EAIR		n (%) EAIR	n (%) EAIR
Any TEAEs	74 (43.8) EAIR 205/100PYs	394 (58.8) EAIR 305/100PYs		1208 (80.8 EAIR 231/100PYS	1465 (81.9) EAIR 238 /100PYs
SAEs	4(4.2) EAIR 7.8/100PYs	11 (1.6) EAIR 5.3/100PYS		96 (6.4) EAIR 6.6/100PYs	118 (6.6) EAIR 6.8/100PYs
Study participant discontinuations due to TEAEs	7(4.1) EAIR 13.8/100PYs	11 (1.6) EAIR 5.3/100PYs		62 (4.1) EAIR 4.3/100PYs	89 (5.0) EAIR 4.9/100PYs
Drug Related TEAEs	15 (8.9) EAIR 30.7/100 PYs	144 (21.5) EAIR 80/100 PYs		550(36.8) EAIR 50/100PYS	644 (36.0) EAIR 47.3/100PYS
Severe TEAEs	4 (2.4%) EAIR 7.8/100 PYs	8 (1.2) EAIR 3.9/100PYs		82 (5.5) EAIR 5.8 /100 PYs	113 (6.3) EAIR 6.4/100PYs
Deaths TEAES leading to death	1(0.6)	1(0.1)		3 (0.2)	5(0.3)

Common Adverse events
Initial 16-week treatment period (Pool S1 and Pool S1C)

In both analyses, the most commonly reported AEs on bimekizumab were nasopharyngitis, oral candidiasis and headache. Upper respiratory tract infection (UTI) and arthralgia, psoriatic arthropathy, psoriasis were reported at a higher incidence in the placebo group compared with the bimekizumab 320mg Q4W group.

Table 41 – TEAEs with an incidence in the bimekizumab group of at least 1 % higher than the placebo group during the initial treatment period (Pool S1 and Pool S1C)

MedDRA v19.0 System Organ Class Preferred Term	Pool S1		Pool S1C	
	Placebo N=169 n (%)	BKZ 320mg Q4W N=670 n (%)	Placebo N=211 n (%)	BKZ 320mg Q4W N=1032 n (%)
Any TEAE	12 (7.1)	173 (25.8)	14 (6.6)	236 (22.9)
Gastrointestinal disorders	0	8 (1.2)	NA	NA
Toothache	0	8 (1.2)	NA	NA
General disorders and administration site conditions	0	7 (1.0)	NA	NA
Fatigue	0	7 (1.0)	NA	NA
Infections and infestations	12 (7.1)	139 (20.7)	14 (6.6)	211 (20.4)
Nasopharyngitis	11 (6.5)	53 (7.9)	13 (6.2)	97 (9.4)
Oral candidiasis	0	49 (7.3)	0	78 (7.6)
Pharyngitis	1 (0.6)	12 (1.8)	1 (0.5)	19 (1.8)
Folliculitis	0	8 (1.2)	0	15 (1.5)
Gastroenteritis	0	8 (1.2)	NA	NA
Oropharyngeal candidiasis	0	8 (1.2)	0	11 (1.1)
Tinea pedis	0	8 (1.2)	0	13 (1.3)
Oral herpes	0	7 (1.0)	NA	NA
Nervous system disorders	0	22 (3.3)	0	31 (3.0)
Headache	0	22 (3.3)	0	31 (3.0)
Skin and subcutaneous tissue disorders	0	15 (2.2)	NA	NA
Acne	0	8 (1.2)	NA	NA
Dry skin	0	8 (1.2)	NA	NA

BKZ=bimekizumab; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary of Regulatory Activities; NA=not applicable; PT=Preferred Term; Q4W=every 4 weeks; SOC=System Organ Class; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least 1 TEAE in the SOC/PT.
Note: Pool S1C includes studies PS0008, PS0009, and PS0013 through Week 16 and PS0010 (placebo and BKZ 320mg Q4W arms) through Week 12.
Note: "NA": TEAEs in Posthoc Table 5.1.2C that did not meet the criteria of incidences at least 1% higher than placebo in the "BKZ 320mg Q4W group".

In the S1 pool the majority of cases were mild to moderate in severity. The incidence of severe TEAEs was 1.2% in the bimekizumab 320mg Q4W group and 2.4% in the placebo group. No severe TEAEs, by PT, were reported by more than 1 study participant.

The commonest drug related TEAEs in Pool S1 were oral candidiasis (5.8%), and oropharyngeal candidiasis and pruritus generalised (1.2% each).

Longer-term treatment (Pool S2)

In Pool S2, during the combined Initial, Maintenance, and OLE Treatment Period, TEAEs were reported by 80.8% (EAIR: 231.4/100 participant-years) in the Phase 3 bimekizumab Total groups. In the S2 Safety Update, TEAEs were reported by 86.9% (EAIR: 210.9/100 participant-years) in the Phase 3 bimekizumab Total groups.

Table 42 - Overview of TEAEs (Pool S2) original MAA submission and Safety Update

	Data in original BLA submission (as of the clinical cut dates for the respective Phase 3 studies)		Data in Safety Update (15 Apr 2020)	
	Phase 3 BKZ Total N=1495 100 participant-yrs=14.61 n (%) EAIR	Phase 2/3 BKZ Total N=1789 100 participant-yrs=18.30 n (%) EAIR	Phase 3 BKZ Total N=1495 100 participant-yrs=20.56 n (%) EAIR	Phase 2/3 BKZ Total N=1789 100 participant-yrs=24.25 n (%) EAIR
Any TEAEs	1208 (80.8) 231.4	1465 (81.9) 238.0	1299 (86.9) 210.9	1556 (87.0) 219.4
SAEs	96 (6.4) 6.8	118 (6.6) 6.6	123 (8.2) 6.2	145 (8.1) 6.2
Study participant discontinuations due to TEAEs	62 (4.1) 4.3	89 (5.0) 4.9	77 (5.2) 3.8	104 (5.8) 4.3
Drug-related TEAEs	550 (36.8) 50.5	644 (36.0) 47.3	622 (41.6) 42.9	716 (40.0) 41.5
Severe TEAEs	82 (5.5) 5.8	113 (6.3) 6.4	104 (7.0) 5.2	135 (7.5) 5.8
Deaths (TEAEs leading to death)	3 (0.2) 0.2	5 (0.3) 0.3	4 (0.3) 0.2	6 (0.3) 0.2

BLA=Biologics License Application; EAIR=exposure-adjusted incidence rate; BKZ=bimekizumab; ISS=Integrated Summary of Safety; SAE=serious adverse event; SU=Safety Update; TEAE=treatment-emergent adverse event; yrs=years
Note: n=number of study participants reporting at least 1 TEAE in that category.

The most frequently reported SOCs were 'Infections and infestations' (EAIR 120.4/100 participant-years), 'Skin and subcutaneous tissue disorders' (EAIR 23.7/100 participant-years), 'Gastrointestinal disorders' (EAIR 21.1/100 participant-years), 'Musculoskeletal and connective tissue disorders' (EAIR 16.8/100 participant-years), and 'General disorders and administration site conditions' (EAIR 9.0/100 participant-years). In the S2 Safety Update, the EAIRs for these SOCs were similar to or lower than those in the original application. (EAIR for gastroenteritis (1.9 vs 2.1) influenza (1.8 vs 2.0) bronchitis (2.5 vs 2.7) and UTI (3.8 vs 4.2)).

The most frequently reported TEAEs were nasopharyngitis (21.2%), oral candidiasis (15.7%), and upper respiratory tract infection (9.6%). All other TEAEs were reported in <5% of participants. Psoriasis was reported by 1.9% of study participants. In the S2 Safety Update, the most frequently reported TEAEs were the same with similar to or lower incidences than those in the original application.

The incidence of severe TEAEs was 5.5%. The following severe TEAEs by PT were reported by more than 1 study participant: acute myocardial infarction and myocardial infarction (0.2% each) cellulitis, oral candidiasis, hepatic enzyme increased (0.2% each), type 2 diabetes mellitus, duodenal ulcer haemorrhage, back pain, abortion spontaneous, and eczema (0.1% each). The EAIRs of severe TEAEs in the Phase 3 bimekizumab Total group in the S2 safety update analysis were slightly lower (5.2/100 participant-years) compared with the original MAA submission (5.8/100 participant-years).

Table 43 - Incidence of all SOCs per 100 participant-years (Pool S2)

MedDRA v19.0 System Organ Class	Data in original BLA submission (as of the clinical cut dates for the respective Phase 3 studies)		Data in Safety Update (15 Apr 2020)	
	Phase 3 BKZ Total N=1495 100 participant-yrs=14.61 n (%) [#] EAIR	Phase 2/3 BKZ Total N=1789 100 participant-yrs=18.30 n (%) [#] EAIR	Phase 3 BKZ Total N=1495 100 participant-yrs=20.56 n (%) [#] EAIR	Phase 2/3 BKZ Total N=1789 100 participant-yrs=24.25 n (%) [#] EAIR
Any TEAE	1208 (80.8) [5177] 231.4	1465 (81.9) [6391] 238.0	1299 (86.9) [6758] 210.9	1556 (87.0) [7972] 219.4
Blood and lymphatic system disorders	41 (2.7) [47] 2.8	59 (3.3) [74] 3.3	49 (3.3) [60] 2.4	67 (3.7) [87] 2.8
Cardiac disorders	30 (2.0) [46] 2.1	39 (2.2) [59] 2.2	36 (2.4) [58] 1.8	45 (2.5) [71] 1.9
Congenital, familial and genetic disorders	6 (0.4) [6] 0.4	9 (0.5) [9] 0.5	6 (0.4) [6] 0.3	9 (0.5) [9] 0.4
Ear and labyrinth disorders	38 (2.5) [47] 2.6	46 (2.6) [56] 2.5	46 (3.1) [55] 2.3	54 (3.0) [64] 2.3
Endocrine disorders	5 (0.3) [5] 0.3	8 (0.4) [8] 0.4	8 (0.5) [8] 0.4	11 (0.6) [11] 0.5
Eye disorders	81 (5.4) [108] 5.8	99 (5.5) [130] 5.6	101 (6.8) [138] 5.1	119 (6.7) [160] 5.1
Gastrointestinal disorders	272 (18.2) [373] 21.1	328 (18.3) [453] 20.5	344 (23.0) [494] 19.6	400 (22.4) [574] 19.3
General disorders and administration site conditions	123 (8.2) [174] 9.0	153 (8.6) [212] 8.9	148 (9.9) [208] 7.7	178 (9.9) [246] 7.9
Hepatobiliary disorders	19 (1.3) [25] 1.3	33 (1.8) [41] 1.8	25 (1.7) [33] 1.2	39 (2.2) [49] 1.6
Immune system disorders	24 (1.6) [26] 1.7	28 (1.6) [33] 1.5	31 (2.1) [33] 1.5	35 (2.0) [40] 1.5

MedDRA v19.0 System Organ Class	Data in original BLA submission (as of the clinical cut dates for the respective Phase 3 studies)		Data in Safety Update (15 Apr 2020)	
	Phase 3 BKZ Total N=1495 100 participant-yrs=14.61 n (%) [#] EAIR	Phase 2/3 BKZ Total N=1789 100 participant-yrs=18.30 n (%) [#] EAIR	Phase 3 BKZ Total N=1495 100 participant-yrs=20.56 n (%) [#] EAIR	Phase 2/3 BKZ Total N=1789 100 participant-yrs=24.25 n (%) [#] EAIR
Infections and infestations	945 (63.2) [2363] 120.4	1130 (63.2) [2821] 117.8	1060 (70.9) [3214] 108.9	1245 (69.6) [3672] 108.5
Injury, poisoning and procedural complications	180 (12.0) [207] 13.3	214 (12.0) [253] 12.6	217 (14.5) [268] 11.6	251 (14.0) [314] 11.3
Investigations	140 (9.4) [192] 10.2	203 (11.3) [316] 12.0	162 (10.8) [223] 8.5	225 (12.6) [347] 10.1
Metabolism and nutrition disorders	64 (4.3) [73] 4.5	90 (5.0) [110] 5.1	87 (5.8) [98] 4.4	113 (6.3) [135] 4.9
Musculoskeletal and connective tissue disorders	222 (14.8) [306] 16.8	262 (14.6) [373] 15.8	272 (18.2) [386] 15.0	312 (17.4) [453] 14.5
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	50 (3.3) [57] 3.5	66 (3.7) [76] 3.7	66 (4.4) [77] 3.3	82 (4.6) [96] 3.5
Nervous system disorders	136 (9.1) [175] 10.0	165 (9.2) [215] 9.7	168 (11.2) [214] 8.9	197 (11.0) [254] 8.8
Pregnancy, puerperium and perinatal conditions	3 (0.2) [4] 0.2	3 (0.2) [4] 0.2	4 (0.3) [5] 0.2	4 (0.2) [5] 0.2
Psychiatric disorders	50 (3.3) [56] 3.5	61 (3.4) [68] 3.4	54 (3.6) [58] 2.7	65 (3.6) [70] 2.7
Renal and urinary disorders	51 (3.4) [67] 3.6	61 (3.4) [84] 3.4	67 (4.5) [83] 3.3	77 (4.3) [100] 3.3
Reproductive system and breast disorders	29 (1.9) [41] 2.0	40 (2.2) [53] 2.2	34 (2.3) [48] 1.7	45 (2.5) [60] 1.9
Respiratory, thoracic and mediastinal disorders	154 (10.3) [196] 11.3	188 (10.5) [240] 11.1	192 (12.8) [255] 10.2	226 (12.6) [299] 10.2
Skin and subcutaneous tissue disorders	300 (20.1) [486] 23.7	359 (20.1) [578] 22.6	363 (24.3) [612] 21.0	422 (23.6) [704] 20.6
Social circumstances	2 (0.1) [2] 0.1	2 (0.1) [2] 0.1	3 (0.2) [3] 0.1	3 (0.2) [3] 0.1
Surgical and medical procedures	3 (0.2) [3] 0.2	4 (0.2) [4] 0.2	2 (0.1) [2] 0.1	3 (0.2) [3] 0.1
Vascular disorders	84 (5.6) [92] 6.0	108 (6.0) [119] 6.2	108 (7.2) [119] 5.5	132 (7.4) [146] 5.7

Drug-related TEAEs by PT (as assessed by the Investigator) were reported primarily for the SOC of 'Infections and infestations' (Pool S1: BKZ Q4W 13.9% vs PLB 3.6% and Pool S2: Phase 3 BKZ total 29.3%; S2 Safety Update Phase 3 BKZ total 33.9%). The EAIR for related TEAEs in the Phase 3 bimekizumab Total group (42.9/100 PYs; 120-Day SU) was lower than that in the original submission (Pool S2 50.5/100 participant-years).

The commonest drug related TEAEs in pool S2 were Oral candidiasis (13.2%), nasopharyngitis (5.1%), folliculitis (1.7%), upper respiratory tract infection (1.5%), oral fungal infection (1.3%), oropharyngeal candidiasis (1.2%), tinea pedis (1.1%), pharyngitis (1.1%), conjunctivitis (1.1%), sinusitis (1.0%), urinary tract infection (1.0%), and eczema (1.0%) in the Phase 3 bimekizumab Total group.

In the S2 Safety Update the most frequently reported drug-related TEAE was oral candidiasis. The EAIR for drug-related oral candidiasis (13.1/100 PYs; 120-Day SU) was lower than that in the original PoolS2 submission (14.8/100 PYs).

An evaluation by duration of treatment showed that the incidence of TEAEs in the Phase 2/3 bimekizumab Total group was highest in the earliest > 0 to 16-week time interval (60.4%) and subsequently decreased to 53.8% in the >16 to 32-week and to 47.1% in the >32 to 48-week time intervals, respectively. A similar picture was seen for the BKZ 320mg Q4W and BKZ 320mg Q8W analyses over the same time intervals.

In a comparison of the safety of Phase 3 bimekizumab 320mg Q4W and 320mg Q8W dosing regimens during the maintenance period, the incidence rate of TEAEs in the Phase 3 bimekizumab was higher in 320mg Q8W group (76.7%) compared with the Q4W group (73.9%) with slightly higher incidences of SAEs, TEAEs leading to discontinuation and severe TEAEs. Drug-related TEAEs were slightly higher in the 320mg Q4W treated group compared to the 320mg Q8W for the following TEAEs potentially linked to the mode of action: Candida infections (15.3% vs 10.9%), Dermatitis and eczema (5.7% vs 2.7%), and Bacterial infections NEC (5.4% vs 2.7%).

Analysis of adverse device effects

Different versions of the IMP were used across the clinical development programme. The devices proposed for marketing (bimekizumab-SS-1mL and bimekizumab-AI-1mL (used in DV0002 and DV0006)) were not used in the pivotal studies. The applicant has undertaken a drug comparability exercise and demonstrated that the change in process at both the drug product and drug substance level is minor and is well supported by comparability data. In addition Study UP0033 a phase I study conducted in healthy subjects demonstrated the bioequivalence of the drug substance formulation used in phase III studies, relative to the drug substance to be administered in a safety syringe (SS) device and on an auto-injection (AI) (i.e. pre-filled pen) presentations proposed for marketing.

Two device presentation studies (DV0002 and DV0006) evaluating self-injection technique and 3 formative human factors evaluations were conducted during the development of the bimekizumab-AI-1mL and bimekizumab-SS-1mL. The device presentation studies (DV0002 andDV0006) were conducted as sub-studies of the ongoing OLE study PS00014. A total of 134 study participants from PS0014 were enrolled in the DV0002 sub study and 88 study participants from PS0014 were enrolled in the DV0006 sub study. Overall, the incidence of TEAEs by SOC from both DV0002 and DV0006 for device type (SS and AI) are comparable (43.2% vs 42.7%). There were no ADEs (adverse device effect) reported; in particular, there were no treatment-emergent ADEs, nor serious ADEs. Further, there was no study participant discontinuations due to treatment-emergent ADEs, and no deaths reported with either investigational device presentation (bimekizumab-SS-1mL or bimekizumab-AI-1mL) or dosing regimen (bimekizumab 320mg Q8W or bimekizumab 320mg Q4W).

Serious adverse event/deaths/other significant events

In Pool S1, incidences of SAEs were low and similar to placebo in the first 16 weeks of treatment (1.6% and 2.4% in the bimekizumab 320mg Q4W and placebo groups, respectively). Serious AEs (bimekizumab 320mg Q4W group vs placebo) were most frequently reported in the SOCs of 'Gastrointestinal disorders' (0.4% vs 0 study participants), 'Infections and infestations' (0.3% vs 0 study participants) and 'Musculoskeletal and connective tissue disorders' (0.3% vs 0 study participants). No SAE was reported by >1 study participant in any treatment group. One case of Retinal detachment, Colitis Ulcerative, enteritis, diverticular perforation, enterovirus, pneumonia, intracranial haemorrhage, cardiac arrest, and myocardial infarction was reported in subjects treated with bimekizumab.

In Pool S2, the incidence of serious adverse events (SAEs) was 4% for study participants (EAIR: 6.8/100 participant-years) in the Phase 3 bimekizumab Total group. Incidences of SAEs in the ustekinumab group and adalimumab group were 7.4% and 3.1% respectively. In the Phase 3 bimekizumab Total group, SAEs were most frequently reported in the SOCs of 'Infections and infestations' (1.5% EAIR: 1.6/100 participant-years), 'Gastrointestinal disorders' (0.9% EAIR: 0.9/100 participant-years), 'Cardiac disorders' (0.7% EAIR: 0.7/100 participant-years), 'Musculoskeletal and connective tissue disorders' (0.6% EAIR: 0.6/100 participant-years), 'Injury, poisoning and procedural complications' and 'Nervous system disorders' (0.5% each EAIR: 0.5/100 participant-years). Acute myocardial infarction, myocardial infarction, cellulitis, and type 2 diabetes mellitus were reported by 3 study participants (0.2% each) and humerus fracture by 2 study participants (0.1%) in the Phase 3 bimekizumab Total group.

The incidence rates of SAE were similar across doses, with 3.1% in the Phase 3 bimekizumab 320mg Q4W group and 11 study participants and 4.3% in the Phase 3 bimekizumab 320mg Q8W group reporting SAEs.

S2 Safety update

The EAIR for SAEs in the Phase 3 bimekizumab Total group (6.2/100 participant-years) was lower than that in the original MAA submission (6.8/100 participant-years). Similar to the original S2 analysis, serious AEs in the Phase 3 bimekizumab Total group were most frequently reported in the SOCs of 'Infections and infestations', 'Gastrointestinal disorders', 'Cardiac disorders', 'Nervous system disorders', 'Musculoskeletal and connective tissue disorders', and 'Injury, poisoning and procedural complications disorders'. A total of 36 additional SAEs were reported in the Phase 3 bimekizumab Total group. The most frequently reported additional SAEs were colon cancer, and Coronary artery stenosis reported by 2 participants each. All other additional SAEs were reported by 1 study participant each.

Table 44 – Incidence of SAEs in at least 3 study participants by PT in the Phase 3 or Phase 2/3 bimekizumab total group (Pool S2)

	Data in original BLA submission (as of the clinical cut dates for the respective Phase 3 studies)		Data in Safety Update (15 Apr 2020)	
MedDRA v19.0 Preferred Term	Phase 3 BKZ Total N=1495 100 participant-yrs=14.61 n (%) [#]	Phase 2/3 BKZ Total N=1789 100 participant-yrs=18.30 n (%) [#]	Phase 3 BKZ Total N=1495 100 participant-yrs=20.56 n (%) [#]	Phase 2/3 BKZ Total N=1789 100 participant-yrs=24.25 n (%) [#]
Any SAE	96 (6.4) [125]	118 (6.6) [157]	123 (8.2) [161]	145 (8.1) [193]
Acute myocardial infarction	3 (0.2) [3]	4 (0.2) [4]	3 (0.2) [3]	4 (0.2) [4]
Cellulitis	3 (0.2) [3]	3 (0.2) [3]	3 (0.2) [3]	3 (0.2) [3]
Colon cancer	1 (<0.1) [1]	2 (0.1) [2]	3 (0.2) [3]	4 (0.2) [4]
Diarrhoea	2 (0.1) [2]	2 (0.1) [2]	3 (0.2) [3]	3 (0.2) [3]
Cataract	1 (<0.1) [1]	2 (0.1) [2]	2 (0.1) [2]	3 (0.2) [3]
Humerus fracture	2 (0.1) [2]	3 (0.2) [3]	2 (0.1) [2]	3 (0.2) [3]
Myocardial infarction	3 (0.2) [3]	4 (0.2) [4]	4 (0.3) [4]	5 (0.3) [5]
Type 2 diabetes mellitus[a]	3 (0.2) [3]	3 (0.2) [3]	2 (0.1) [2]	2 (0.1) [2]

AE=adverse event; BKZ=bimekizumab; BLA=Biologics License Application; ISS=Integrated Summary of Safety; MedDRA=Medical Dictionary for Regulatory Activities; PT=Preferred Term; SAE=serious adverse event; SU=Safety Update; TEAE=treatment-emergent adverse event; yrs=years
Note: n=number of study participants reporting at least 1 SAE within a PT.
Note: [#] is the number of individual occurrences of the SAE.
[a] Study participant PS0013-250-07256 had an SAE of type 2 diabetes mellitus in the original BLA submission. On further review, it was a pre-planned hospitalization and that it did not qualify as an SAE.

Deaths

Of 8 deaths, 5 were reported in bimekizumab-treated study participants. One TEAE leading to death occurred in each of the placebo, ustekinumab, and adalimumab treatment groups. The Cardiovascular

Clinical Event Adjudication Committee (CV-CAC) and the Neuropsychiatric Adjudication Committee adjudicated all TEAEs with a fatal outcome. All of the deaths occurred in the bimekizumab 320mg Q4W group. Two fatal events in the bimekizumab group were adjudicated as MACE: one was adjudicated as sudden cardiac death (PT: cardiac arrest) and 1 was adjudicated as other CV death (PT: cardiopulmonary failure); both occurred in study participants with significant CV risk factors. Both events were considered not related to bimekizumab by Investigators.

S2 Safety update

One additional death has been reported. This additional fatal TEAE (myocardial infarction) was adjudicated as MACE (sudden cardiac death) by the CV-CAC; a brief summary is provided below.

- a patient in the bimekizumab 320mg Q8W group experienced a TEAE of myocardial infarction during the OLE study PS0014; the event was serious, severe, assessed by the investigator as not related to investigational medicinal product (IMP), and fatal. The event occurred 437 days after first bimekizumab dose and 36 days after the most recent bimekizumab injection. Cardiac risk factors included body mass index (BMI) above 30 kg/m2, hypertension, cerebrovascular accident (10 years prior to death), and alcohol use within the past 6 months (2 units/week).

Other significant treatment-emergent adverse events

Infections, malignancies, MACE, neutropenia, suicidal ideation and behaviour (SIB), inflammatory bowel disease (IBD), anaphylactic, hypersensitivity, and injection site reactions, and hepatic TEAEs and liver function test (LFT) elevations were prespecified as being of special interest and were further evaluated.

Table 45 – Overview of adverse events (Pool S1 and S2)

Parameter	Pool S1[a]				Pool S2[b]	
	Placebo N=169 100 participant-yrs=0.52		BKZ 320mg Q4W N=670 100 participant-yrs=2.08		Phase 2/3 BKZ Total N=1789 100 participant-yrs=18.30	
	n (%)	EAIR	n (%)	EAIR	n (%)	EAIR
Any TEAE	74 (43.8)	205.0	394 (58.8)	305.8	1465 (81.9)	238.0
Any SAE	4 (2.4)	7.8	11 (1.6)	5.3	118 (6.6)	6.6
Any TEAE leading to discontinuation	7 (4.1)	13.8	11 (1.6)	5.3	89 (5.0)	4.9
Deaths	1 (0.6)	1.9	1 (0.1)	0.5	5 (0.3)	0.3
Safety topics of interest						
Serious infections	0	NA	2 (0.3)	1.0	25 (1.4)	1.4
Fungal infections (HLGT)	2 (1.2)	3.9	85 (12.7)	43.4	405 (22.6)	26.0
Candida infections (HLT)	0	NA	60 (9.0)	30.1	304 (17.0)	18.7
Fungal infections NEC (HLT)	2 (1.2)	3.9	12 (1.8)	5.8	67 (3.7)	3.7
Tinea infections (HLT)	0	NA	14 (2.1)	6.8	61 (3.4)	3.4
Opportunistic infections defined by UCB convention	0	NA	10 (1.5)	4.9	30 (1.7)	1.7
Malignancies per malignant tumours SMQ	1 (0.6)	1.9	1 (0.1)	0.5	15 (0.8)	0.8
Adjudicated MACE[c]	0	NA	1 (0.1)	0.5	12 (0.7)	0.657
Neutropenia TEAEs	0	NA	5 (0.7)	2.4	22 (1.2)	1.2
TEMA neutrophil low count	1 (0.6)	NA	4 (0.6)	NA	16 (0.9)	NA
SIB-adjudicated neuropsychiatric TEAEs	0	NA	0	NA	1 (<0.1)	0.1
IBD	0	NA	1 (0.1)	0.5	1 (<0.1)	0.055
Hypersensitivity reactions (SMQ)	1 (0.6)	1.9	28 (4.2)	13.8	186 (10.4)	10.9
Anaphylactic reactions	0	NA	0	NA	0	NA
Injection site reactions (HLT)	2 (1.2)	3.9	19 (2.8)	9.4	56 (3.1)	3.1
Hepatic TEAEs[d]	2 (1.2)	3.9	14 (2.1)	6.8	99 (5.5)	5.6
Liver function analyses (HLT)	2 (1.2)	3.9	13 (1.9)	6.3	85 (4.8)	4.8
ALT or AST >5x ULN	0	NA	3 (0.4)	NA	19 (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; 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; 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 S1: data to assess safety of bimekizumab vs placebo through Week 16 in Phase 3 placebo-controlled studies (PS0009, PS0013)

[b] Pool S2: data from all blinded PSO studies and their respective OLE studies (PS0010, PS0011, PS0016, PS0018, PS0008, PS0009, PS0013, and PS0014) for investigation of long-term exposure and safety data in all bimekizumab-treated study participants with moderate to severe plaque PSO.

[c] A MACE was defined as cardiovascular death, non-fatal MI, and stroke.

[d] By MedDRA SMQ Drug related hepatic disorders (excluding sub-SMQs Liver neoplasms, benign [incl cysts and polyps] and Liver neoplasms, malignant and unspecified).

Infections

Overall, infections were the most frequently reported TEAEs. The vast majority >98% were non-serious, mild to moderate in intensity, and did not lead to study drug discontinuation. In Pool S1, 36% of bimekizumab treated patients versus 22.5% of placebo treated patients reported any infection. In Pool S2, 63.2% of bimekizumab Phase 2/3 BKZ Total population reported any infection. The EAIR in Pool S2 was 117.8/100 participant-years and 141.7/100 participant-years in S1. In the S2 Safety update EAIRs were lower (108.5/100 participant-years; 120-Day SU) than those in the original MAA submission (117.8/100 participant years).

In Pool S1, the incidence of serious infections was 0.3%; EAIR: 1.0/100 PYs in the bimekizumab 320mg Q4W group. No study participant experienced a serious infection while receiving placebo.

In Pool S2, the incidence of serious infections was 1.4%; EAIR: 1.4/100 PYs in the Phase 2/3 bimekizumab Total group and 2.5%; EAIR: 2.6/100 PYs in the ustekinumab and 0.6%; EAIR: 1.4/100 PYs in the adalimumab groups. There was no evidence of an increase in infection with increased duration of treatment, the incidences of serious infections across time intervals were (>0 to 16 weeks

[0.3%] ;> 16 to 32 weeks [0.5%]; and >32 to 48 weeks [0.3%]). BY High Level Term (HLT) infections were most commonly reported in the gastrointestinal infections, Bacterial infections not elsewhere classified (NEC), Muscle and soft tissue infections, Upper respiratory tract infections subcategories. Of the 25 serious infections observed on bimekizumab, 9 were moderate in intensity and 16 were severe. None of the serious infections led to a fatal outcome. Cellulitis (3 study participants,) appendicitis and staphylococcal abscess (2 study participants) were the only PTs reported in more than 1 study participant. Study drug was permanently discontinued in 2 study participants due to TEAEs of oesophageal candidiasis and anal abscess. All serious infections were resolved at the time of reporting.

The EAIR for serious infections in Pool S2 Safety update Group was 1.2/100 PYs, compared with 1.4/100 PYs in the original MAA submission. Events were mostly related to skin (cellulitis, abscess), ear infections, and the gastrointestinal tract. A total of 3 additional serious infections (abscess limb, erysipelas, and ophthalmic herpes zoster) were reported. All 3 of these additional serious infections were resolved. None of the participants had a recurrence of serious infections.

There were no opportunistic infections reported with bimekizumab in the PSO studies other than localized mucocutaneous fungal events. In Pool S2, the proportion of study participants reporting a fungal infection TEAE was 22.6%; EAIR: 26.0/100 PY) in the bimekizumab Total group compared to ustekinumab and adalimumab groups (2.5%; EAIR: 2.6/100 PYs and 0.6%; EAIR: 1.4/100 PYs, respectively). Fungal infection TEAEs were observed in the 3 HLTs of Candida infections, Fungal infections NEC, and Tinea infections. Within the HLTs, TEAEs (≥2%) were observed for PTs oral candidiasis (15.1%, 0.6%, and 0%, respectively) and tinea pedis (2.0%, 0.6%, and 0%, respectively). One study participant had a serious fungal infection (oesophageal candidiasis) that resulted in discontinuation from the study. Seven study participants discontinued due to a fungal infection: oral candidiasis (3 participants), oesophageal candidiasis (2 participants), oropharyngitis fungal and oropharyngeal candidiasis (1 participant each). There were no cases of active tuberculosis (TB) among bimekizumab-treated study participants.

The EAIR for opportunistic infections in Pool S2 Safety update Group was 2.2/100 PYs, compared with 2.3/100 PYs in the original MAA submission. In Pool S2 Safety update group, the proportion of study participants reporting a fungal infection TEAE was 23.4%; EAIR: 37.2/100 PY compared with 22.6%; EAIR: 26.0/100 PY in the original MAA. opportunistic infections were localized fungal events classified as opportunistic by internal company convention, with the exception of one ophthalmic herpes zoster. The reported event of ophthalmic herpes zoster was serious, severe, related to IMP, resolved, and did not lead to discontinuation.

There were no cases of active TB or reactivation of TB in study participants with a history of latent TB among bimekizumab-treated study participants. A QuantiFERON TB test laboratory reporting error impacted on 5 samples from pivotal psoriasis (PSO) studies (PS0009 and PS0013) was reported. All 5 study participants rolled over into the PS0014 Open Label Extension (OLE) study. A review of all adverse events reported for these subjects during the feeder studies (PS0009 and PS0013) and the OLE study revealed no cases of active TB.

Serious Hypersensitivity Reactions

In Pool S1, there were no serious hypersensitivity reactions. In Pool S2, in the Phase 2/3 bimekizumab Total group, 3 study participants (0.2%; EAIR 0.2/100 PY [95% CI: 0.0, 0.5]) experienced a serious hypersensitivity reaction: anaphylactic shock, dermatitis atopic, and circulatory collapse in 1 study participant each. The TEAE of anaphylactic shock was reported as 'anaphylactic shock due to insect sting' and considered unrelated to bimekizumab. The TEAE of circulatory collapse was not related to hypersensitivity but an unrelated post-surgical complication. This event was fatal. The event atopic dermatitis was attributed to an environmental factor. TEAEs of hypersensitivity and drug

hypersensitivity were reported only in study participants who were ADAb-negative throughout the studies.

In Pool S2 safety update, the EAIR for hypersensitivity (10.3/100 PYs; 120-Day SU) was lower than that in the original MAA submission (10.9/100 PYs). No additional serious hypersensitivity reactions were reported during this Safety Update. The majority of hypersensitivity reactions in the Phase 2/3 bimekizumab Total group were reported in the SOC of 'Skin and subcutaneous tissue disorders' (EAIR: 8.3/100 PYs compared with EAIR: 8.8/100 PYs in the original MAA submission); mainly from the HLT Dermatitis and eczema. One additional severe TEAE (PT: dermatitis contact) and 1 additional TEAE leading to discontinuation (PT: dermatitis contact) were reported in the updated S2 analysis.

Injection Site Reactions

In Pool S1 the incidence of injection site reactions (ISR) was 2.8% in the bimekizumab 320mg Q4W group and 1.2% in the placebo group. In Pool S2, the incidence of ISR overall was 3.1%; EAIR: 3.1/100 PYs in the Phase 2/3 bimekizumab Total group). Incidences in the ustekinumab and adalimumab groups were 1.8% [EAIR: 1.9/100 PYs] and 3.1% [EAIR: 7.0/100 PYs], respectively). All ISRwere non-serious, mild or moderate in intensity, and did not lead to study discontinuation. All ISR started before the first ADAb-positive result was observed or occurred in study participants who were always ADAb-negative.

The EAIR ISR in the Phase 2/3 bimekizumab Total group was lower (2.6/100 PYs) in the S2 safety update analysis compared to the original MAA submission (3.1/100 PYs). All ISR were non-serious, mild or moderate in intensity, and did not lead to study discontinuation.

Inflammatory bowel disease (Crohn's disease and ulcerative colitis)

In Pool S1, one study participant (0.1%; EAIR 0.5/100py) in the bimekizumab 320mg Q4W group reported a TEAE of inflammatory bowel disease (IBD) (PT: Ulcerative colitis). No study participants in the placebo group reported an IBD TEAE. In Pool S2, no additional TEAEs of IBD were reported in any treatment group.

The EAIR for IBD events was 0.041/100 participant-years in the Phase 2/3 bimekizumab Total group (S2 Safety update), compared with 0.055/100 participant-years in the original MAA submission. No additional events of IBD were reported; however, a case of gastrointestinal inflammation was reported 3.5 months after the first dose of bimekizumab 320mg Q4W in PS0013. The event was serious, moderate, related to IMP, resulted in temporary interruption of IMP, and had an outcome of resolved. Treatment with IMP was re-introduced. A diagnosis of non-infectious gastroenteritis and colitis suggestive of a very early stage of Crohn's disease was made.

Major adverse cardiovascular events (MACE)

In Pool S1, the incidence of any adjudicated MACE in the Initial Treatment Period was low in the bimekizumab 320mg Q4W group (cardiac arrest in 1 study participant [0.1%]; EAIR: 0.5/100 PY). This event was fatal. No adjudicated MACE TEAE was reported in the placebo group.

In Pool S2, MACE TEAEs were reported in 12 study participants (0.7%; EAIR 0.7/100PYs) in the Phase 2/3 bimekizumab Total group. No MACE was observed for active comparator groups in Pool S2 analysis. MACE TEAEs reported for 2 or more study participants were myocardial infarction (4 study participants, 0.2%), acute myocardial infarction (3 study participants, 0.2%), and cerebral infarction (2 study participants, 0.1%). There was one additional fatal event of cardiopulmonary failure, and an event of myocardial infarction which resolved with sequelae. The remaining TEAEs were reported as resolved.

In the S2 safety update, the EAIRs for adjudicated MACE, extended MACE, and adjudicated CV events in the Phase 2/3 bimekizumab Total group were similar to or lower than those in the original MAA submission. In the Pool S2 update, MACE TEAEs were reported in 14 study participants (0.8%; EAIR 0.6/100PYs) in the Phase 2/3 bimekizumab Total group compared with 12 study participants (0.7%; EAIR 0.7/100PYs) in the original MAA. Two additional adjudicated MACE (1 sudden cardiac death and 1 nonfatal ischemic stroke) were reported. A patient experienced a fatal TEAE of myocardial infarction (also discussed in Section on Deaths). The second patient experienced a TEAE of cerebral ischemia approximately 18 months after first bimekizumab dose; the event was serious, moderate in intensity, not related to IMP, resulted in temporary interruption of IMP, and was considered resolved. The patient had a history of and its medical history was also significant for migraine headaches and an intracerebral developmental venous anomaly.

No notable trends were observed in the post-baseline ECG outlier values across all treatment groups in Pool S1. In Pool S1, no trends in QTcF increases were observed and no study participant had QTcF >500ms. In Pool S2, 1 study participant had QTcF >500ms that was asymptomatic and no TEAE related to this finding was reported. In addition to TEAEs related to ECG measurements, review was performed for TEAEs of ventricular tachycardia or fibrillation, syncope, and seizures to evaluate potential clinical consequences of severe arrhythmias. Overall, the incidences of those TEAEs were low and their review did not indicate a safety concern.

Malignancy

In Pool S1, one study participant in the bimekizumab 320mg Q4W group experienced a TEAE of basal cell carcinoma. One study participant in the placebo group experienced a TEAE of oesophageal adenocarcinoma. In Pool S2, the incidence of malignant tumour TEAEs in the Phase 2/3 bimekizumab Total group was 0.8% (EAIR: 0.8/100 PY) compared with 0.6% (EAIR: 0.6/100 participant-years) in the ustekinumab treatment group and 0.6%; EAIR: 1.4/100 participant-years) in the adalimumab. Malignant tumour TEAEs reported in the Phase 2/3 bimekizumab Total group are basal cell carcinoma (7 study participants (0.4%)), colon cancer (2 study participants (0.1%)), gastric cancer, anal squamous cell carcinoma, acute myeloid leukaemia, squamous cell carcinoma (in 1 participant who also experienced basal cell carcinoma), squamous cell carcinoma of lung, squamous cell carcinoma of skin, and keratoacanthoma (1 study participant (<0.1%)) each.

In the Pool S2 safety update analysis, the EAIR for any malignancy (0.8/100 participant-years) is the same as that in the original MAA submission. Six additional malignancies (colon cancer (2 cases), colon cancer metastatic, squamous cell carcinoma of skin (2 cases], and bronchial carcinoma) were reported. No malignancy was considered drug-related by the Investigator. The patients ranged in age from 49 to 70 yrs, Time to onset ranged from 16 to 22 months after first bimekizumab injection. Two of the 3 cases of colon cancer occurred in patients <60yrs. Four of the cases resulted in withdrawal from the

study (colon cancer (2 cases), colon metastatic (1case) and bronchial carcinoma (1 case)). All cases had contributing risk factors that confound causality assessment.

Suicidal ideation and behaviour (SIB)

The incidence rate of adjudicated SIB was 0.1 per 100 participant-years. No completed suicide or suicidal attempt was reported in study participants on bimekizumab in the PSO development program. One TEAE was adjudicated as suicidal ideation. This case was confounded by a diagnosis of schizoaffective disorder- bipolar type and medical history of suicide attempt.

Three study participants (0.2%) had a PHQ-9 Total Score ≥20 post-Baseline (indicating severe major depression). This was also captured as TEAE of psychiatric evaluation abnormal. The TEAEs were assessed as related to bimekizumab by the Investigator and the patients were withdrawn from the study.

In the Pool S2 updated safety analysis, no additional adjudicated SIB was reported. The EAIR of SIB as adjudicated by the Neuropsychiatric Adjudication Committee under bimekizumab was 0.0/100 participant-years, compared with 0.1/100 participant-years in the original MAA submission. The EAIR of TEAEs in the Psychiatric disorders SOC was 2.7/100 PYs, which is lower than that in the original MAA submission (3.4/100 PYs).

Hepatic TEAEs and LFT elevations

In Pool S1, the incidences of hepatic TEAEs were 2.1%; (EAIR: 6.8/100 PY) in the bimekizumab 320mg Q4W group and 1.2%; (EAIR: 3.9/100 participant-years) in the placebo group. Most of the TEAEs in the bimekizumab 320mg Q4W group were reports of isolated laboratory abnormalities (MedDRA HLT Liver function analyses). None of the hepatic TEAEs reported in Pool S1 was serious or severe in intensity. The rate of abnormal LFTs (ALT elevation >3xULN and AST elevation >3xULN) was 6% of placebo group and 1% of BKZ 320mg Q4W. One case of AST exceeding 20xULN and was attributed to gallstones.

In Pool S2, 5.5% (EAIR: 5.6/100 PYs) in the Phase 2/3 bimekizumab Total group experienced hepatic TEAEs, which was slightly higher than on ustekinumab (2.5%; EAIR: 2.6/100 PYs). Compared to adalimumab, the EAIR was lower (6.9%; EAIR: 15.8/100 PYs). The majority of reported hepatic TEAEs across all 3 groups were reports of laboratory abnormalities (HLT Liver function analyses). In the BKZ treated patients there were 8 cases (0.4%) of non-alcoholic fatty liver ,3 (0.2%) each of drug-induced liver injury and hepatic function abnormal, 2 (0.1%) each hepatic steatosis in non-alcoholic steatohepatitis and steatohepatitis. Hepatomegaly, autoimmune hepatitis, liver injury, and blood alkaline phosphatase increased were reported in 1 study participant (0.1% each). The incidence of hepatic TEAEs reporting laboratory abnormalities with bimekizumab (4.8%; EAIR: 4.8/100 participant-years), was higher than with ustekinumab (2.5%; EAIR: 2.6/100 participant-years), but lower than with adalimumab (6.9%; EAIR: 15.8/100 participant-years). Hepatic disorders (n=24), was the most frequent cause of discontinuation of study drug and included the 3 reports of drug-induced liver injury reported in Pool S2. The incidence rates of hepatic TEAEs in Phase 3 studies were similar between the Phase 3 bimekizumab 320mg Q4W and Q8W dose regimens.

In the Pool S2 Safety Update analysis, the EAIR for hepatic TEAEs (4.8/100 participant-years) was lower than that in the original MAA submission (5.6/100 participant-years). No new serious or severe hepatic TEAEs were reported, and no new hepatic TEAEs led to study discontinuation.

In terms of treatment-emergent markedly abnormal liver function (Pool S2), either AST or ALT elevations >3xULN were observed in 2.8% of the Phase 2/3 bimekizumab Total group in Pool S2. Two bimekizumab-treated study participants reached the threshold of Hy's Law based on laboratory values. However, in both cases non-drug-related causes for the observed LFT abnormalities were reported.

Three study participants experienced hepatic TEAEs reported as serious. Five additional study participants had LFT elevations with ≥8xULN, with no reported SAE.

In the Pool S2 Safety Update analysis, the EAIR for the HLT Liver function analyses (4.1/100 PYs) was lower than that in the original MAA submission (4.8/100 participant-years) There were no new study participants meeting Hy's Law laboratory criteria during this Safety Update. In this Safety Update, no new TEMA (>5xULN) of ALT increased were reported. One study participant experienced an AST elevation >5xULN and ≤8xULN. Also reported as TEAE of hepatic enzyme increased and a TEAE of fatty liver alcoholic, both were reported as nonserious, not leading to discontinuation, and resolving.

Neutropenia

The percentage of study participants with shifts from normal at baseline to low post-baseline minimum values was generally small across all treatment groups with no dose related trend. In the BKZ 320mg Q4W 5.2% reported Grade 1, 1.3% Grade 2 and 0.6% Grade 4 reduction in neutrophils. 5.1% shifted from Baseline 0 to Common Terminology Criteria for Adverse Events (CTCAE) Grade 1, 1.0% shifted to Grade 2 and 0.3% shifted to grade 3. In the placebo group 1.2% reported a CTCAE Grade 1 and 1.2% Grade 2 reduction in neutrophils. In Pool S2, 5.7% reported CTCAE Grade 1, 4.7% Grade 2, 0.8% Grade 3 and 0.1% Grade 4 decreases in neutrophils.

In Pool S1, the incidence of neutropenia TEAEs reported in the bimekizumab 320mg Q4W group was 0.7%; (EAIR: 2.4/100 PYs). In Pool S2, the incidence of neutropenia TEAEs in the Phase 2/3 bimekizumab Total group was 1.2%; (EAIR: 1.2/100 participant-years). Of these, 3 participants had Grade 3 and 2 participants had neutrophil Grade 4 value. There were no SAEs. One TEAE was reported as severe. None of the patients with Grade 3 neutropenia had reports of concurrent serious infections.

In the Pool S2 Safety Update the EAIR for neutropenia TEAEs (1.0/100 PYs) was lower than that in the original MAA submission (1.2/100 PYs). The 2 additional neutropenia TEAEs reported were for two study participants. Both events were non-serious and transient.

Laboratory findings

Haematology

Haemoglobin and platelets

The majority of Shift from Baselines in Pool S1 were to CTCAE Grade 1 and Grade 2. The changes in values in both haematology parameters were similar in the bimekizumab 320mg Q4W compared to the placebo groups. In Pool S2 Phase 2/3 BKZ Total (N=1789) there were 6 (0.3%) Grade 3 and 1 (<0.1%) grade 4 reductions in haemoglobin (Hb). There were no markedly abnormal haemoglobin values in Pool S1. In Pool S2 there were 2 report of Hb <8.0g/dl and 1 report of platelet low ($<50x10^9$/L).

The most frequently reported TEAEs related to abnormal haematology values within the 'Investigations and Blood and lymphatic system disorders' SOCs were related to neutropenia (see Adverse Event of Special Interest)

The results from the Pool S2 Safety Update were similar to those of Pool S2 in the original MAA submission. The majority of the shifts from Baseline values were small, transient and not considered to be clinically relevant.

Biochemistry laboratory values

In Pool S1, mean and median changes in biochemistry laboratory values (Observed and Change from Baseline) for Calcium (mmol/L), Chloride (mmol/L) and Sodium (mmol/L) for BKZ 320mg Q4W (N=670) were generally small and similar to placebo; and not considered to be clinically meaningful. Similarly, for Creatinine, (umol/L) mean and median changes in biochemistry laboratory values (Observed and Change from Baseline) were small and similar between BKZ 320mg Q4W and placebo treated groups.

In Pool S2 in general, the percentage of study participants with shifts from Baseline to minimum/maximum post-Baseline values in any biochemistry parameter was similar between treatment groups.

In the Pool S2 Safety update, the results were similar to those in the original MAA submission. 6.4% of study participants in Phase 2/3 bimekizumab Total group reported any treatment-emergent markedly abnormal (TEMA) biochemistry laboratory value compared with 5.6% in the original MAA submission.

Glucose (mmol/L)

In the BKZ 320mg Q4W (N=670) group, 165 (24.6%) recorded high glucose values. Of these 30 (4.5%) shifted from normal to high values during the study. A total of 38 (22.5%) of the placebo treated group reported high glucose levels. Of these 3.6% developed high readings during treatment. In the BKZ 320mg Q4W (N=670) group there was a very modest increasing trend from the baseline in blood glucose level apart from week 16 when a slight decrease from mean baseline was reported. A similar picture was seen in the placebo group.

In Pool S1, in terms of markedly abnormal biochemistry values, the most frequently reported biochemistry value was high glucose (bimekizumab 320mg Q4W group [3.9%] and the placebo group [3.6%], respectively. In Pool S2 the most frequently reported TEMA biochemistry value was high glucose (4.0%). In The updated Pool S2 safety analysis the TEMA value for Glucose was 4.8%.

Potassium (mmol/L)

Potassium high (>6.0 mmol/L) was reported in Pool S1 bimekizumab 320mg Q4W group [0.7%] and the placebo group [0%], respectively) and S2 (0.8%).

Lipid profile

The impact of bimekizumab on lipid profile during the induction and maintenance periods has been provided by the applicant. Total cholesterol levels were measured only in Phase 2 studies PS0010, PS0011, PS0016, and PS0018 (total cholesterol was not fractionated into low density lipoprotein [LDL] or very low density lipoprotein [VLDL]). No study participants had markedly abnormal (Grade 3 or 4) total cholesterol values at any point in time up to 76 weeks. In Pool S2 the number of TEAEs of blood cholesterol increased and hypercholesterolaemia were low: 8 (0.4%) reported blood cholesterol increased and 10 (0.6%) reported hypercholesterolaemia. None of these events were serious or severe, and none led to study discontinuation.

Safety in special populations

The safety analysis of intrinsic factors included an evaluation of TEAEs by age, gender, race, and body weight. Extrinsic factors included evaluations by geographic region. The subgroups assessed were age, gender, and race (for Pool S1 and Pool S2), and body weight (Pool S2 only). Within the body weight category, an additional analysis by dosing regimen (Pool S2C) was presented.

Age

In Pool S1 in the bimekizumab 320mg Q4W group, the older age group (≥65 years: (70.9%)) had a higher incidence of TEAEs compared with the younger groups <40 yrs: (59.8%) and >=40-64 yrs: (56.3%). This trend was not observed in the placebo group. The highest difference (≥5%) in bimekizumab-treated study participants was observed in the SOC of 'Skin and subcutaneous tissue disorders' (<40 years), 40 to <65 years, and ≥65 years: 9.2%, 11.7%, 20.0%) which was mainly driven by the HLT Dermatitis and eczema (<40 years), 40 to <65 years, and ≥65 years: 1.6%, 3.6%, 7.3%). Although there was no clear pattern of an increase in TEAES across age groups in the SOC of Infections and infestations 40.6%, 32.0%, 41.8%) Candida infections (7.6%; 8.5%; 18.2% respectively) mainly driven by the increase in oral candidiasis were increased in the ≥65 years group.

In the longer term S2 Pool, there was a trend towards increase in TEAES with increasing age. In Pool S2, in the Phase 2/3 bimekizumab Total group, the overall incidence of TEAEs was 80.6% and 82.1%, respectively in the <40 years and 40 to <65 year age group and slightly higher in the ≥65 years group (86.3%). There was a higher overall incidence of TEAEs (≥5%) in the ≥65 years group compared to <40 yrs and >=40-64 yrs, in the SOCs of 'Skin and subcutaneous tissue disorders' (32.7%, 16.4% and 20.5% respectively) and 'Musculoskeletal and connective tissue disorders' (22.2%, 10.9% and 16.0% respectively). These differences were driven by the HLTs Dermatitis and eczema (17.0%, 5.5%, 10.7% and respectively) and Musculoskeletal and connective tissue pain and discomfort (7.8%, 3.8% and 5.4% respectively).

In the Pool S2 Safety Update a higher incidence of TEAEs was also observed in the elderly age group ≥65 years group compared to <40 yrs and >=40-64 yrs age groups, in the SOCs of 'Eye disorders', 'Metabolism and nutrition disorders', 'Musculoskeletal and connective tissue disorders', 'Neoplasms benign, malignant and unspecified (including cysts and polyps)', 'Skin and subcutaneous tissue disorders', and 'Vascular disorders'. These differences were driven by HLTs cataract conditions, diabetes mellitus (incl subtypes), joint related signs and symptoms, musculoskeletal and connective tissue pain and discomfort, osteoarthropathies, dermatitis and eczema, pruritus NEC, rosaceas, skin preneoplastic conditions NEC and vascular hypertensive disorders NEC. Incidences of TEAEs were higher in the updated Pool S2 analysis compared to the original S2 analysis due to the longer exposure.

Study participants ≥65 years of age in Pool S2 were further stratified using age categories of <65 years, 65 to 74 years, 75 to 84 years, and ≥85 years. There 18 participants>75 years of age and none above 85 years of age. There was a trend towards an increase in serious cases across age groups (5.9% <65 yrs, 14.1% 65 to 74 years and 11.1% 75 to 84yrs respectively).

Gender

The majority of bimekizumab-treated study participants were male (72.2% in Pool S1 and 70.0% in Pool S2.) In Pool S1, the incidence of TEAEs was higher in females than in males in both bimekizumab and placebo study participants. Treatment-emergent AEs with a notably higher incidence in females were observed in the 'Infections and infestations' SOC: 71.5% vs 59.6% respectively. 'Upper respiratory tract infections' (40.8% vs 34.3%), 'Urinary tract infections' (11.4% vs 2%), 'Candida infections' (19.2% vs 16.1%) and 'Injection site reactions' were more commonly reported in females (5.4%) than men (2.2%). In the Pool S2 safety update the trends for TEAEs by gender were consistent with those observed in the original MAA submission.

Race

Most study participants treated with bimekizumab were White (82%), 2% were Black and 16% were classified as other. The most frequently reported TEAEs in White and other study participants were in the SOCs of Infections and infestations, gastrointestinal disorders, and Skin and subcutaneous tissue

disorders. Noticeable differences were noted in the Skin and subcutaneous tissue disorders SOC for the HLT Dermatitis and eczema (≥5%) where the incidence was higher in the other study participants compared with White study participants. In the Pool S2 safety update the trends for TEAEs by race were consistent with those observed in the original MAA submission.

Body Weight

In Pool S2, (Phase 2/3 BKZ population) the incidence of TEAEs by body weight for the categories: <70kg, ≥70 to <95kg, ≥95 to <115kg, and ≥115kg was 83.6%, 80.1%, 80% and 89.8% respectively. Heavier study participants had a higher incidence of TEAEs (≥5%) compared with participants of lower body weights particularly in the 4 SOCs of Injury, poisoning and procedural complications (11.7%, 11.2%, 9.1%, and 21.4%,respectively), Metabolism and nutrition disorders (0.8%, 4.9%, 7.0%, and 8.7%, respectively), Musculoskeletal and connective tissue disorders (12.3%, 15.1%, 14.2%, and 18.0%, respectively, and Vascular disorders (2.2%, 5.4%, 7.5%, and 12.1%, respectively). Lower body weight patients had more Candida infections than higher body weight patients did. The incidence of SAEs by body weight for the categories: <70kg, ≥70 to <95kg, ≥95 to <115kg, and ≥115kg was 5.0%, 4.9% 9.6% and 9.7% respectively

The incidence of severe TEAEs by body weight for the categories: <70kg, ≥70 to <95kg, ≥95 to <115kg, and ≥115kg was 5.0%, 5.4%, 7.2% and 10.2% respectively.

Table 46 - Overview of TEAEs by body weight during the combined Initial, Maintenance, and OLE Treatment Period (Pool S2)

Category	Phase 2/3 BKZ Total group - body weight n (%) [#]			
	<70kg N=359	≥70-<95kg N=795	≥95-<115kg N=429	≥115kg N=206
Any TEAEs	300 (83.6) [1382]	637 (80.1) [2740]	343 (80.0) [1460]	185 (89.8) [809]
SAEs	18 (5.0) [25]	39 (4.9) [45]	41 (9.6) [60]	20 (9.7) [27]
Discontinuation due to TEAEs	21 (5.8) [26]	34 (4.3) [37]	24 (5.6) [29]	10 (4.9) [12]
Drug-related TEAEs	158 (44.0) [476]	281 (35.3) [677]	137 (31.9) [324]	68 (33.0) [154]
Severe TEAEs	18 (5.0) [25]	43 (5.4) [54]	31 (7.2)[47]	21 (10.2) [30]
All deaths (AEs leading to death)	0	0	2 (0.5) [2]	3 (1.5) [5]
Deaths (TEAEs leading to death)	0	0	2 (0.5) [2]	3 (1.5) [5]

AE=adverse event; BKZ=bimekizumab; ISS=Integrated Summary of Safety; OLE=open-label extension; SAE=serious adverse event; TEAE=treatment-emergent adverse event
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.

The increase in serious and severe TEAEs in heavier study participants was most marked in the Infections and infestations SOC without any clear pattern.

Further analyses by body weight based on Pool S2C were presented using weight categories of ≤120kg and >120kg.

Some differences between the Phase 3 bimekizumab 320mg Q4W and the Q8W group were noted for the ≤120kg and >120kg weight categories. The incidence of TEAEs was slightly lower in the Phase 3 bimekizumab 320mg Q4W group (73.0%) compared with the Phase 3 bimekizumab 320mg Q8W group (76.7%) in the ≤120kg weight category and higher in the >120kg weight category (85.0% vs 76.0%, respectively). Slightly higher incidences of drug-related TEAEs in the Phase 3 bimekizumab 320mg Q4W group (28.6%) compared to the Phase 3 bimekizumab 320mg Q8W group (25.9%) were

observed in the ≤120kg weight category, while the incidence was similar in the >120kg weight category (35.0% and 36.0%, respectively).

In the Q4W dosing regimen, the incidence of TEAEs were similar in both body weight groups (≤120kg and >120kg) for the SOCs of Gastrointestinal disorders, Musculoskeletal and connective tissue disorders, and Vascular disorders and for HLTs of Candida infections and Bacterial infections NEC. In the ≤120kg body weight group, a higher incidence of TEAEs (≥5%) was observed in the SOC of Investigations. The HLT Dermatitis and eczema was also higher in the lower weight group.

In the heavier body weight (>120kg) group, a difference of ≥10% was observed in SOCs of Infections and infestations, Injury, poisoning and procedural complications, and a difference ≥2.5% was observed in the SOCs of Metabolism and nutrition disorders, and Skin and subcutaneous tissue disorders.

In the Q8W dosing regimen, study participants in the higher body weight group (>120kg) tended to have a higher incidence (≥5%) at SOC level for TEAEs in Metabolism and nutrition disorders, Gastrointestinal disorders, Skin and subcutaneous tissue disorders, Vascular disorders, and Musculoskeletal and connective tissue disorders. At HLT level, incidences were higher (≥5%) for the heavy weight group for Candida infections, Bacterial infections NEC, and Dermatitis and eczema. The ≤120kg body weight group had more TEAEs (≥5%) in the SOC of Infections and infestations and Investigations, as well as a higher incidence (≥2.5%) of events related to Injury, poisoning and procedural complications.

In S2 Pool Safety Update, similar to the original S2 analysis, heavier study participants had a higher incidence of TEAEs (≥5%) compared with participants of lower body weights particularly in the 4 SOCs of Injury, poisoning and procedural complications, Metabolism and nutrition disorders, Musculoskeletal and connective tissue disorders, and Vascular disorders. These differences (≥5%) were most noticeable in the HLT Vascular hypertensive disorders NEC.

Of note, lower body weight study participants had more Candida infections than higher body weight participants did. There was a tendency for more serious and severe TEAEs in heavier study participants driven by the Infections and infestations SOC without any clear pattern, and more drug-related TEAEs in lower body weight participants driven by the HLT Candida infections.

Pregnancy

A total of 11 maternal bimekizumab exposure pregnancies have been reported in the studies included in Pool S2. Five pregnancies resulted in the live birth of a healthy baby, 2 pregnancies ended due to spontaneous abortion during the first trimester, 1 induced abortion was performed during the first trimester, and 3 pregnancies were ongoing. No congenital anomalies were reported. One new serious TEAE of haemorrhage in pregnancy was reported in one subject, but outcome was unknown and no further information could be obtained. There are no safety data regarding exposure during lactation available.

Immunological events

The number of study participants who became ADAb positive for the first time increased with duration of treatment and repeat dosing with bimekizumab in both of the tested dosing regimens.

During the Initial Treatment Period (Pool S3), the overall incidence of ADAb was 22.6%. During the combined Initial and Maintenance Treatment Period (Pool S2A), the incidence of ADAb was 37.6% following a year of treatment with bimekizumab 320mg Q4W and 45.1% (116 of 257 participants) following a year of treatment with bimekizumab 320mg Q4W/Q8W.

The total number of study participants who were ADAb positive for the first time seemed to saturate by Week 28 in the bimekizumab 320mg Q4W group and by Week 36 in the bimekizumab 320mg Q4W/Q8W group, with few study participants becoming positive after these time points.

TEAEs were most frequently reported in ADAb-positive (EAIR 12.4/100 PYs) study participants compared to first those who had an ADAb-positive result starting before the AE (9.8/100 PYs) and ADAb-negative patients (EAIR 7.8/100PYs). In all groups, TEAEs were most frequently reported in the SOCs of Infections, infestations, Skin, and subcutaneous tissue disorders. Dermatitis and eczema were slightly higher for AEs starting on/after the first ADAb-positive result (7.0%) compared with AEs starting before the first ADAb-positive result (3.5%), and similar to the group who was always ADAb negative (6.3%). The EAIR of TEAEs in the Infections and infestations SOC was highest in the groups whose AEs started before the first ADAb-positive result (EAIR: 152.2/100 PYs) and on/after the first ADAb-positive result EAIR 142.6/100PY compared with always negative ADAb and EAIR: 120.5/100 PYs.

Across the Phase 3 studies in Pool S2A, 14.6% (91 of 625 participants) on bimekizumab 320mg Q4W throughout and 15.6% (40 of 257 participants) on bimekizumab 320mg Q4W/Q8W were positive for antibodies that neutralize the binding of bimekizumab to its IL-17 target. The overall incidence of TEAEs and EAIRs were higher in study participants who were overall NAb-positive: 87.3% (N=150 study participants; EAIR: 277.6/100-participant-years) compared with 82.1% (N=262 study participants; EAIR: 229.0/100-participant-years) in study participants who were overall NAb-negative.

Treatment-emergent AEs in overall NAb-negative and overall NAb-positive participants were most frequently reported in the SOCs of Infections and infestations and Skin and subcutaneous tissue disorders. Study participants who were overall NAb-negative had a greater incidence of TEAEs in the HLT of Candida infections compared with study participants who were overall NAb-positive (21.0% [EAIR: 25.1/100 PYs] vs 14.0% [EAIR: 16.5/100 PYs]).

Safety related to drug-drug interactions and other interactions

No specific drug-drug interaction study with bimekizumab has been conducted.

In PS0008, study participants switched from adalimumab to bimekizumab treatment without a washout period as per study design. Overall, there appeared to be a generally similar safety profile and no unexpected safety findings in study participants who switched directly from adalimumab to bimekizumab at Week 24 relative to study participants who received continuous bimekizumab treatment.

Discontinuation due to adverse events

In Pool S1, the incidence of TEAEs leading to discontinuation was 1.6%; EAIR: 5.3/100 PYs in the bimekizumab 320mg Q4W group compared with 4.1%; EAIR: 13.8/100 PYs the placebo group. TEAEs leading to study discontinuation reported by >1 study participant in any treatment group, were eczema in the bimekizumab 320mg Q4W group (0.3%) and psoriasis in the placebo group (1.8%). In Pool S2, the incidence of TEAEs leading to discontinuation was low overall (4.1%; EAIR: 4.3/100 PYs) and were most frequently reported in the SOCs of Infections and infestations (1.0%), Skin and subcutaneous tissue disorders (0.9%), and Investigations (0.7%). The most frequently reported TEAEs leading to discontinuation by PT were hepatic enzyme increased and psoriasis in 4 study participants (0.3%) each.

In the Pool S2 Safety Update, the EAIRs for TEAEs leading to discontinuation in the Phase 3 bimekizumab Total group (3.8/100 participant-years) was lower than that in the original MAA

submission (4.3/100 participant-years). A total of 16 additional TEAEs leading to discontinuation were reported. The most common additional TEAEs leading to discontinuation were psoriasis and colon cancer, each reported by 2 study participants in the Phase 3 bimekizumab Total group.

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

The safety data from 8 phase 2, phase 3 and OLE studies in PSO (PS0010, PS0011, PS0016, PS0018, PS0008, PS0009, PS0013, and PS0014) were pooled to summarize the safety of bimekizumab. For studies PS0008, PS0009, and PS0013 treatment periods up to Week 52 or Week 56 were completed. A small number of study participants were still in the safety follow up (SFU) period at the time of the cut-off date for the individual studies. Regarding the open-label study PS0014, safety data were included through the cut-off date for the submission (01 November 2019). Upon request by CHMP, the Applicant issued on 19 October 2020, the 120-Day Safety Update report which provided 5.5 months of additional long-term safety data from the open-label extension (OLE) study (PS0014) up to the designated clinical cut-off date (15 April 2020).

Patient Exposure

1789 patients were treated with bimekizumab. As of the 120-Day Safety Update clinical cut-off date, the total time at risk was 2424.7 participant-years (PY) in the Phase 2/3 bimekizumab Total group compared with 1830.4 PY in the original MAA submission. A total of 1371 study participants (compared with 1073 study participants in the original MAA submission) were exposed to bimekizumab for ≥12 months at any dose, out of which 214 study participants (compared with 59 in the original MAA submission) were treated with the maintenance dose of bimekizumab 320mg Q8W for ≥12 months which helps further characterise the long term safety of the 320mg Q8W maintenance regimen. The study duration for active comparators was 52 weeks for ustekinumab and 24 weeks for adalimumab and included a total of 163 and 159 study participants (156.4 and 72.6 participant-years respectively). A total of 2178 subjects have been exposed to bimekizumab across all indications accounting for a total of 1932.7 participant-years of exposure. Overall exposure exceeded the ICH E1 safety exposure requirements of >1500 patients exposed, 300 to 600 for 6 months, > 100 for 1 year and is considered adequate to characterize more frequently reported ADRs.

Safety pools

The safety of bimekizumab was assessed using 5 main integrated datasets (S1, S2, S3, S4, and S5). The focus was primarily based on the 8 Studies in participants with moderate to severe PSO included in the S1 and S2 integrated safety sets.

In pool S1, evaluating safety over the 16 weeks initial treatment period, only 2 of the pivotal phase 3 studies were pooled (P0009 and P00013) on the basis that they had similar study designs and were placebo-controlled through Week 16. In the original pool S1, 670 study participants received bimekizumab 320mg Q4W compared with placebo (n=169). In response to a concern regarding the completeness of Pool S1 (including only Week 16 data from placebo-controlled periods of studies PS0009 and PS0013), the applicant included additional exposure and safety data from the 16-week Treatment Period of PS0008 (active-comparator-controlled study with adalimumab) and from the 12-week Treatment Period of PS0010 (placebo and bimekizumab 320mg every 4 weeks [Q4W] treatment arms) to create a new Pool S1C across PS008, PS0009, PS0010/11 and PS0013.

Pool S2 which included data from all blinded phase 2 and 3 studies and their respective extension studies investigated long-term exposure. The "Phase 2/3" treatment group included data from all study participants while treated with bimekizumab during PS0010, PS0011, PS0016, PS0018, PS0008, PS0009, PS0013, and PS0014 up to a cut-off point of the 20th April 2020. Comparative data with ustekinumab and adalimumab were also provided in this analysis. However, the duration of exposure varied considerably. The duration of exposure for comparators was limited to Week 52 for ustekinumab and to Week 24 for adalimumab which led to a large imbalance in PYs of exposure between bimekizumab and these comparators. Safety data collected during the randomized withdrawal from bimekizumab in Study PS0013 was not included in Pool S2. No new safety concerns were identified with maintenance of response (through Week 56) on continued bimekizumab dosing versus withdrawal of bimekizumab (placebo) as outlined in the CSR for Study PS0013.

In Safety Pool S5 which combines PSO data with data from other indications in the bimekizumab programme, no new safety concerns were identified.

Overall, the patients recruited to the phase 2 and 3 studies included in Pool S1 and Pool S2 had moderate to severe plaque PSO, poorly controlled by topical treatments and or systemic treatments. Patients recruited had high levels of background morbidity. Over 80% reported a previous or ongoing medical condition at baseline. As expected, hypertension, obesity hyperlipidaemia and type 2 diabetes mellitus were the most commonly reported conditions. Baseline morbidity and co-morbidity, as well as use of concomitant medications were generally well balanced between the study groups, throughout the studies. There was some slight variability in baseline rates of hypertension and gastro-oesophageal reflux in bimekizumab patients compared to placebo. However, these imbalances are unlikely to have any impact on the interpretation of safety findings.

Treatment Emergent Adverse Events (TEAES)

The most frequently reported AEs (at least 1% higher than the placebo group) were infections and infestations and were more common in the bimekizumab treated patients compared to placebo (20.4% vs 6.6%), with nasopharyngitis (9.4%), oral candidiasis (7.6%) being the most common events in BKZ treated patients in this SOC.

The short term safety profile is in line with the expected safety profile for a medication targeting IL-17A and IL-17F and its impact on muco-epidermal immunity resulting in impaired host defences against extracellular bacteria and fungi at mucosal surfaces with small imbalances in incidence by HLT observed for Upper respiratory tract infections, Candida infections, Skin structures and soft tissue infections, Fungal Infections NEC, Abdominal and gastrointestinal infections, bacterial infection NEC, Viral infections NEC, Herpes viral infections, Dental and oral soft tissue infections, Ear infections, and Tinea infections.

The most common TEAEs reported ≥1% Higher than the Placebo Group were Nasopharyngitis, Oral candidiasis, Pharyngitis, Folliculitis, Tinea Pedis, Oropharyngeal candidiasis, Headache.

The long-term safety of bimekizumab (Pool S2 updated), over 48 weeks of treatment, was mainly similar to the 16 week initial treatment period (Pool S1C). There was no evidence of a clinically relevant increase in TEAEs with increased exposure.

The most frequently reported SOCs over longer term use were SOCs of Infections and infestations, Skin and subcutaneous tissue disorders, and Gastrointestinal disorders. At the PT level, the most frequently reported TEAEs were nasopharyngitis, oral candidiasis, and upper respiratory tract infection.

Upon request by CHMP, long term safety data collected during the randomised withdrawal from bimekizumab (bimekizumab 320mg Q4W/placebo group re-randomized to withdrawal from bimekizumab) were provided. No new safety concerns were identified with maintenance of response (through Week 56) on continued bimekizumab dosing versus withdrawal of bimekizumab (placebo).

Devices related side effects

No unexpected events were observed in the safety profile of the study participants that received across both device sub studies. The overall safety profile was consistent with the Phase 3 pivotal studies, which used the bimekizumab-TN syringe. In DV0002, a total of 8 injection site reaction (ISR) AEs (4 with bimekizumab-SS-1mL and 4 with bimekizumab-AI-1mL) were reported across 6 study participants. All were assessed as not device-related, not serious, not severe, and did not lead to discontinuation. There was some variability in the reporting of ISR, with increased reports for subjects administered the Q8W regimen. Nevertheless, the differences between treatment Q4W and Q8W groups are difficult to interpret due to the small numbers. Although self-injection of bimekizumab using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL was well-tolerated, the applicant was requested by CHMP to continue monitoring AE reporting rates by device with particular emphasis on ISR, in future PSURs. No further update to the SmPC or RMP was deemed necessary by CHMP.

Serious Adverse Events (SAEs)

The incidence of any SAE in bimekizumab treated patients was lower than placebo (1.6% vs 2.4%) in Pool S1. No particular pattern of concern was identified for Pool S1C. For Pool S2, the incidence of SAEs was higher at 6.4%. This was lower than the ustekinumab group (7.3%) but higher than adalimumab group (3.1%).

SAEs were most commonly reported in GI, infections and infestations, Musculoskeletal, cardiovascular, Injury, poisoning and procedural complications and Nervous system disorders SOCs. Most SAEs were single occurrences of SAEs apart from acute myocardial infarction, myocardial infarction, cellulitis, and type 2 diabetes mellitus were reported by 3 study participants (0.2% each) in the Phase 3 bimekizumab Total group. The previously described heavy co-morbidity at baseline is likely to have contributed to many of the SAEs. Overall the safety profile is similar to other similar products in the same class. The EAIR for SAEs in the Phase 3 bimekizumab Total group (6.2/100 PY) was lower than that in the original MAA submission (6.8/100 PY) and therefore does not indicate an increase in risk with longer exposure to bimekizumab.

Of 8 deaths, 5 were reported in bimekizumab-treated study participants. All of the deaths occurred in the bimekizumab 320mg Q4W group. Two fatal events in the bimekizumab group were adjudicated as MACE: one was adjudicated as sudden cardiac death (PT: cardiac arrest) and 1 was adjudicated as other CV death (PT: cardiopulmonary failure); both occurred in study participants with significant CV risk factors. Both events were considered not related to bimekizumab by Investigators. One additional death was reported in the Pool S2 safety update and was adjudicated as MACE. None of the deaths were considered to be related to study medication. Overall the mortality rate with bimekizumab has been shown to be similar to the background rate in PSO and to mortality rates in the general populations of the EU and the US.

There was no clear pattern of SAE distribution across SOCs for either of the 2 maintenance treatment regimens.

Safety topics of interest

<u>Infections</u>

Increased risk of infections is an identified risk associated with IL-17 inhibitors. Despite a higher rate of infection-related TEAEs in bimekizumab treatment group compared with placebo within the pivotal studies initial treatment period (16 weeks) the majority of infections were non-serious, mild to moderate in intensity, and did not lead to study drug discontinuation. There was no evidence of an increase in infections with greater exposure.

Serious Infections

In Pool S1, the incidence rate of serious infections in bimekizumab-treated study participants was low and no study participant experienced a serious infection while receiving placebo. However, populations

with a current or recent history of serious infection were excluded from trials. In Pool S2, the incidence of serious infections remained low in the Phase 2/3 bimekizumab Total group and was comparable to ustekinumab and adalimumab treated patients.

Skin infections

Bacterial skin and soft tissue infections under different HLTs and SOCs that are likely to be staphylococcal in origin were reviewed. There was no evidence of an increased risk of skin infections.

Opportunistic infections (including TB)

No reactivation of TB in study participants with a history of latent TB was observed in the PSO development programme and no study participant developed active TB. Overall, there was no evidence of any patients converting to active TB infection in the studies. The proposed warnings in section 4.3 and 4.4 of the SmPC and further follow up in studies PS0014 and PS0015 and the planned Bimekizumab real-world outcomes study is endorsed by CHMP as agreed in the RMP.

Opportunistic infections were mainly localized fungal events classified as opportunistic. In Pool S2, the proportion of study participants reporting a fungal infection TEAE was noticeably higher in the bimekizumab Total group (EAIR: 26.0/100 PY) compared to ustekinumab (EAIR: 2.6) and adalimumab (EAIR: 1.4) groups. In particular, oral candidiasis and tinea pedis were more commonly reported for bimekizumab compared to ustekinumab or adalimumab. However, the different extent of exposure across the treatment groups need to be taken into consideration. These cases were generally mild to moderate in severity and resolved, however 7 study participants all of whom developed oro-mucosal candidiasis (oral candidiasis (3 participants), oesophageal candidiasis (2 participants), oropharyngitis fungal and oropharyngeal candidiasis (1 participant each) did discontinue treatment due to the fungal infection. One serious, opportunistic fungal infection (oesophageal candidiasis) was reported with bimekizumab in the original analysis and a further serious event of ophthalmic herpes zoster was reported in the S2 safety follow up analysis. This case was severe, related to IMP, resolved, but did not lead to discontinuation. From the clinical studies, no clearly defined subgroup could be identified that would benefit from prophylactic antifungal use.

An increased susceptibility to candida infections in particular for oropharyngeal forms of candidiasis has been identified with a trend towards higher Candida infection rates in the higher plasma exposure associated with bimekizumab 320mg Q4W group. Section 4.8 includes oral candidiasis and tinea infections as ADRs. Warnings in section 4.4 regarding the risk of infections and monitoring of infections are considered adequate. Section 4.3 has been updated to include clinically important active infections (e.g. active tuberculosis) as a contraindication. Serious infections is included as an important identified risk in the RMP and will be further evaluated as part of ongoing studies PS0014 and PS0015 and as part of the planned Bimekizumab real world outcomes PASS study as agreed in the RMP. Furthermore, additional information have been included in section 4.8 regarding increased reports of candida in patients with a lower body weight and the elderly. This is endorsed by CHMP.

<u>Malignancies</u>

Incidences of malignant tumour TEAEs were low in the Phase 2/3 bimekizumab Total group (0.8%; EAIR: 0.8/100 PY) similar to low incidences reported in the ustekinumab (0.6%; EAIR: 0.6/100 PY) and adalimumab (0.6%; EAIR: 1.4/100 PY) treatment groups. However, it is difficult to compare across groups as the extent of exposure in terms of 100 PY varied significantly across the three groups. Limited duration of exposure in the Pool S2 studies does not permit an accurate assessment of any effect of duration of treatment with bimekizumab on the risk of malignancy.

The most commonly reported cases were non-melanoma skin cancer (NMSC). Eight cases of NMSC were reported (7 events of Basal cell, 1 event each squamous cell carcinoma and Keratoacanthoma.) An increased background risk of NMSC has been previously reported in patients with PSO and

especially in patients who have received psoralen and UV-A (PUV-A) therapy. Nevertheless, it is agreed with the applicant that there is no clear evidence of an increased risk of malignancy overall in bimekizumab-treated study participants or evidence that bimekizumab-treated participants with prior phototherapy are at higher risk of skin malignancies in the safety data presented as part of this application.

Four of the TEAEs for a specific malignant tumour reported with bimekizumab treatment were in the gastrointestinal tract: colon cancer, gastric cancer and anal squamous cell carcinoma. The majority of cases (3/4 cases) were reported with a time to onset of a few days or months or presented with metastatic disease which suggests that such malignancies were likely to be pre-existing. Six additional malignancies (colon cancer (2 participants), colon cancer metastatic, squamous cell carcinoma of skin (2 participants), and bronchial carcinoma) were reported in the S2 Safety follow up analysis. Despite these additional reports, the EAIR for any malignancy (0.8/100 PY) is the same as that in the original MAA submission, however within this there is a small increase in malignancies (excluding Non-melanomic Skin Cancers): EAIR increased from 0.4 to 0.5. This is driven by an increase in colon cancer TEAEs (EAIR increased from 0.1 to 0.2) and possibly indicates an increase in risk with longer exposure to bimekizumab. Nevertheless, the observed time is still limited considering the length of tumour induction. Causality assessment is confounded by the overall increased risk for cancer development in PSO and underlying risk factors in all cases. It is agreed that there is currently insufficient information to support inclusion of a warning regarding malignancy in the SmPC. In order to further characterise this risk, Malignancy is included as an important potential risk in the RMP and will be carefully evaluated in the category 3 Bimekizumab Real-World Outcomes PASS study and in ongoing safety studies (PS0014 and PS0015). In addition, Malignancy, with particular reference to colon cancer will be monitored carefully as an item of special interest in future PSURs.

MACE

In Pool S1 the overall incidence of MACE, extended MACE and other CV events were low. In Pool S2 the overall incidence of MACE and extended MACE remained low. In the S2 Safety Update, although 2 additional adjudicated MACE were reported, the EAIR was lower compared with the original MAA submission. There was no increase in risk with the additional 5.5 months exposure to bimekizumab. The most frequently reported MACE was myocardial infarction. No MACE was observed in the placebo group in the Pool S1 analysis or for active comparator groups in Pool S2 analysis. Differences in incidence of MACE between BKZ and active comparator groups are difficult to interpret due large imbalances in patient-years of exposure. The overall rate of MACE with bimekizumab was comparable to rates observed with other 1L-17 inhibitors approved for treatment of PSO published in the literature.

Mean changes from Baseline in ECG variables were generally small and similar between treatment groups. No notable trends were observed in the post-baseline ECG outlier values across all treatment groups in Pool S1. In addition to TEAEs related to ECG measurements, review was performed for TEAEs of ventricular tachycardia or fibrillation, syncope, and seizures to evaluate potential clinical consequences of severe arrhythmias. Overall, the incidences of those TEAEs were low and their review did not indicate a safety concern.

Taking into consideration the background cardiovascular morbidity in this group, there is no indication of an increase in MACE that could be attributed to treatment with bimekizumab. MACE is included as an important potential risk in the RMP and will be further assessed as part of ongoing studies (PS0014 and PS0015) and Bimekizumab Real-World Outcomes PASS study. This is endorsed by the CHMP.

Inflammatory Bowel disease (IBD)

An increased prevalence of IBD among PSO patients compared with the general population is well-established. One study participant who was treated with bimekizumab 320mg Q4W group in the induction period reported an IBD TEAE (colitis ulcerative). Cases of new or exacerbations of IBD have been reported with IL-17 inhibitors. A case of gastrointestinal inflammation that was thought to possibly be early Crohn's disease was reported in the S2 Safety update report. A revised warning regarding IBD has been included in Sections 4.4 and 4.8 of the SmPC. IBD (Crohn's disease and ulcerative colitis) will continue to be monitored as important potential risk in the RMP and will be

further evaluated as part of ongoing studies (PS0014 and PS0015) and Bimekizumab Real-World Outcomes PASS study.

Suicide and Depression

Overall, despite these 4 cases (1SIB and 3 severe depression) being considered to be related to study medication and three subjects being withdrawn from the study, taking into consideration the higher background rates of suicidal ideation and depression in patients with PSO, there was no clear indication of an increased risk of development or worsening depression and anxiety or suicidality (thoughts or behaviours) following treatment with bimekizumab.

Neutropenia

In Pool S1, the incidence of neutropenia TEAEs reported in the bimekizumab 320mg Q4W group was (0.7%; EAIR: 2.4/100 PY) and included the PT neutrophil count decreased (0.4%; EAIR: 1.4/100 PY). No neutropenia cases were reported in placebo group.

In Pool S2, the incidence of neutropenia TEAEs in the Phase 2/3 bimekizumab Total group was 1.2%; EAIR: 1.2/100 PYs. In general, neutropenia was transient, and was not associated with an increased frequency of infections. There were no SAEs associated with neutropenia. One severe case resulted in discontinuation of bimekizumab. There is a slight increase in neutropenia TEAEs with longer duration of treatment (Pool S1 EAIR 0.7 vs Pool S2 1.2) however in the S2 safety follow up analysis, the EAIR for neutropenia TEAEs (1.0/100 PYs) was lower than that in the original MAA submission (1.2/100 PYs). No serious infections emerged within 30 days of a CTCAE Grade 3 or Grade 4 low neutrophil value. The incidence of TEAES observed in bimekizumab treated patients neutrophil counts were similar to the adalimumab and ustekinumab groups in Pool S2. Neutropenia is included as an uncommon side effect in section 4.8 and will be followed-up as part of ongoing studies (PS0014 and PS0015) and Bimekizumab Real-World Outcomes PASS study as part of the safety concern 'serious infection' included as an important identified risk in the RMP.

Hepatic Function

Six TEAEs (5 in the bimekizumab 320mg Q4W and 1 in placebo group) were assessed as drug-related by the Investigator. All TEAEs resolved. Only one study participant in the bimekizumab 320mg Q4W group discontinued the study due to hepatic enzyme increased.

In Pool S2, 5.5% of study participants in the Phase 2/3 bimekizumab Total group experienced hepatic TEAEs. The majority were reports of laboratory abnormalities (HLT Liver function analyses 4.8%). Most other reports related to Non-alcoholic fatty liver (0.4%) but there was 3 reports of drug-induced liver injury, and 2 reports of liver injury, reported in BKZ treated patients. The percentage of patients treated with BKZ Q4W reporting markedly abnormal liver function results was low (2.7%). A total of 24 reports linked to abnormal liver function that resulted in pts discontinuing from the phase 2/3 studies. The majority of the TEAEs leading to discontinuation (15/24 events) occurred in the Phase 2b study PS0010 and its extension study PS0011, where due stringent withdrawal criteria in the phase 2 clinical trials.

The incidence of TEAEs (HLT Liver function analyses) was slightly higher in the Phase 3 bimekizumab 320mg Q4W group (2.9%) compared to 320mg Q8W group (1.6%). Three patients experienced an SAE (liver function test increased).

Upon request from the CHMP, the applicant conducted a review of all cases of potential drug-induced liver injury (DILI) identified in Pool S2. In total, twenty cases were identified as potential drug-induced liver damage (ALT or AST elevation >5xULN at any point in time, cases meeting Hy's Law laboratory criteria, and cases with a reported term of "drug-induced liver injury). Of these, two met Hy's Law laboratory criteria and it is agreed that following alternative diagnoses (cholelithiasis with possibly a migrating gallstone and autoimmune hepatitis) neither case are likely to be related to study drug. The remaining events had significant confounding factors or alternative diagnoses. Of note two of the cases were associated with concomitant treatment with fluconazole. Overall no signal of hepatoxicity associated with treatment with Bimekizumab and no hepatotoxic effect with IL-17 AF inhibition has been identified in the literature.

Biochemistry values

A significant proportion of participant reported high glucose values at baseline and reported high maximum values during the study. This is likely to reflect the increased incidence of metabolic syndrome and Type 2 diabetes as co-morbidities in PSO.

The impact of bimekizumab on total cholesterol measured only in Phase 2 studies has been provided for review. No TEMA ≥Grade 3 cholesterol values were reported in any of the studies. In a review of TEAEs for raised cholesterol in the S2 safety population, 8 cases (0.4%) of blood cholesterol increased and 10 (0.6%) of hypercholesterolaemia were reported. It is acknowledged that increased cholesterol or increases in pro-atherogenic components of the lipid panel have not been identified as side effects for other marketed IL-17 inhibitors. Despite the limitation of the dataset, there was no evidence from the data presented of increased total cholesterol levels following treatment with bimekizumab. Nevertheless, the applicant will continue to monitor pro-atherogenic components of the lipid panel low-density lipoprotein (LDL) or very low-density lipoprotein (VLDL) in study PS0015 which is ongoing and in which lipid panel, including LDL levels is being measured. Complete results will be provided when the final clinical study report will be available (i.e. by 30 May 2023).

Blood Pressure

Markedly abnormal increases in SBP and DBP were reported at comparable rates in the bimekizumab 320mg Q4W and placebo treatment groups (0.9% and 1.8%, respectively). Markedly abnormal SBP and DBP rates were <3% in Pool S2. Normal SBP and DBP values were maintained in >98% of study participants in the bimekizumab 320mg Q4W group and >96% of study participants in the placebo group despite the fact that more than 30% of study participants had a medical history of hypertension. Hypertension was reported as a TEAE in 4.4% of Phase 3 BKZ Total population. Small increases in BP, particularly in the patients with other underlying cardiac risk factors can be significant. However, there does appear to be a trend towards a greater increase in Stage 1 or 2 hypertension in patients with normal BP at baseline treated with BKZ which was identified across the initial 16 week treatment period for S1 and is also evident across the longer term S2 analysis. The clinical relevance of this overall trend towards elevation of BP particularly in patients with normal BP at baseline is unclear. Elevation of BP in patients who are normotensive at baseline will be monitored as a topic of special interest/discussed in future PSURs.

Hypersensitivity reactions

In the initial treatment period (Pool S1), hypersensitivity reactions were reported at a higher incidence in the bimekizumab 320mg Q4W group (4.2%) compared with the placebo group (0.6%). The majority of hypersensitivity reaction were in the SOC Skin and subcutaneous tissue disorders (2.8% in the bimekizumab 320mg Q4W group vs 0 in the placebo group), mainly from the HLT Dermatitis and eczema (eczema (0.9%) and dermatitis contact (0.6%). These were mostly mild to moderate in severity and 66.8 % resolved.

Other hypersensitivity reactions included events in the SOCs of Eye disorders and Respiratory, thoracic and mediastinal disorders and appeared to be mainly linked to seasonal allergies. Drug hypersensitivity (7.6%), seasonal allergy (7.6%) were among the most frequently reported medical history conditions in the Phase 3 bimekizumab Total group.

In Pool S2 the majority of hypersensitivity reaction were also in the SOC of Skin and subcutaneous tissue disorders (8.5%); mainly from the HLT Dermatitis and eczema (6.7%). These were mostly mild to moderate in intensity. There was no evidence of an increase in incidence of events reported under the HLT of Dermatitis and eczema with time. A significant proportion were considered related to study medication. There was only one TEAE of serious atopic dermatitis which occurred >1yr after starting treatment. There were three serious hypersensitivity reactions (anaphylactic shock, dermatitis atopic,

and circulatory collapse, respectively). There was no clear evidence of causality with bimekizumab with any of the three cases reported. The case of anaphylactic shock was related to a bee-sting.

Although it is acknowledged that urticaria, conjunctivitis allergic, and rhinitis allergic were the most commonly reported TEAES in the overview of hypersensitivity-related TEAEs in Pool S2 (excluding PTs from HLT Dermatitis and eczema), there were individual reports of angioedema, swelling face, pharyngeal oedema, lip swelling, laryngeal oedema which are suggestive of a more systemic type of allergic reaction.

The increased incidence of cases of eczematous/dermatitic eruptions in PSO patients, particularly elderly patients, was further discussed by the applicant upon request by CHMP. Th applicant considered that this observation was in line with data from bimekizumab non-clinical studies and related molecules from the class. Several hypotheses are discussed exploring possible mechanisms (Th1/Th2 immune response, impact on skin microbiome homeostasis, Potential for IL-17C or IL-22 overexpression) for the occurrence of eczematous eruptions with anti-IL-17 treatment. The higher incidence in elderly may be associated with an age-related decline in skin barrier function. Development of atopic eczema in patients with a history of PSO is a potential source of diagnostic confusion.

Dermatitis and eczema are included as common side effects in section 4.8. Serious hypersensitivity reactions are included as an important potential risk with additional wording in SmPC Section 4.3 (Contraindication). The warning regarding hypersensitivity in section 4.4 has been updated to indicate that there have been reports of serious hypersensitivity reactions with other similar type agents. A warning, related to serious hypersensitivity reactions including anaphylactic reactions observed with IL-17 inhibitors, has been included in section 4.8 of the SmPC. This is agreed by CHMP.

Injection site reactions (ISR)

Overall, number of reported ISR was low (3.1%). Furthermore, none were assessed as device-related, serious, severe, or led to discontinuation. No association between ISR and ADAbs or NAbs has been established. ISR are included as common ADRs in section 4.8 of the SmPC. Incidence rates for ISRs were similar between the bimekizumab 320 mg Q4W and Q8W treatment regimens (1.1% vs 1.9%). Some differences between studies and between treatment Q4W and Q8W groups were noted in the device sub studies in Study PS0014.These are difficult to interpret due to the small numbers. Nevertheless, the applicant agreed to monitor adverse event reporting rates by device type with particular emphasis on ISR, in future PSURs. This is considered adequate by the CHMP.

Immunogenicity

The exposure adjusted incidence of TEAEs were higher in study participants who were overall ADAb negative. However, the exposure adjusted incidence of infection TEAEs was higher in the ADAb positive group. This was due to an increase in folliculitis, oral candidiasis and nasopharyngitis.

In patients who were Nab positive the overall EAIR of TEAEs were higher than in study participants who were overall NAb-negative (EAIR 277.6 vs 229). Exposure adjusted incidence of infection TEAEs was higher in the NAb-positive group. This was driven by increases in, otitis externa (4% vs 1.5%), URTI (12.7%vs 8.8%), and UTI (6.7% vs 3.8%) in the NAb-positive compared to the NAb-negative group. Study participants who were overall NAb-negative had a greater incidence of candidiasis and folliculitis compared with study participants who were overall NAb-positive (17.9% vs 12.0% and 5.0% vs 3.3% respectively). The applicant suggested that this may be due to incomplete IL-17A and IL-17F blockade in NAb-positive study participants. A higher proportion of study participants who were NAb-positive experienced ISR (3.3% vs 1.5%). Overall, immunogenicity had no direct impact in terms of hypersensitivity or allergic type local reactions at injection site but may indirectly pact the side effect profile through incomplete IL-17A and IL-17F blockade.

Upon request from CHMP, the Applicant provided additional data that showed that ADAb titer values did not tend to increase with multiple administrations and the variability in titers was generally

consistent across time. The pooled Phase 3 studies (Pool S2A [combined data from Initial and Maintenance Treatment Periods]) indicated that ADAb titer had a limited impact on efficacy at both Week 16 and Week 52/56. However, there were a low number of study participants in the antibody positive groups at these time points, results are thus difficult to interpret, and no firm conclusions can be drawn. As the safety impact of ADAb status on safety is limited, the applicant confirmed that samples for anti-drug antibodies (ADAb) and neutralizing antibodies (NAb) will be collected in PS0014 and their impact on safety and on the SmPC will be further investigated.

Adverse drug reactions (ADRs)

The update of Pool S1 to Pool S1C provided >50% additional data to characterize the safety during the initial treatment period (Pool S1C BKZ n=1032 vs n= 670 in original pool S1). No important differences compared with the previous Pool S1 analysis were identified. No new ADRs were identified, and there was no impact on the proposed ADR frequency categories. Some ADR terms identified in the original Pool S1, no longer met the criteria of being at least 1% higher than placebo (toothache, fatigue, gastroenteritis, oral herpes, acne, and dry skin). The proposal to maintain these terms (except for toothache and dry skin which were considered not relevant for labelling as an ADR) on the basis of biological plausibility and being causally related is endorsed by CHMP. The applicant has adequately justified the rational for omitting staphylococcal skin infections from Section 4.8. The applicant provided an overview of serious skin infections. All of the cases presented were confounded by risk factors that predispose towards serious infection. The increased background risk of serious skin and soft tissue infections in moderate to severe PSO population is also acknowledged. The CHMP agreed that no additional risk has been identified for bimekizumab. Further, clinically important active infections is included as a contraindication in Section 4.3 and a warning and precaution is also included to minimize the risk of serious infections in Section 4.4 along with an entry in section 4.8. Serious infections which includes serious skin infections is also included as an important identified risk in the RMP and will also be further evaluated in ongoing studies (PS0014 and PS0015) and as part of the planned Bimekizumab real world outcomes study (see RMP).

Although the number of non-skin related hypersensitivity reports is low, hypersensitivity is biologically plausible and is included in the product information of all of the other 1L-17 inhibitors approved for the treatment of PSO. Taking into account that there is insufficient evidence for an association between bimekizumab and hypersensitivity-related TEAEs; the applicant's rationale for excluding hypersensitivity reactions as an ADR is accepted. However, a warning in SmPC section 4.4 regarding serious hypersensitivity reactions is included. A similar warning is included under the description of selected events in section 4.8 of the SmPC to highlight that serious hypersensitivity reactions including anaphylactic reactions are a class side effect for IL-17 inhibitors.

TEAES in Renal and urinary disorders, Psychiatric disorders and Eye disorders SOCS were further reviewed by the applicant. CHMP agreed that there is insufficient information to include any of the TEAEs as ADRs to bimekizumab. However renal side effects, Psychiatric disorders and Eye disorders, in particular eyelid disorders and cataract will continue to be monitored and reviewed in the future PSURs. In addition, the applicant considered that conjunctivitis could potentially be a consequence of impaired muco-epithelial immunity to infectious agents induced by IL-17 inhibition. The proposal to include Conjunctivitis (listed in the SOC of Infections and infestations) as an uncommon ADR in SmPC section 4.8 is endorsed by CHMP. Further, upon detailed review, the applicant did not consider TEAEs under the HLT of Urinary tract infections as ADRs to bimekizumab. In Pool S1, TEAEs in the HLT of Urinary tract infections were indeed reported at a numerically higher incidence in the placebo group (3.6%; EAIR: 11.9/100 PY) than in the bimekizumab group (2.1%; EAIR: 6.8/100 PY). Also, based on the data in Pool S2, the incidence decreased over time. Therefore, it is accepted not to include Urinary tract infection as an ADR.

Safety in special populations

Age

The majority (>90%) of bimekizumab-treated study participants were <65 years of age. Over the initial treatment period, there was an age-related increase in TEAEs overall and in cases of eczema and

dermatitis and candida infections (oromucosal) in subjects treated with bimekizumab. This has been adequately reflected in SmPC – section 4.8.

In the longer term S2 Pool, there was a trend towards overall increase in TEAES with increasing age. These differences were mainly driven by the HLTs Dermatitis and eczema and Musculoskeletal and connective tissue pain and discomfort and oromucosal candida infections. Increases in Musculoskeletal and connective tissue pain and discomfort HLT could be due to a higher prevalence in the elderly population however higher rates of eczema and dermatitis are not necessarily readily explained by older age.

Small increases in TEAEs across the age groups <65 Years to 75-84 Years were noted in Psychiatric disorders (3.4-5.6%), Cardiac disorders (2.1-5.6%) Infections and infestations SOCs (63.5% -72.2%) and any TEAE coding to Postural hypotension, Fall, Blackout, Syncope, Dizziness, Ataxia, or Fracture PTs (3.4%- 11.1%). However, there were a very small number of study participants >75 years of age (N=18) and none above 85 years of age making it difficult to interpret comparative safety datasets across the difference age groups.

Race

Most study participants treated with bimekizumab were White >80%. The most frequently reported TEAEs in White and other study participants were in the SOCs of Infections and infestations, Gastrointestinal disorders, and Skin and subcutaneous tissue disorders. Noticeable differences were noted in the Skin and subcutaneous tissue disorders SOC for the HLT Dermatitis and eczema (≥5%) where the incidence was higher in the other study participants compared with White study participants.

Weight

The TEAE profiles in both weight subgroups (≤120kg and >120kg) were generally similar to the overall bimekizumab Phase 2/3 PSO study population safety profile insofar as no new safety concerns were identified but there was some variability in the reporting rates of TEAEs across both regimens with a trend towards increased TEAEs, SAEs and drug related AEs in >120KG group. There was some evidence of an increased overall incidence of infection TEAEs in the >120kg group treated with the maintenance dose of Q4W but the rates of the commonest TEAEs, oral candidiasis and Bacterial infection NEC were comparable to the other wt groups.

Regarding safety, in the ≥120kg subgroup, a slightly higher incidence of any TEAEs was noted in the Q4W treatment group compared with the Q8W group, although incidences and exposure-adjusted incidence rates were comparable to what was observed in participants weighing <120kg. No pattern was observed in the serious and severe TEAE terms reported for either treatment regimen. Altogether, no safety concerns were identified that indicate that patients weighing 120 kg or more who continue bimekizumab Q4W are more at risk than patients weighing less than 120 kg using bimekizumab Q8W in the maintenance treatment phase.

Taking into account that women, those of lower body weights, and those of non-white race accounted for a lower % of the study population; the applicant agreed to closely monitor safety in those patients in the post marketing setting i.e. in future PSURs.

Pregnancy and lactation

There is limited amount of data from the use of bimekizumab in pregnant women. Furthermore, there are no safety data regarding exposure during lactation available. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonic/foetal development, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of Bimzelx during pregnancy (SmPC – section 4.6). Use in pregnant and lactating women has been added as a missing information in the list of safety concerns in the RMP. The safety of bimekizumab use in pregnant and lactating women will be monitored in observational PASS and a pregnancy outcome registry; listed as category 3 in the RMP.

Prior systemic therapy

75.9% of study participants were treated with prior systemic therapy of any kind. The incidence of TEAEs was higher in participants with prior systemic therapy compared with those who didn't receive prior systemic therapy. This was mainly driven by increased reports in Gastrointestinal and Skin and Subcutaneous tissue disorder SOC. It is agreed with the applicant that there were no notable differences across the 2 SOCs. A higher rate of TEAEs in pre-treated patients could be expected on the basis that these patients are likely to have more severe disease and be more medically complex.

However, TEAEs in the Investigations SOC was lower in participants with prior systemic therapy (9.8%) compared with participants with no prior systemic therapy (16.2%). There were no notable differences across the 2 groups within any HLT under the Investigations SOC. Overall no new safety concerns have been identified and no additional warnings are required for the SmPC.

Overall, the safety data base although considerable, is smaller than that presented for similar type IL-17 inhibitors. Nevertheless, it is sufficient to support the evaluation of the safety bimekizumab in the proposed indications taking into consideration the known safety profile of other similar products authorised in the treatment of PSO. 'Long-term safety' is included as missing information in the RMP. Ongoing studies PS0014 and PS0015, listed as category 3 in the RMP, are expected to provide further safety data on the long term (final CSR are expected to be submitted by 31 Jan 2024 and 30 May 2023, respectively).

2.6.2. Conclusions on the clinical safety

The safety data base is sufficient to support evaluation of the safety bimekizumab in the proposed indication. As expected with this class of medicines, TEAEs were most frequently reported in the SOC of Infections and infestations. The most frequently reported TEAEs in bimekizumab-treated study participants were nasopharyngitis, oral candidiasis, and upper respiratory tract infections. Furthermore, eczema and dermatitis were reported following treatment with bimekizumab particularly in patients over 65. This information is adequately reflected in SmPC section 4.8. A slightly higher incidence of oral candidiasis was reported in patients <70 kg, this is also reflected in SmPC section 4.8. Long term safety data and exposure during pregnancy and lactation are included as missing data in the RMP and will be further assessed in the post-marketing setting – see RMP. Reporting rates of adverse events particularly those considered to be of special interest will be further monitored with routine pharmacovigilance, in ongoing safety studies (PS0014 and PS0015) and in the planned Bimekizumab real world outcomes study.

2.7. Risk Management Plan

Safety concerns

Important identified risks	Serious infections
Important potential risks	Serious hypersensitivity reactions
	Inflammatory bowel disease (Crohn's disease and ulcerative colitis)
	Major adverse cardiovascular events
	Malignancy
Missing information	Use during pregnancy and lactation
	Long-term safety data

Pharmacovigilance plan

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
None proposed				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
None proposed				
Category 3 - Required additional pharmacovigilance activities				
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 patients compared to PSO 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	Within 3 months of receipt of Commission Decision (currently expected by end Nov 2021)
			Interim reports	The first interim report will be submitted when 1 year of potential bimekizumab exposure is available in the data source. Thereafter, interim reports will be submitted annually.
			Final study report	31 Dec 2033
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	Within 3 months of receipt of Commission Decision (currently expected by end Nov 2021)
			Annual recruitment report	Yearly after marketing authorization
			Interim feasibility assessment	End of third year of registry

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
			Final study report	31 Dec 2033
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	Within 3 months of receipt of Commission Decision (currently expected by end Nov 2021)
			Final study report	31 Dec 2033
PS0014 (EudraCT Number: 2016-003427-30) A multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult study participants with moderate-to-severe chronic plaque PSO Ongoing	Assess the safety and efficacy of long-term use of bimekizumab	Incidence of serious infections, serious hypersensitivity reactions, MACE, malignancy, and IBD will be characterized as part of the safety assessments. The study will also address missing information item of long-term safety	Submission of clinical study report	No later than 1 year after LPLV (projected LPLV [including SFU] 31 Jan 2023)
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 clinical study report	No later than 1 year after LPLV (projected LPLV [including SFU] 30 May 2022)

EudraCT=European Union Drug Regulating Authorities Clinical Trials Database; IBD=inflammatory bowel disease; IL=interleukin; LPLV=last patient last visit; MACE=major adverse cardiovascular events; PRAC=Pharmacovigilance Risk Assessment Committee; PSO=psoriasis; SFU=Safety Follow-Up; TNF=tumor necrosis factor

Risk minimisation measures

Safety concern	Risk minimization measures	Pharmacovigilance activities
Serious infections	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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:** Bimekizumab real-world outcomes study PS0014; PS0015
Serious hypersensitivity reactions	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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:** Bimekizumab real-world outcomes study PS0014; PS0015
Inflammatory bowel disease (Crohn's disease and ulcerative colitis)	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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:** Bimekizumab real-world outcomes study PS0014; PS0015

Safety concern	Risk minimization measures	Pharmacovigilance activities
Major adverse cardiovascular events	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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:** Bimekizumab real-world outcomes study PS0014; PS0015
Malignancy	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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:** Bimekizumab real-world outcomes study PS0014; PS0015
Use during pregnancy and lactation	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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:** Bimekizumab pregnancy exposure and outcomes registry An observational cohort study to evaluate bimekizumab exposure during pregnancy
Long-term safety	**Routine risk minimization measures:** Bimekizumab is intended for use under the guidance and supervision of a physician experienced in the diagnosis and treatment of plaque psoriasis (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

Conclusion

The CHMP and PRAC considered that the risk management plan version 0.3 is acceptable.

2.8. Pharmacovigilance

Pharmacovigilance system

The CHMP considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The requirements for submission of periodic safety update reports for this medicinal product are set out in the Annex II, Section C of the CHMP Opinion. The applicant did not request alignment of the PSUR cycle with the international birth date (IBD). The new EURD list entry will therefore use the EBD to determine the forthcoming Data Lock Points.

2.9. New Active Substance

The applicant declared that bimekizumab has not been previously authorised in a medicinal product in the European Union.

The CHMP, based on the available data, considers bimekizumab to be a new active substance as it is not a constituent of a medicinal product previously authorised within the Union.

2.10. Product information

2.10.1. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.10.2. Additional monitoring

Pursuant to Article 23(1) of Regulation No (EU) 726/2004, Bimzelx (bimekizumab) is included in the additional monitoring list as it contains a new active substance.

Therefore, the summary of product characteristics and the package leaflet includes a statement that this medicinal product is subject to additional monitoring and that this will allow quick identification of new safety information. The statement is preceded by an inverted equilateral black triangle.

3. Benefit-Risk Balance

3.1. Therapeutic Context

3.1.1. Disease or condition

Bimekizumab is intended for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy.

PSO is predominantly a skin disease, which can manifest as various phenotypes of which plaque PSO is by far the most common form. Symptoms that are shared by all phenotypes can include itching, burning and soreness. Most types of PSO have a cyclic evolution, flaring for a few weeks or months, then subsiding for some time or even going into a period of remission. Plaque PSO has a disproportionate effect on quality of life when it involves certain regions such as the face, palms and soles, nails, or intertriginous areas.

Individuals with PSO are at increased risk of developing other chronic and serious health diseases. Comorbidities in patients with psoriasis include PsA, cardiovascular disease, metabolic syndrome, chronic pulmonary disease, peptic ulcer disease, renal disease, IBD, depression, suicidality, hyperlipidaemia, hypertension, and diabetes. There is a small increased risk of certain malignancies, including non-melanoma skin cancers among patients with PSO which is believed to be due to conventional PSO treatments including methotrexate, phototherapy, and immunosuppressants, including cyclosporine. The burden of comorbidities increases with increasing disease severity. Some comorbidities including cardiovascular disease are thought to have shared inflammatory pathways, cellular mediators, genetic susceptibility, and common risk factors to psoriasis.

Current biologic therapies target the inflammatory process responsible for development of the clinical features of psoriasis.

3.1.2. Available therapies and unmet medical need

Therapy for patients with PSO varies per the severity of disease. Limited or mild disease is often treated with topical therapies, such as corticosteroids and vitamin D analogues, fumarates, and retinoids. Patients with more severe disease are often treated with photochemotherapy, ciclosporin, MTX, or biologic agents. Each therapy has unique characteristics that contribute to benefits and risks of treatment.

Biologics including, but not limited to, tumour necrosis factor alpha (TNFα) inhibitors and interleukin (IL) inhibitors (e.g., IL-17 and IL-23), are available treatment options for patients with moderate to severe plaque PSO who are candidates for systemic therapy. The effectiveness of TNFα inhibitors in the treatment of PSO has been demonstrated in many Phase 3 clinical studies and has led to the approval of multiple TNFα inhibitors for use in patients with moderate to severe plaque PSO. Interleukin inhibitors approved for PSO include the IL-12/23 inhibitor ustekinumab, the IL-17A inhibitors secukinumab and ixekizumab, the IL-17 receptor antagonist brodalumab, and the IL-23p19 inhibitors guselkumab, tildrakizumab, and risankizumab. These products are injected subcutaneously (s.c.) or delivered via intravenous (iv) infusion. Key safety concerns associated with the use of these biologic treatments include an increased risk of developing serious infections and malignancies; however, the associated risks vary across the different classes of biologic treatments.

These agents provide therapeutic options for many patients with moderate to severe plaque PSO, allowing achievement of at least a 75% reduction on the Psoriasis Activity and Severity Index (PASI75). However, fewer patients experience greater improvement (PASI90) or complete clearance (PASI100), and as PSO affects all aspects of a patient's life, an inability to achieve clear skin also negatively impacts their QOL. Furthermore, not all patients respond to current therapies and loss of response often occurs over time, which leads to patients switching to another medication for symptom relief. Thus, despite the number of currently available therapies, there remains an unmet need in the PSO treatment landscape for therapeutic agents that can provide more meaningful improvement in the extent and severity of plaque PSO.

3.1.3. Main clinical studies

The bimekizumab PSO clinical development programme consists of 3 pivotal Phase 3 studies designed to provide evidence of the safety and efficacy of bimekizumab through 52 weeks (PS0009) or 56 weeks (PS0008 and PS0013) in adults with moderate to severe plaque PSO ≥6 months, defined as PASI ≥12, body surface area (BSA) affected by PSO ≥10%, and Investigator's Global Assessment (IGA) score ≥3 (on a 5-point scale).

Study PS0008 – "BE SURE"

PS0008 is a Phase 3, multicenter study consisting of a 16-week, randomized, double-blind, parallel-group, active comparator-controlled Initial Treatment Period followed by a 40-week Maintenance Treatment Period to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque PSO. The active comparator was adalimumab.

Study PS0009 – "BE VIVID"

Study PS0009 is a Phase 3, multicenter study consisting of a 16-week, randomized, double-blind, placebo- and active comparator-controlled Initial Treatment Period followed by a 36-week Maintenance Treatment Period to evaluate the efficacy and safety of bimekizumab in adults with moderate to severe chronic plaque PSO. The active comparator was ustekinumab.

Study PS0013 – "BE READY"

PS0013 is a Phase 3, multicenter, randomized, double-blind, placebo-controlled study consisting of a 16-week Initial Treatment Period followed by a 40-week Randomized-Withdrawal Period to evaluate the efficacy and safety of bimekizumab in adult study participants with moderate to severe chronic plaque PSO.

All of the Phase 3 studies had the same co-primary efficacy endpoints, i.e. the proportion of participants who achieved a PASI90 response at Week 16 and the proportion of participants who achieved an IGA 0/1 response at Week 16. The Initial Treatment Phase for all 3 Phase 3 studies was 16 weeks with a follow-up Maintenance Treatment Period to Week 56/52, respectively (Studies PS0008 and PS0009) or a Randomized Withdrawal Period to Week 56 (Study PS0013).

3.2. Favourable effects

Clinical efficacy: Individual pivotal studies

Co Primary response at week 16 (PASI 90 and IGA0/1)

In **Study PS0008**, the bimekizumab total group was superior compared with the adalimumab group for the co-primary endpoints of PASI90 and IGA 0/1 response rates at Week 16. The differences were

statistically significant and clinically meaningful for both co-primary endpoints, with odds ratios versus adalimumab of 7.459 (p<0.001) and 4.341 (p<0.001), respectively.

Bimekizumab total group had a higher PASI100 response rate compared with the adalimumab group at Week 16 (60.8% vs 23.9%, respectively; p<0.001) and Week 24 (66.8% vs 29.6%, respectively; p<0.001), a difference that was statistically significant and clinically meaningful at both time points.

A higher PASI75 response rate compared with the adalimumab group was seen at Week 4 after only a single dose of bimekizumab (76.5% vs 31.4%, respectively; p<0.001), which was a statistically significant and clinically meaningful difference.

Bimekizumab total group had a higher PASI90 response rate compared with the adalimumab group at Week 24 (85.6% vs 51.6%, respectively; p<0.001) and had a higher IGA 0/1 response rate compared with the adalimumab group at Week 24 (86.5% vs 57.9%, respectively; p<0.001). These differences were statistically significant and clinically meaningful. For the bimekizumab total group, the PASI90 and IGA 0/1 response rates observed at Week 24 were sustained through Week 56 (83.7% and 82.8%, respectively).

Quality of life scores showed the DLQI 0 or 1 rate was higher in the bimekizumab total group compared with the adalimumab group from Week 1 through Week 24 (nominal p<0.001 for Week 16).

PSD response rates in the bimekizumab total group were higher than response rates in the adalimumab group from Week 1 through Week 16 (nominal p=0.010, nominal p<0.001, and nominal p<0.001 for Week 16 comparisons for pain, itch, and scaling, respectively) and at Week 24.

Study participants who switched from adalimumab to bimekizumab at Week 24 in Study PS0008, achieved and maintained similar response levels across endpoints to those study participants that were randomized to bimekizumab from the start of the study. The PASI90 response rates for study participants who switched from adalimumab to bimekizumab 320mg Q4W at Week 24 (55.0%) rapidly increased after 1 bimekizumab dose at Week 28 (78.5%). After 16 weeks of bimekizumab 320mg Q4W treatment (ie, by Week 40), the PASI90 response rates in the adalimumab/bimekizumab 320mg Q4W group were similar to the rates observed in the bimekizumab 320mg Q4W and bimekizumab 320mg Q4W/Q8W groups (87.2%, 89.5%, and 88.6%, respectively), and the similar response rates were sustained across treatment groups through Week 56 (87.2%, 88.2%, and 89.3%, respectively). In addition, among study participants on adalimumab treatment who failed to achieve a PASI90 response at Week 24, after switching to bimekizumab 320mg Q4W, 78.5% achieved a PASI90 response at Week 40 and 83.1% achieved a PASI90 response at Week 56 (after 32 weeks of treatment with bimekizumab 320mg Q4W).

In **Study PS0009**, the bimekizumab 320mg Q4W group PASI90 (Odds ratio 6.056, p-value <0.001) and IGA 0/1 (Odds ratio 4.809, p-value <0.001) response rates were also superior compared to the ustekinumab group at Week 16.

In Study PS0009, the bimekizumab 320mg Q4W group also had a higher PASI100 response rate compared with the ustekinumab group at Week 16 (58.6% vs 20.9%, respectively; nominal p<0.001) and a higher IGA 0 response rate compared with the ustekinumab group at Week 16 (58.6% vs 22.1%, respectively; nominal p<0.001). The bimekizumab 320mg Q4W group had a higher PASI75 response rate compared with the placebo and ustekinumab groups at Week 4 after one dose of bimekizumab (76.9% vs 2.4% and 15.3%, respectively; p<0.001 for both comparisons).

In Study PS0009, the bimekizumab 320mg Q4W group also had higher PSD response rates based on pain, itch, and scaling item scores compared with the ustekinumab group at Week 16 (77.3% vs 68.2%; nominal p=0.053; 76.6% vs 65.8%; nominal p=0.035, and 78.5% vs 59.5%; nominal p<0.001, respectively).

Bimekizumab 320mg Q4W treatment demonstrated clinically meaningful and statistically superior response rates compared to placebo for the co-primary efficacy variables, PASI90 and IGA 0/1 response at Week 16 (Initial Treatment Period) in the individual placebo-controlled pivotal Phase 3 studies (PS0009, PS0013). Superiority was also demonstrated compared to active comparators Adalimumab and Ustekinumab.

In Study PS0013, the bimekizumab 320mg Q4W group was superior compared with the placebo group for the co-primary endpoint of PASI90 response rate at Week 16 (90.8% vs 1.2%, respectively). This difference was statistically significant and clinically meaningful, with an odds ratio of 496.318 ($p<0.001$). The bimekizumab 320mg Q4W group was superior compared with the placebo group for the co-primary endpoint of IGA 0/1 response rate at Week 16 (92.6% vs 1.2%, respectively). This difference was statistically significant and clinically meaningful, with an odds ratio of 657.255 ($p<0.001$). The results of the sensitivity analyses of the co-primary efficacy variables were supportive of the co-primary efficacy results. When PASI90 and IGA 0/1 response rates were analyzed with alternative missing data assumptions (MI using MCMC monotone or reference-based regression, OC, or LOCF), with additional analysis sets (FAS or PPS), and an additional analysis method (logistic regression), the bimekizumab 320mg Q4W group maintained higher PASI90 and IGA 0/1 response rates compared with the placebo group (nominal $p<0.001$ for all comparisons).

Among Week 16 PASI90 responders, the bimekizumab 320mg Q4W/Q4W + Q8W group had a higher PASI90 response rate compared with the bimekizumab 320mg Q4W/placebo group at Week 56, a difference that was statistically significant and clinically meaningful (88.8% vs 16.2%, respectively; $p<0.001$). When compared by individual treatment groups, a clinically meaningful difference in the PASI90 response rate was observed in study participants in the bimekizumab 320mg Q4W/Q4W and bimekizumab 320mg Q4W/Q8W groups compared with study participants in bimekizumab 320mg Q4W/placebo group at Week 56 (86.8% and 91.0% vs 16.2%, respectively; nominal $p<0.001$ for both comparisons). The results of the sensitivity analyses of the secondary efficacy variables were supportive of the secondary efficacy results. When secondary efficacy variables were analyzed with alternative missing data assumptions (MI using MCMC monotone regression or OC), the bimekizumab group had higher response rates for all secondary variables compared with the placebo group (nominal $p<0.001$ for all comparisons).

Across the spectrum of other efficacy endpoints measuring disease symptoms and severity (PASI, IGA, scalp IGA, BSA affected by PSO, IGAxBSA, pp-IGA, mNAPSI), study participants who remained on bimekizumab 320mg Q4W or Q8W maintained clinically meaningful improvements from Week 16 to Week 56 compared with study participants who were re-randomized to withdrawal from bimekizumab. Loss of clinical improvements generally became evident after 12 weeks of withdrawal from bimekizumab treatment (ie, after Week 24). Few study participants receiving bimekizumab relapsed during the study. No study participants experienced a rebound (defined as when a study participant experienced a $\geqslant$25% increase from Initial Treatment Period Baseline in PASI score occurring within 2 months [60 days] of stopping therapy [i.e., being re-randomized to placebo]).

Pooled Phase 3 data

Initial treatment response up to week 16

Bimekizumab 320mg Q4W was superior compared with placebo for PASI90, IGA 0/1, PASI100, IGA 0, and DLQI response rates at Week 16 (Initial Treatment Period).

Clinically meaningful differences in PASI90 and IGA 0/1 response rates were observed by Week 2.

Bimekizumab 320mg Q4W demonstrated higher response rates (nominal $p<0.001$) at Week 16 compared with placebo for PASI100 and IGA 0 response rates. For both PASI100 and IGA 0, a

difference in the response rate began at Week 2 and clinically meaningful difference was observed by Week 4.

Bimekizumab 320mg Q4W demonstrated higher response rates compared with placebo for PASI75 response rate at Week 4 (76.4% versus 1.8%, respectively; nominal p<0.001). A clinically meaningful difference in PASI75 response rate was observed by Week 2.

Treatment with bimekizumab 320mg Q4W resulted in higher PSD response rates at Week 16 (nominal p<0.001) for pain, itch and scaling compared to placebo, based on the pre-specified response thresholds.

A supportive sensitivity analysis for PSD response using a more stringent threshold of ≥4 in the 3 PSD items performed for placebo-controlled data up to Week 16 (Placebo controlled data to Week 16) confirmed the results of the pre-specified main analysis (Nominal p<0.001 for all comparisons).

In Pool E1, in the bimekizumab 320mg Q4W group, the DLQI 0 or 1 rate increased rapidly through Week 8 and continued to increase steadily through Week 16. The DLQI 0 or 1 rate was higher in the bimekizumab 320mg Q4W group compared with the placebo group at Week 1 through Week 16; with a clinically meaningful difference at Week 16 (nominal p<0.001).

In Pool E1, bimekizumab 320mg Q4W demonstrated superior response rates compared with placebo for the efficacy endpoint of BSA ≤1 response rate at Week 16 (76.4% versus 0.6%, respectively; nominal p<0.001). A clinically meaningful response in BSA affected was observed by Week 4 (25.7% versus 1.2% for bimekizumab 320mg Q4W and placebo, respectively; nominal p<0.001).

Maintenance of response up to week 52

Maintenance of response in week 16 responders treated with bimekizumab 320mg Q4W or Q8W up to week 52 was demonstrated in both treatment arms and no particular numerical differences in response rate were observed between maintenance treatment arms. Response rates at week 52 for bimekizumab 320mg Q4W and Q8W maintenance treatment in week 16 responders were 90% (both dosings, PASI90), 88% and 92% (IGA 0/1), 83% and 89% (PASI100) and 83% and 89% (IGA 0), respectively.

Consistent, clinically meaningful improvements were observed for all the subgroups analysed for PASI90, IGA 0/1, and PASI100 response rates. Overall, there were no notable differences in the key subgroups of baseline disease severity, age, weight or prior treatment with biologics. NAb antibody status had no effect on the maintenance of response in week 16 responders up to week 52.

In about 50% of patients not having a PASI90 or IGA 0/1 response at week 16 (61 and 68, respectively) but further receiving bimekizumab in the maintenance treatment period, a treatment response was observed at week 28, regardless of whether patients received bimekizumab 320mg Q4W or Q8W, and this response was maintained until week 52.

Persistence of response up to week 52

Persistence of response was demonstrated in all three main trials and in the analysis of the E3 pool data, independent of the bimekizumab maintenance dose. Pool E3 study participants (n=479, bimekizumab 320mg Q4W only) achieved a rapid response for all primary (PASI90 and IGA 0/1) and secondary (PASI100, IGA 0, scalp IGA 0/1) outcomes which was sustained through Week 52. Response rates at week 16 and 52 were 86% and 83% (PASI90), 85% and 80% (IGA 0/1), 59% and 67% (PASI100) and 60% and 67% (IGA 0). Scalp IGA 0/1 was >73% from week 4 on through week 52.

For study participants treated with bimekizumab 320mg Q4W for 1 year, consistent, clinically meaningful improvements in PASI90, IGA 0/1, and PASI100 responses were maintained at Week 52 for the subgroups analysed. There were no notable differences in PASI90 or IGA 0/1 response rates in the

key subgroups of baseline disease severity, age, or weight. Neutralizing antibody status had no impact on efficacy.

The analysis of the pooled data further demonstrated that whether or not a patient had received prior biologic treatment did not affect treatment response, and this was confirmed when prior exposure was narrowed down to either anti-TNF or anti-IL17 biologic response modifiers, the latter group being composed of patients with secondary failure to anti-IL17 products.

Withdrawal, relapse, re-treatment and rebound

In study PS0013, a randomized withdrawal was implemented on week 16 responders, of which 105 were re-randomised to placebo, 100 received bimekizumab 320mg Q8W and 106 received bimekizumab 320mg Q4W in the maintenance treatment period. The median time to relapse was 197 days for the BKZ/PBO arm, while median time to relapse could not be determined for the BKZ Q4W and BKZ Q8W maintenance arms. At week 56, about 10% of patients had relapsed in the BKZ arms compared to 73% in the placebo arm. No cases of rebound occurred in study participants who were re-randomized to placebo. Retreatment of study participants who relapsed after withdrawal of bimekizumab was successful: in patients receiving bimekizumab escape treatment an 88% PASI90 response rate was observed after 12 weeks which is similar to the response rate in the initial treatment period.

3.3. Uncertainties and limitations about favourable effects

A strong impact of body weight on drug distribution and elimination was observed in the popPK model in addition to a strong effect on the two PD endpoints (PASI and IGA) according to the PK/PD models.

The applicant presented additional data in patients weighing 120 kg or more from ongoing study PS0015 to complement the limited patient numbers that were considered previously. In the phase 3 clinical program, 116 patients have now been identified with a body weight of minimum 120 kg at baseline (in previous analysis 86).

In the initial treatment period, the efficacy outcomes reported at week 16 for the subgroup of patients weighing 120 kg or more are consistent with those reported previously in this patient group. Especially for the more stringent endpoints PASI100 and IGA 0, there remains a significant lower response compared to patients that weigh less than 120 kg.

For the maintenance treatment period, the applicant conducted post-hoc subgroup analyses (<120kg vs ≥120kg) for the key efficacy endpoints PASI90, IGA 0/1, PASI100, and IGA 0 for the pooled data across studies PS0008, PS0009, and PS0015. Study participants in the ≥120kg group (N=88 [Q4W/Q8W=37; Q4W=51]) on the Q4W maintenance regimen showed greater improvement in PASI100 between Week 16 (39.2%) and Week 48 (68.6%), compared with those on the Q8W maintenance regimen (Week 16: 45.9% vs Week 48: 51.4%). As such, Q4W maintenance appears more effective at week 48 compared to Q8W maintenance therapy in patients weighing 120 kg or more in the most stringent endpoints, with the new data set on the expanded patient group confirming the previously reported outcomes. Thus, SmPC – section 4.2 highlights that for some patients with a body weight ≥ 120 kg who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response.

No subjects aged ≥85 years were recruited to the pivotal studies and thus empirical clinical data for this age group are not available.

Long-term treatment effect is unknown at present, ongoing studies (PS0014 and PS0015) are expected to provide additional information on long term effect. Additionally, the potential for development of

neutralizing antibodies following long-term treatment is also unknown as yet. It cannot be excluded that lower efficacy may become an issue over time if a higher number of patients became anti-drug antibody (ADAb) positive. This will be closely followed up in the post marketing setting as part of ongoing study PS0014

Information with regards to prior biologic failure is limited. The following information has been reflected in SmPC – Section 5.1: 'Efficacy in patients with primary failure to anti-IL17 has not been investigated'.

The subgroup analyses also suggested that subjects from Western Europe had less favourable results than those from Central and Eastern Europe, however, it is unclear if this is a true effect or reflects differences in regional medical practice. This is acknowledged however it was considered that it is unlikely that different effect would be expected and therefore was not further pursued.

3.4. Unfavourable effects

Infections were more commonly reported in bimekizumab treated patients compared to placebo. The rate of reporting of infections did not increase with increased duration of exposure. The vast majority of infections (>98%) were nonserious, mild to moderate in intensity, and did not lead to study drug discontinuation. This imbalance was mainly due to an increase in nasopharyngitis, oral candidiasis, and upper respiratory tract infection. The incidence rate of events was generally similar across placebo or active comparator groups, with the exception of oral candidiasis which was higher in bimekizumab-treated study participants. In general, fungal infections were reported more frequently in the bimekizumab treated patients. Fungal infection TEAEs were observed in the 3 HLTs of Candida infections, Fungal infections NEC, and Tinea infections. The majority were nonserious and mild to moderate in severity. Rates of discontinuation were very low (7 patients in total discontinued including one patient who reported a SAE for oesophageal candidiasis). The incidence rate of fungal infections during the Maintenance Treatment Period was numerically lower for the 320mg Q8W compared to the Q4W dosing regimen. Fungal infections were more commonly reported in older patients and in females compared with males. Serious infections were more commonly reported in Phase 3 BKZ 320mg Q4W compared with Phase 3 BKZ 320mg Q8W treated groups. There was no clear pattern in SAEs, which were reported across gastrointestinal infections (n=5), Bacterial infections NEC (n=5), Muscle and soft tissue infections (n=3) and, Staphylococcal infections (n=2) Upper respiratory tract infections (n=2) HLTs. The majority of participants continued on study drug and no further serious infections were reported. Although 8 of these patients did have their treatment temporarily stopped, the majority (n=6) had their treatment re-introduced (after TEAEs of erysipelas, cellulitis, soft tissue infection, sinusitis, appendicitis, and pneumonia). There was no recurrence of serious infections.

The incidence of hypersensitivity AEs in bimekizumab treated patients was higher than with placebo, driven by higher rates of dermatitis and eczema. Other hypersensitivity reactions included events in the SOCs of Eye disorders and Respiratory, thoracic and mediastinal disorders and appeared to be linked to seasonal allergies. There was no evidence of an increase in incidence of events reported under the HLT of Dermatitis and eczema with time. A significant proportion were considered related to study medication. TEAEs other than those in the HLT of Dermatitis and eczema, were assessed as not drug related. There were higher rates of eczema and dermatitis with increasing age. There was only one TEAE of serious dermatitis atopic which occurred >1yr after starting treatment. There were three serious hypersensitivity reactions (anaphylactic shock, dermatitis atopic, and circulatory collapse, respectively). There was no clear evidence of causality with bimekizumab with any of the three cases reported. There were slightly increased reports of TEAEs in Dermatitis and eczema in ADA b-positive patients compared to ADAb-negative patients.

Although the EAIR for any malignancy (0.8/100 participant-years) in the S2 safety update was the same as that in the original submission, when non-melanomic skin cancers are excluded, the EAIR for malignancy increases slightly. This is due to an increase in cases of colon cancer. Events related to colon cancer (4 events of colon cancer, 1 event of colon cancer metastatic) were the second most frequently reported malignancy after basal cell carcinoma. While it is agreed that these cases are confounded by past medical history and had a short time to onset, the clustering of these cases is a concern. This will be further followed-up in the post marketing setting as part of ongoing studies, planned PASS and future PSURs.

Neutropenia was more commonly reported in bimekizumab patients compared to placebo. The incidence was lower compared to adalimumab but slightly higher than ustekinumab. In general, neutropenia was transient, and was not associated with an increased frequency of infections. There were no SAEs associated with neutropenia. One severe case resulted in discontinuation of bimekizumab. The incidence of markedly abnormal low neutrophil counts (<1x109/L) were similar between placebo (0.6%) and 320mg Q4W group (0.6%). 14 (0.8%) Grade 3 and 2 (0.1%) Grade 4 decreases in neutrophils were reported. None of the Grade 3 or 4 neutropenias were associated with severe or serious infections. 8 nonserious infection TEAEs were reported. Most of the events resolved except 1 event of folliculitis.

An increased prevalence of IBD among PSO patients compared with the general population is well-established. One study participant who was treated with bimekizumab 320mg Q4W group in the induction period reported an IBD TEAE (colitis ulcerative). Cases of new or exacerbations of IBD have been reported with IL-17 inhibitors. Of note a case of gastrointestinal inflammation that was thought to possibly be early Crohn's disease was reported in the S2 Safety update report. A revised warning regarding IBD has been included in Sections 4.4 and 4.8 of the SmPC. IBD (Crohn's disease and ulcerative colitis) will continue to be monitored as potential important risk in the safety specification of the RMP and will be further evaluated as part of ongoing studies (PS0014 and PS0015) and planned PASS.

Overall, the incidence rate of TEAEs in the Phase 3 bimekizumab was higher in 320mg Q8W group (76.7%) compared with the Q4W group (73.9%) with slightly higher incidences of SAEs, TEAEs leading to discontinuation and severe TEAEs. Drug-related TEAEs were slightly higher in the 320mg Q4W treated group. The incidence rate of TEAEs potentially linked to the mode of action was higher in the Phase 3 bimekizumab 320mg Q4W group. The incidence of TEAEs was higher in participants with prior systemic therapy compared with those who didn't receive prior systemic therapy.

Over the initial treatment period there was an age-related increase in subjects treated with BKZ Q4W which was attributed to higher rates of eczema and dermatitis and candida skin infections. In the longer term S2 Pool there was some evidence of a trend towards overall increase in TEAES with increasing age including increases in SAEs. These increases were mainly driven by the HLTs Dermatitis and eczema and Musculoskeletal and connective tissue pain and discomfort.

3.5. Uncertainties and limitations about unfavourable effects

The overall safety data base although considerably smaller than that presented for similar type IL-17 inhibitors is sufficient to support evaluation of the safety bimekizumab in the proposed indications taking into consideration the known safety profile of other similar type products such as ixekizumab and secukinumab licensed for use in treatment of psoriasis. The ongoing studies (PS0014 and PS0015) are expected to provide further data on long term safety.

For the serious identified and potential risks, serious infections, serious hypersensitivity, malignancies, MACE, long-term surveillance in larger and real-world patient populations is planned, to detect late

developing ADRs, increased incidences to an already increased background rate of comorbidities and low-frequency adverse drug reactions.

A single case of IBD (new onset colitis ulcerative [EAIR 0.055/100py]) was reported in the PSO clinical development program. A further case of possible early Crohn's disease was reported in the Pool S2 safety follow up period. Although there was no clear evidence of an increased risk of IBD with bimekizumab in the PSO development program, exacerbation or new onset of CD and UC were observed in bimekizumab treated patients during clinical studies in other diseases and IBD has been reported in patients treated with IL-17 inhibitors. Section 4.4 and 4.8 include warnings regarding IBD. IBD is included as a potential risk in the safety specification.

The overall event rate for malignancy is low. There is no clear evidence of an increased risk of malignancy with bimekizumab but there was a slight increase in EAIR for colon cancer in the updated safety analysis. Overall rates of malignancy are similar to other IL-17 –inhibitors. Malignancy will be followed up as a potential identified risk in the RMP and as part of ongoing studies (PS0014 and PS0015), planned PASS and in future PSURs.

So far, the impact of ADAb status on safety is considered to be limited. ADA/NAb and safety data will be further investigated in the ongoing study PS0014.

Some differences between studies and between BKZ Q4W and Q8W treatment groups in the incidence of ISRs were noted in DV002 and DV006 substudies. These are difficult to interpret due to the small numbers. The applicant has committed to monitoring adverse event reporting rates by device with particular emphasis on injection site reactions in future PSURs.

Review of Hypersensitivity-related treatment-emergent adverse events other than Dermatitis identified urticaria, conjunctivitis allergic, and rhinitis allergic, the most commonly reported hypersensitivity TEAEs and that TEAEs' other than those in the HLT of Dermatitis and eczema, as not drug related. In the Hypersensitivity SOC individual reports of angioedema, swelling face, pharyngeal oedema, lip swelling, laryngeal oedema which are suggestive of a more systemic type of allergic reaction were also identified. Hypersensitivity events other than skin-related reactions are a well described class side effect for IL-17 inhibitors and are included as side effects for all of the other the IL-17 inhibitors currently approved in the EU (secukinumab, brodalumab, ixekizumab). Serious hypersensitivity reactions are included as an 'Important potential risk' in the RMP. The warning regarding hypersensitivity in section 4.4 has been updated to indicate that that there have been reports of hypersensitivity reactions with IL-17 inhibitors. No cases of acute or delayed anaphylactic reactions associated with bimekizumab treatment have been reported in the PSO development program to date. A general statement in section 4.4 regarding the risk of serious hypersensitivity reaction is acceptable. A statement has also been included in section 4.8 regarding serious hypersensitivity reactions such as anaphylactic reactions.

The increased incidence of cases of eczematous eruptions in psoriasis patients has been further discussed. No clear mechanism of action has been identified but several hypotheses were discussed exploring possible mechanisms (Th1/Th2 immune response, impact on skin microbiome homeostasis, Potential for IL-17C or IL-22 overexpression) for the occurrence of eczematous eruptions with anti-IL-17 treatment. The higher incidence in elderly may be associated with an age-related decline in skin barrier function. Development of atopic eczema in patients with a history of psoriasis is a potential source of diagnostic confusion. In a systematic review by Al-Jabani et al of 92 patients who developed eczema following treatment of psoriasis with biologic agents including IL-17 inhibitors, the implicated biologic was discontinued in the majority of cases. In patients treated with bimekizumab who developed eczema most eczema events resolved, very few events led to bimekizumab interruption or discontinuation, although the majority required treatment. Elderly patients are special populations at

increased risk of experiencing these product related adverse reactions. This information has been adequately included in section 4.8 of the SmPC.

The impact of bimekizumab on lipid profile (total cholesterol) has been provided for review during the phase 2 study only. No data has been provided for the phase 3 studies in the induction and maintenance periods Pro-atherogenic components of the lipid panel have only been partially evaluated. Data is only available for total cholesterol results from phase 2 studies. The review of interim analysis of PS0015 data through Week 48 did not identify any safety concerns in terms of change from baseline in total cholesterol, high-density lipoprotein (HDL) cholesterol, LDL cholesterol, or triglyceride levels during bimekizumab exposure. There is no evidence that that bimekizumab impacts total or LDL cholesterol in a clinically meaningful way. The applicant will continue to monitor these indices in Study PS0015.

The clinical relevance of the trend towards elevation of BP particularly in patients with normal BP at baseline is unclear. The applicant has committed to monitoring elevation of BP, in particular new onset in normotensive patients, in ongoing studies as well as relevant cases of elevation of BP in future PSURs.

There is still some uncertainty regarding renal, psychiatric and eye disorders in particular eyelid disorders and cataracts. These should continue to be monitored. The applicant has committed to reviewing these adverse events as topics of special interest in the future PSURs.

Although the incidence of Serious Infections is low the incidence rate for bimekizumab (EAIR 1.4/100 subjects years) was comparable with the rate of these events reported for other IL-17 inhibitors used to treat psoriasis (ixekizumab 1.5 /100 subject years and brodalumab 1.91/100 subj-yrs) both of which include serious infection or in the case of brodalumab, infections, as important identified risks in their respective RMPs. Section 4.3 and 4.8 include similar risk minimisation measures advising on specific clinical actions to be taken to minimise the risk of infection. Serious infection will be further evaluated as part of the planned PASS study. Serious infection has been included as an important identified risk in the safety specification of the RMP.

Bimekizumab has not been studied in pregnant or lactating women, and no information on the excretion of bimekizumab in human milk or effects on the nursing infant is available. There is currently insufficient clinical data available to draw conclusions about the safety of using bimekizumab during pregnancy. Animal studies have not shown any effects on male and female reproductive organs and on sperm count, motility, and morphology. As a precautionary measure, it is preferable to avoid the use of bimekizumab during pregnancy. Use in pregnant and lactating women has been added as a missing information in the list of safety concerns in the RMP. The safety of bimekizumab us in pregnant and lactating women will be monitored in observational PASS and pregnancy outcome registry.

3.6. Effects Table

Table 47 - Effects Table for Bimzelx for the treatment of moderate to severe plaque psoriasis

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References	
		Favourable Effects						
PASI 90 Week 16	Psoriasis Area and Severity Index, percentage of patients achieving 90% response	%	BZK 275/319 86.2% 273/321 85.0% 317/349 90.8%	Placebo 4/83 4.8% 1/82 1.2%	UST 81/163 49.7%	ADA 75/159 47.2%	 P<0.001 P<0.001 P<0.001	 PSO008 PSO009 PSO0013
IGA0/1 Week 16	Investigators global assessment, percentage of patients achieving a score of 1 or 0	%	272/319 85.3% 270/321 84.1% 323/349 92.6%	 4/83 4.8% 1/82 1.2%	 87/163 53.4 % %	91/159 57.2%	P<0.001 P<0.001 P<0.001	PSO008 PSO009 PSO0013

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References	
PASI 90 week 56	Psoriasis Area and Severity Index, percentage of patients achieving 90% response	%	183/206 88.8%	17/105 16.2%			P<0.001	PSO0013
	Unfavourable Effects							
			BKZ	placebo	UST	ADA		
Infections and Infestations SOC	Pool S1 BKZ n=839 ; Placebo n=169) Pool S1C BKZ n=1032; Placebo n=211 UST n=163 ADA n=159		36% EAIR: 141.7/100 PYs 37.6% EAIR: 152.7/100PYs	22.5% EAIR: 84.6/100 PYs 22.3% EAIR: 88.1/100PYs	20.9% EAIR: 75.2/100PYs	49.1% EAIR: 151/100PYs	*Pool S1, **Pool S1C	
			63.2% EAIR: 117.8/100 participant-years				***Pool S2 (applies to all effects below).	
Serious Infections	Pool S1 n=839)		0.3% EAIR: 1.0/100 PYs	No cases			no clear pattern in SAEs. The majority of participants continued on study drug	1.

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References	
	Pool S2 Pool S2C		1.4% EAIR: 1.4/100 PYs 1.6% EAIR 1.2/100 PYs		2.5% EAIR: 2.6/100 PYs	0.6% EAIR: 1.4/100 PYs		2.
Any Fungal Infection (HLT)	Pool S2 Pool S2C		22.6% EAIR: 26.0/100 PYs) 26.1% EAIR 23.4/100 PYs		2.5% EAIR: 2.6/100 PYs	0.6% EAIR 1.4/100 PYs	mainly mucocutaneous candial and tinea infections	2.
Candida Infections *(PT)*	Pool S2 Pool S2C		17% EAIR 18.0/100 PYs) 19.8% EAIR 16.9/100 PYs)		1.2% 1.3/100 PYs	0.6% 1.4/100 PYs	generally mild to moderate in severity and resolved	2.
Hypersensitivity	Pool S1		4.2%; EAIR 13.8/100 PYs	0.6%; EAIR 1.9/100 PYs				1.

Effect	Short Description	Unit	Treatment		Control	Uncertainties/ Strength of evidence	References	
	Pool S2 Pool S2C		10.4% EAIR: 10.9/100 PYs 12.9% EAIR: 10.3/100 PYs		9.2% EAIR: 10.2/100 PYs	3.1% EAIR: 7.1/100 PYs	Skin and subcutaneous tissue disorders mainly from the HLT Dermatitis and eczema	2.
Dermatitis and eczema (HLT)	Pool S2 Pool S2C		6.7% EAIR 6.8/100 PYs 9.7% EAIR 7.1/100PYs		4.3% 4.6/100 PYs)	0.6% 1.4/100 PYs)	mostly mild to moderate, non serious, and not leading to discontinuation and occurred more commonly in older patients and pts from Australia and Asia.	2.
Any neutropenia TEAE (HLT)	Pool S2 Pool S2C		1.2% EAIR 1.2/100 PYs 1.3% EAIR 1.0/100 PYs		0.6% 0.6/100 PYs	2.5% 5.6/100PYs		2.

Abbreviations: 1. BKZ: bimekizumab; UST: ustekinumab ; ADA:adalimumab
EAIR/100PYs: Exposure adjusted incidence rate per 100 participant years. PT; Prefferred term, HLT: Higher level term
Notes: 1. Pool S1 (n=839) is the primary safety pool comparing bimekizumab 320mg Q4W (N=670) and placebo (N=169) during the Initial Treatment Period up to Week 16 in Phase 3 Studies PS0009 and PS0013.
Pool S1C includes 211 study participants in the placebo group and 1032 participants in the bimekizumab 320mg Q4W group and contains comparative data with adalimumab (N=159) and ustekinumab (N=163). This analysis also includes safety data from the 16-week Treatment Period of PS0008 (active-comparator-controlled study with adalimumab) and from the 12-week Treatment Period of PS0010 (placebo and bimekizumab 320mg every 4 weeks (Q4W) treatment arms)
2. Pool S2 (BKZ Total n=1789) includes all Phase 2 and Phase 3 data from PSO studies (data from Phase 2 studies (PS0010, PS0011, PS0016, and PS0018) and Phase 3 studies (PS0008, PS0009, PS0013, and PS0014) with study participants exposed to bimekizumab 320mg Q4W and Q8W.

Pool S2C is an update to Pool S2. It includes 5.5 months of additional data. The update primarily consists of additional long-term safety data from the open-label extension (OLE) study (PS0014) as of the designated clinical cut-off date (15 Apr 2020). In addition, safety follow-up (SFU) information from completed pivotal Phase 3 studies PS0008, PS0009. No new study participants were included in this Safety Update. A total of 1371 study participants were exposed to BKZ in Phase 2 and 3 studies for at least 12 months, compared with 1073 study participants in the original MAA submission.
* BKZ 320mg Q4W vs placebo. Initial treatment period week 0-16
**Pool S1C 320mg Q4W vs placebo. Includes additional comparative data with adalimumab (N=159) and ustekinumab (N=163). This analysis also includes safety data from the 16-week Treatment Period of PS0008 (active-comparator-controlled study with adalimumab) studies. 12-week Treatment Period from PS0010 included to avoid introducing a comparison bias
***Pool S2 includes all phase 2 and 3 PSO studies.
**** Pool S2 day120 safety update includes additional long-term safety data from the open-label extension (OLE) study (PS0014).

3.7. Benefit-risk assessment and discussion

3.7.1. Importance of favourable and unfavourable effects

The onset of response to bimekizumab treatment is rapid and the magnitude of the effects are considered highly clinically relevant. The absolute response rates observed for all endpoints overall are high, even for the most stringent endpoints PASI100 or IGA 0, and initial responses are maintained up to 52 weeks. The results were both statistically and clinically significant. Both physician assessed and patient reported outcomes favoured bimekizumab over comparators. Consistency of treatment effect for the primary efficacy variables across the three pivotal studies was seen. Maintenance of effect was demonstrated for up to 1 year. During the Maintenance Treatment Phase, the Q8W dose was demonstrated to be as effective as the Q4W dose in the majority of subjects. This finding provides an advantage to patients due to fewer required administrations to maintain control of their psoriasis. In the Randomized Withdrawal Phase of Study PS0013, response rates declined, which was evident after 12 weeks after bimekizumab withdrawal.

Several other biologics are approved at present for treatment of moderate to severe psoriasis, including several anti-IL17 molecules: ixekizumab (Taltz, anti-IL-17A and anti-IL-17A/F), secukinumab (Cosentyx, anti-IL17A) and brodalumab (Kyntheum, anti-IL17RA). Bimzelx is superior to adalimumab and ustekinumab for the investigated endpoints.

In patients weighing 120kg or more, who did not achieve complete skin clearance at week 16, 320 mg every 4 weeks after week 16 may further improve treatment response.

Each adult dose requires subcutaneous administration of two 160 mg injections as no 320 mg containing bimekizumab presentation is available, which is not most convenient for the patients. Other formulations may be developed in future.

The most notable safety concern identified related to infections, the majority of which were upper respiratory and mucocutaneous candida and tinea infections. These were mainly resolvable and did not impact on treatment compliance. The incidence rate of serious infections in bimekizumab-treated study participants was low and was comparable to ustekinumab and adalimumab treated patients. No particular patterns of serious infection were identified. In addition, no major concerns have been identified of serious hypersensitivity reactions, injection site reactions, inflammatory bowel disease, malignancies, major cerebro-cardiovascular events, and neutropenia.

Warnings are included in the SmPC regarding hypersensitivity reactions, eczema in elderly patients and oral candidiasis in elderly patients and patients with lower body weight.

Further data on long term safety of bimekizumab in plaque PSO will be provided through the post-marketing setting.

3.7.2. Balance of benefits and risks

The pivotal studies have demonstrated efficacy for bimekizumab use in moderate to severe plaque psoriasis in adults, up to one year of treatment. More frequent maintenance dosing may be required in some patients weighing ≥120 kg who have not achieved clear skin after 16 weeks of initial treatment. The most significant safety concern associated with bimekizumab treatment is infection which is expected for this class of product. No safety concerns have been identified in a review of malignancies, MACE, neutropenia, SIB, IBD, anaphylactic hypersensitivity, injection site reactions, and hepatic TEAEs and LFT. The safety profile is similar to other IL-17 inhibitors. There were no clinically relevant differences between the safety profile of the 320 mg Q4W and Q8W doses. The safety profile is favourable based on the current safety dataset. Serious infections, serious hypersensitivity reactions, MACE, malignancy and IBD will be further evaluated in a PASS (Bimekizumab real-world outcomes study) and as part of ongoing studies (PS0014 and PS0015). Overall, the favourable effects outweigh the unfavourable effects.

3.8. Conclusions

The overall B/R of Bimzelx in the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy is positive.

4. Recommendations

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the benefit-risk balance of Bimzelx is favourable in the following indication:

Bimzelx is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy.

The CHMP therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

Other conditions and requirements of the marketing authorisation

Periodic Safety Update Reports

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.

The marketing authorisation holder shall submit the first periodic safety update report for this product within 6 months following authorisation.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

Risk Management Plan (RMP)

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States

Not applicable.

New Active Substance Status

Based on the CHMP review of the available data, the CHMP considers that bimekizumab is a new active substance as it is not a constituent of a medicinal product previously authorised within the European Union.