CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761151Orig1s000

MULTI-DISCIPLINE REVIEW

Summary Review
Office Director
Cross Discipline Team Leader Review
Clinical Review
Non-Clinical Review
Statistical Review
Clinical Pharmacology Review
Clinical Microbiology/Virology

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA (Resubmission after Complete Response)
Application Number(s)	761151
Priority or Standard	Standard
Submit Date(s)	November 21, 2022
Received Date(s)	November 21, 2022
PDUFA Goal Date	May 21, 2023
Division/Office	Dermatology and Dentistry/Office of Immunology and Inflammation
Review Completion Date	October 16, 2023
Established/Proper Name	Bimekizumab-bkzx
(Proposed) Trade Name	BIMZELX
Pharmacologic Class	a humanized interleukin-17A and F antagonist
Code name	UCB4940 (CDP4940)
Applicant	UCB, Inc.
Dosage form	injection
Applicant proposed Dosing Regimen	320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For patients weighing ≥120 kg, a dose of 320 mg every 4 weeks after Week 16 may be considered.
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	200965009 |Plaque psoriasis (disorder)
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	For the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Recommended SNOMED CT Indication Disease Term for each Indication	200965009 |Plaque psoriasis (disorder)
Recommended Dosing Regimen	320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For patients weighing ≥120 kg, a dose of 320 mg every 4 weeks after Week 16 may be considered.

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OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DCN=Division of Cardiology and Nephrology
CDRH =Center for Devices and Radiological Health
DRM=Division of Risk Management
DP= Division of Psychiatry
DG= Division of Gastroenterology
DHN= Division of Hepatology and Nutrition
PLT= Patient Labeling Team
DEPI= Division of Epidemiology
DMEPA=Division of Medication Error Prevention and Analysis

Signatures

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	Signature:			

Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AR	adverse reaction
BKZ	bimekizumab
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls

COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
C-SSRS	Columbia Suicide Severity Rating Scale
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
EAIR	exposure-adjusted incidence rate
ECG	electrocardiogram
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
HADS	Hospital Anxiety and Depression Scale
HELLP	Hemolysis, Elevated Liver enzymes and Low Platelets syndrome
ICH	International Conference on Harmonisation
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
ITT	intent to treat
MACE	Major Adverse Cardiovascular Events
MedDRA	Medical Dictionary for Regulatory Activities
MedGuide	Medication Guide
mITT	modified intent to treat
NAC	Neuropsychiatric Adjudication Committee
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
MPPRC	Medical Policy and Program Review Council
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PHQ-9	Patients' Health Questionnaire 9
PI	prescribing information

PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSA	psoriatic arthritis
PSO	psoriasis
PSUR	Periodic Safety Update report
PT	preferred term
Q4W	every 4 weeks
Q8W	every 8 weeks
ROC	REMS Oversight Committee
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SIB	suicidal ideation and behavior
SGE	special government employee
SOC	standard of care
SS	Safety Set
SUR	Safety Update Report
TEAE	treatment emergent adverse event
W&P	Warnings and Precautions

1 Executive Summary

1.1. Product Introduction

BIMZELX (bimekizumab-bkzx, hereafter referred to as bimekizumab) is a recombinant humanized, immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to IL-17A and IL-17F. The proposed indication is the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

This resubmission is a complete response to the deficiencies outlined in the Complete Response Letter (CRL dated May 12, 2022, Appendix 18.6). The original BLA for bimekizumab (BLA 761151) was submitted on July 15, 2020. The Agency issued a CR during the initial review cycle because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356) by the Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing (OPMA/DBM). Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022.

The Applicant submitted their complete response to the CR on November 21, 2022. This resubmission contained information to address the GMP deficiencies. The Office of Pharmaceutical Quality (OPQ) evaluated the information in the resubmission related to the drug substance (DS), drug product (DP), immunogenicity assay, facilities, microbiology, potency and categorical exclusion claim for Environmental Assessment (EA) for BIMZELX. The OPQ team concluded that the data submitted are adequate to support the conclusion that the manufacture of BIMZELX is well-controlled and leads to a product that is pure and potent and recommended that this product be approved for human use under conditions specified in the package insert (Review by Kelley Burridge, PhD dated May 19, 2023).

In addition, the Applicant also submitted new safety data from Trial PS0014 [an open- label extension (OLE) trial that enrolled 1343 subjects] and Trial PS0015 [a double-blind, active comparator-controlled, parallel group (secukinumab) trial that enrolled 743 subjects]. The Agency identified a new safety signal of suicidal ideation and behavior (SI/B) associated with the use of bimekizumab. The new safety data included a report of a completed suicide in a subject with no prior psychiatric history and three cases of suicide attempt associated with the use of bimekizumab. There were nine and five cases of serious neuropsychiatric AEs in subjects exposed to bimekizumab in PS0014 and PS0015, respectively. The new data prompted a re-evaluation of all relevant data (including the data from trials PS0008, PS0009 and PS0013) by the Division of Psychiatry. Following a thorough re-analysis of previously submitted suicidal ideation and behavior (SI/B) data and new SI/B data, the Agency considers this information to be new safety information that would require adequate labeling (Warnings and Precautions and Section 6 and 17; MedGuide) to communicate this potential risk to healthcare providers and patients to ensure the safe use of the product.

After communicating these concerns to the Applicant via teleconferences held on May 3, 2023, and May 10, 2023, the Division consulted with the REMS Oversight Committee (ROC meetings on June 2, 2023, and June 13, 2023), and Medical Policy and Program Review Council (MPPRC meeting on July 19, 2023) to gain advice from CDER Senior Leadership on the most effective risk management strategies to ensure safe use of this product. There is no identifiable risk factor to predict depression or SI/B. Currently, SI/B is not preventable, but is treatable if identified. Therefore, the focus of the labeling and other post-marketing activities will be on patient and provider education.

The Division of Medication Error Prevention and Analysis [DMEPA] reviewed the proprietary name request for BIMZELX that was included with the Class 2 resubmission of BLA 761151. The DMEPA team concluded that the proposed proprietary name, BIMZELX, was acceptable from both a promotional and safety perspective under BLA 761151 (Proprietary Name Review by Loretta Holmes, BSN, PharmD, dated February 7, 2023). In addition, the DMEPA team reassessed the proposed suffix, -bkzx, for BLA 761151, which was found to be conditionally acceptable on March 12, 2021. The DMEPA team concluded "We find the suffix -bkzx acceptable and recommend the nonproprietary name bimekizumab-bkzx be used throughout the labels and labeling." (Review by Carlos M Mena-Grillasca, BS PharmD dated March 3, 2023).

The Applicant adequately addressed the GMP deficiency and labeling. Therefore, we recommend approval of this application.

1.2. Conclusions on the Substantial Evidence of Effectiveness

During the initial review cycle for BLA 761151, the Applicant provided substantial evidence of the effectiveness of bimekizumab (BKZ) for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval. Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bimekizumab is a recombinant humanized, immunoglobulin G1 (IgG1) monoclonal antibody (mAb) that binds to IL-17A and IL-17F. The proposed indication for BIMZELX (bimekizumab) injection, for subcutaneous use is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022. This resubmission is a complete response to the deficiencies outlined in the Complete Response Letter (CRL dated May 12, 2022). The Applicant submitted their complete response to the CR letter on November 21, 2022. This resubmission contained information to address the GMP deficiencies.

In addition, the resubmission contained new safety data from Trial PS0014 [an open- label extension (OLE) trial in 1343 subjects] and Trial PS0015 [a double-blind, active comparator-controlled (secukinumab) and parallel group trial in 743 subjects]. The review team identified a new potential safety issue of suicidal ideation and behavior (SI/B) associated with the use of bimekizumab. New safety data included a report of completed suicide in a subject with no prior psychiatric history and three cases of suicide attempt associated with the use of bimekizumab. There were five and nine cases of serious neuropsychiatric adverse events (AEs) in subjects exposed to bimekizumab in trials PS0015 and PS0014, respectively. These new data prompted a re-evaluation of all relevant data by the Division of Psychiatry. A re-review of controlled SI/B data collected in previously submitted Trials PS0008, PS0009, and PS0013, using the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) found nearly threefold more positive responses in a pooled bimekizumab group compared to a pooled placebo/active group (most reporting passive wish to be dead, 1.7% versus 0.6%, respectively). Of the 17 positive responses in bimekizumab-treated subjects, only 4 were in subjects with a previous psychiatric history. Pooled analysis of eC-SSRS data from two 16-week, placebo-controlled trials indicated that 12/670 (1.8%) bimekizumab -treated subjects and 1/169 (0.6%) placebo-treated subjects reported passive suicidal ideation with an estimated relative risk of 3.0 (95% confidence interval: 0.39, 22.74). In contrast, analyses did not show a difference in the risk for SI/B between bimekizumab and active comparators over 16 weeks or over one year.

It should be noted that the study population was not representative of real-world population (target population) for use of this product as subjects with risk factors for SI/B were excluded from trials such as active suicidal ideation or suicidal ideation within the month prior to Screening, history of suicide attempt within the past 5 years prior to screening and moderately severe major depression or severe major depression indicated by a score of ≥15 using the screening Patient Health Questionnaire-9 (PHQ-9). Furthermore, during the conduct of clinical

trials, subjects who developed an elevated risk of SI/B based on Patient Health Questionnaire-9 (PHQ-9) ≥ 15 or positive scores on the eC-SSRS were discontinued from treatment with bimekizumab. This safety monitoring likely reduced the number of attempted or completed suicides in the clinical trials.

Taken together, the completed suicide and suicide attempts, the neuropsychiatric adverse event cases and eC-SSRS responses are consistent with a possible increased risk for SI/B with bimekizumab use. The potential risk of SI/B will be adequately described in product labeling (Warnings and Precautions and Section 6 and 17 and Medication Guide [MedGuide]) to convey the importance of these potentially fatal adverse events to healthcare providers and patients. The REMS Oversight Committee (ROC meetings held June 2, 2023, and June 13, 2023) and the Medical Policy and Program Review Council (MPPRC meeting held on July 19, 2023) provided advice regarding the communication of the potential risk of SI/B associated with bimekizumab use to healthcare providers and patients.

There is no identifiable risk factor to predict the development of depression or SI/B. Currently, SI/B is not preventable, but is treatable if identified. Therefore, the target population should include all patients with moderate to severe psoriasis who are candidates for systemic therapy or phototherapy and the recommended indication for BIMZELX (bimekizumab) is as follow:

> BIMZELX is a humanized interleukin-17A and F antagonist indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Therefore, based on our review, the review team concludes that the benefit-risk of bimekizumab is favorable in the proposed population with appropriate labeling and recommend approval of this application.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the U.S. is approximately 4.6 %, of which an estimated 20% have moderate to severe disease. One third of patients have concomitant	• Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and co-morbidities

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.	
Current Treatment Options	• FDA approved drugs for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab), IL-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekizumab), an IL-17A receptor antagonist (brodalumab), IL-23 blockers (guselkumab, tildrakizumab, risankizumab), a T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband). • All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic, hepatotoxic, and nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific	• There are several FDA-approved products with an acceptable benefit-risk profile for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional effective and safe therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	labeled safety issues for each product.	
Benefit	• Data from Trial PS0009 and PS0013 provided substantial evidence of the effectiveness of bimekizumab for the treatment of moderate to severe plaque psoriasis. Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022.	• The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive.
Risk and Risk Management	• Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022, for the original risk assessment. In the resubmission, the Applicant provided new safety data from Trial PS0014 [an open- label extension (OLE) trial enrolled 1343 subjects] and Trial PS0015 [a double-blind, active comparator-controlled (secukinumab) trial enrolled 743 subjects]. New safety data included a report of completed suicide in a subject with no prior psychiatric history and three cases of suicide attempt associated with the use of bimekizumab. There were five and nine cases of serious neuropsychiatric AEs in subjects exposed to bimekizumab in PS0015 and PS0014, respectively. The new data prompted a re-evaluation of all relevant data by the Division of Psychiatry (DP). Pooled analysis of C-SSRS data from two 16-week, placebo-controlled clinical trials indicated that 12/670 (1.8%) bimekizumab -treated subjects and 1/169 (0.6%) placebo-treated subjects reported passive suicidal ideation with an estimated relative risk of 3.0 (95% confidence interval: 0.39, 22.74).	• Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022. • The new safety signal of SI/B is identified and should be adequately described in product labeling to convey the importance of this potentially fatal AE to the healthcare provider and patient. The potential risk of SI/B should be described in a Warning and Precaution, Section 6 and Section 17 and Medication Guide (MedGuide) of the product labeling. • Members of senior leadership from the REMS Oversight Committee (ROC

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• Based on re-analysis of previously submitted SI/B data and new SI/B data, in the context of the completed suicide, the AE cases and eC-SSRS differences may be seen as consistent with a possible signal for an association between bimekizumab use and SI/B. • This new safety information should be adequately described in product labeling to convey the importance of this potentially fatal AE to the healthcare provider and patient. The potential risk of SI/B will be described in Section 5 Warnings and Precautions, Sections 6, and 17 and MedGuide of the product labeling. • Post approval activities for patient and physician education of SI/B risk o Patient education through advocacy groups o Provider education through professional organizations (e.g., American Academy of Dermatology [AAD])	meetings held June 2, 2023, and June 13, 2023) and Medical Policy and Program Review Council (MPPRC meeting held on July 19, 2023) provided advice regarding the communication of the potential risk of SI/B associated with bimekizumab use to healthcare providers and patients.

1.4. Patient Experience Data

The resubmission included no new patient experienced data. Refer to the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for information regarding the patient experience data submitted in support of this BLA.

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder with characteristic sharply demarcated erythematous plaques surmounted by micaceous scale. For a discussion of this condition, refer to the Therapeutic Context section of the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022.

2.2. Analysis of Current Treatment Options

The current treatment armamentarium for moderate-to-severe plaque psoriasis is summarized in Table 1 of the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022).

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BLA 761151 received a Complete Response (CR) during the initial review cycle because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356) by the Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing (OPMA/DBM) (CR letter dated May 12, 2022). As such, the product is not currently marketed in the United States.

3.2. Summary of Presubmission/Submission Regulatory Activity

Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022, for a summary of the regulatory activity prior to submission of the original BLA. A brief summary of the regulatory activity prior to resubmission is presented below.

On August 17, 2022, the Agency held a Type A End of Review Meeting with the Applicant. The Applicant provided a summary of the information they intended to submit to address the

deficiencies noted in the CR letter. The Agency agreed that the proposed data package appeared to be adequate to support the (b) (4) changes but clarified that the adequacy of the data would be evaluated during the review of the BLA resubmission. The Agency agreed that if the deficiencies noted in the Post-Application Action Letter (PAAL) for the Braine manufacturing facility were found to be satisfactorily addressed through compliance review and inspectional activities (if applicable) and the submitted data supported the proposed changes, the approvability issue could be resolved. The Agency further stated that the need for re-inspection of the Braine manufacturing facility would be determined after the BLA was resubmitted, and that the facility would be informed if an inspection was to be conducted. The Agency requested that the Applicant provide a preliminary manufacturing schedule for the UCB4940 drug product in the resubmission.

The Applicant also provided a proposal for the submission of updated safety information. In the resubmission, the Applicant proposed to provide a safety update to include additional pooled safety data from Trial PS0014 (an open-label extension to phase 3 trials PS0008, PS0009, and PS0013) and new data from Trial PS0015. Trial PS0015, a phase 3, randomized, double-blind, active comparator (secukinumab)-controlled trial, was ongoing and blinded at the time of the initial BLA submission. The Applicant also proposed to submit pooled safety data from the development programs for psoriatic arthritis and axial spondyloarthritis. Because the Applicant planned to provide a substantial amount of new clinical data, the resubmission would be a Class 2 resubmission.

The Agency provided advice regarding the content and format of the resubmission, agreed with the proposal for the Applicant to submit updated milestone dates for the proposed postmarketing requirements (PMRs) and to resubmit the Request for Proprietary Name Review.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The review team did not request additional clinical site inspections during review of the resubmission. Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022) for information regarding clinical site inspections conducted during review of the initial BLA.

4.2. Product Quality

The Office of Pharmaceutical Quality (OPQ) evaluated the information in the resubmission related to the drug substance (DS), drug product (DP), immunogenicity assay, facilities, microbiology, potency and categorical exclusion claim for Environmental Assessment (EA) for

BIMZELX. The OPQ review provided the following summary and recommendation (BLA Executive Summary dated May 19, 2023):

> "The overall BIMZELX control strategy incorporates control (b) (4) [redacted]. The manufacturing processes and overall control strategies for BIMZELX are appropriately established to ensure consistency and quality of the final product: therefore, lot variability is not a concern. The assays used for immunogenicity assessment in the clinical studies to support this BLA are adequately validated and suitable for their intended purpose. The BLA is recommended for approval from the product quality, facility, microbiology and sterility assurance perspectives."
>
> Recommendation and Conclusion on Approvability
>
> "Recommendation: Approval
> The Office of Pharmaceutical Quality, CDER, recommends approval of BLA 761151 for BIMZELX manufactured by UCB, Inc. The data submitted in this application are adequate to support the conclusion that the manufacture of BIMZELX is well-controlled and leads to a product that is pure and potent. It is recommended that this product be approved for human use under conditions specified in the package insert."

Refer to the BLA Executive Summary dated May 19, 2023, by Kelley Burridge, PhD.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

Reviewers from the Center for Devices and Radiological Health (CDRH), Porsche Bennett and Courtney Evans, provided a technical engineering consult assessment of the device constituent of the combination product for the Class 2 resubmission of BLA 761151 (Review dated March 29, 2023). The review of the pre-filled syringe with needle safety feature and autoinjector concluded:

> "The complete response hold for facility inspection observations does not include device observations. CDRH lead reviewer confirmed with the lead inspector that the inspection did not conclude with observations pertaining to the device constituent parts of the combination product. The ORA investigator Roger Zabinski covered the device portion of the inspection, with no observations.

> The previous CDRH reviewer conducted the engineering and facilities review for both constituent parts and concluded at the end of review that an approval was recommended pending adequacy of the pre-approval inspection. Therefore, as the pre-approval inspection did not conclude with any device observations per the EIR and 483 for FEI3003909356, therefore demonstrating adequate device compliance, an approval is recommended for the device constituent parts of the proposed combination products."

The original CDRH review of the safety syringe and autoinjector devices completed by Matthew Ondeck and Courtney Evens (dated March 17, 2021) is attached to the updated review.

5 Nonclinical Pharmacology/Toxicology

No new Pharmacology/Toxicology information was included in the BLA resubmission. Therefore, this section is not applicable. Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022) for information regarding the Nonclinical Pharmacology/Toxicology data submitted in support of this BLA.

6 Clinical Pharmacology

No new Clinical Pharmacology data was included in the BLA resubmission. Therefore, this section is not applicable. Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022) for information regarding the Clinical Pharmacology data submitted in support of this BLA.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

The SUR provided in the BLA resubmission is comprised of data from Trials PS0014 and PS0015 as summarized in the table below. For a summary of the clinical trials reviewed during the initial BLA submission, refer to the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022).

Table 1: Listing of Clinical Trials Relevant to the BLA 761151 Resubmission

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of subjects enrolled	Study Population	No. of Centers and Countries
		Trials to Support Safety						
PS0014	03598790	Open-label extension (ongoing)	BKZ 320mg SC Q4W or Q8W (Dependent on subject's treatment regimen and PASI response in the feeder study)	Primary (safety): Incidence of TEAEs adjusted by duration of subject exposure to treatment. Secondary (efficacy): IGA response and PASI90 at Week 144	144 weeks	1343	Moderate to Severe plaque PSO who completed 1 of the Phase 3 Feeder trials (PS0008, PS0009, or PS0013)	Number of sites not provided: Australia, Belgium, Canada, Germany, Hungary, Italy, Japan, Poland, Republic of Korea, Russian Federation, Taiwan, UK, &US
PS0015		Randomized, double-blind, active comparator-controlled, parallel-group trial (ongoing)	Initial Treatment Period (Weeks 0-16): BKZ 320mg Q4W or Secu 300 mg SC Q4W Maintenance Treatment Period (Weeks 16-48): Subjects in the BKZ 320 Q4W arm were rerandomized 1:2 to BKZ 320 mg Q4W or BKZ 320 mg Q8W. OLE Period (Weeks 48-144): Subjects were assigned to BKZ 320 mg Q4W or BKZ 320 mg Q8W based on their treatment arm and PASI90 response dung the Maintenance Period	Primary efficacy: PASI 100 at Week 16 (per the protocol schematic included in the Safety Update. No further information was provided regarding endpoints in the Safety update.)	144 weeks	743 enrolled at Baseline 716 initiated mainten-ance Tx 691 included in pool S2-3b	Moderate to Severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for systemic PSO therapy and/or phototherapy	Not provided in the Safety Update

AEs- adverse events, BKZ- Bimekizumab, BSA-body surface area, IGA- Investigator's Global Assessment Score, OLE- open-label extension, PASI- Psoriasis Area and Severity Index Score, PSO-Psoriasis, Secu- Secukinumab, TEAE- treatment-emergent adverse event, Tx=treatment

7.2. Review Strategy

The BLA resubmission contained no new data to support efficacy. The sources of data used for the safety analysis included the safety update submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references. This application was submitted in eCTD format and entirely electronic, and were in the following data path:

- BLA Resubmission: \\CDSESUB1\evsprod\BLA761151\0068

Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022, for the sources of data used for the evaluation of the efficacy and safety of bimekizumab for the proposed indication during the review of the initial BLA submission.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

The BLA resubmission included only quality information and safety data. No new efficacy data was provided or reviewed to inform Section 14 (Clinical Studies) of labeling. Refer to the Multi-disciplinary Review and Evaluation dated for BLA 761151 May 11, 2022, for a review of the data used to support the efficacy of bimekizumab for the proposed indication of the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Refer to Section 8.2 of this review for a discussion of the content of the Safety Update Report (SUR).

8.2. Review of Safety

8.2.1. Safety Review Approach

This review of safety will focus on data provided by the Applicant in the SUR included in the BLA resubmission. The SUR contained additional data from two ongoing phase 3 trials: the open-label extension (OLE) Trial PS0014 and a new active- controlled Trial PS0015. Due to differences in the study designs, the review team analyzed the safety data from Trials PS0014 and PS0015 separately. Data from Trials PS0015 and PS0014 were the primary analysis datasets for treatment-emergent adverse events (TEAEs), serious AEs (SAEs), and AEs leading to discontinuation. In addition, the review team evaluated rare TEAEs using Pool S2-3b and Pool S1 as follows:

- Pool S2-3b: This data pool provided in the resubmission includes data from phase 2 trials PS0010, PS0011, PS0016, and PS0018 as well as phase 3 trials PS0008, PS0009, PS0013, PS0014, and PS0015 through data cutoff dates of 10/23/2021 (PS0014) and 5/6/2022 (PS0015). This pool was used in the analysis of some adverse events of special interest (AESI) (e.g., suicidal ideation and behavior [SI/B], inflammatory bowel disease, infections, malignancies, neutropenia, etc.) in comparison with data from the 120-day Safety Update in the Initial BLA submission.
- Pool S1: This was the primary analysis dataset for the review of safety during review of the initial BLA. Pool S1 included pooled data from the Initial Treatment Period (Week 0-16) of the placebo-controlled phase 3 Trials PS0009 and PS0013. Data from this pool was also used to evaluate the new safety signal for SI/B. Refer to Section 8.2.5.1 of this review for more details regarding this safety signal.

The review team analyzed the following types of pooled data: exposure, demographics and baseline characteristics, treatment emergent adverse events (TEAEs), serious AEs (SAEs), and AEs leading to discontinuation. In addition, the safety evaluation included the following adverse events of special interest (AESI): infections, malignancies, major adverse cardiovascular events (MACE), neutropenia, suicidal ideation/behavior (SI/B), inflammatory bowel disease (IBD), anaphylactic, hypersensitivity, and injection site reactions, and elevated liver enzymes and hepatic events.

Brief summaries of the trial designs of PS0014 and Trial PS0015 are provided below.

Trial PS0014: open-label extension (OLE) trial

This is a multicenter, open-label trial to evaluate the long-term safety, tolerability, and efficacy of bimekizumab in adult subjects with moderate to severe plaque psoriasis who completed one of three phase 3 trials (PS0008, PS0009, or PS0013). In Trial PS0014, 1343 subjects received bimekizumab 320mg Q4W or 320mg Q8W based on their treatment regimen and PASI response in the feeder trial.

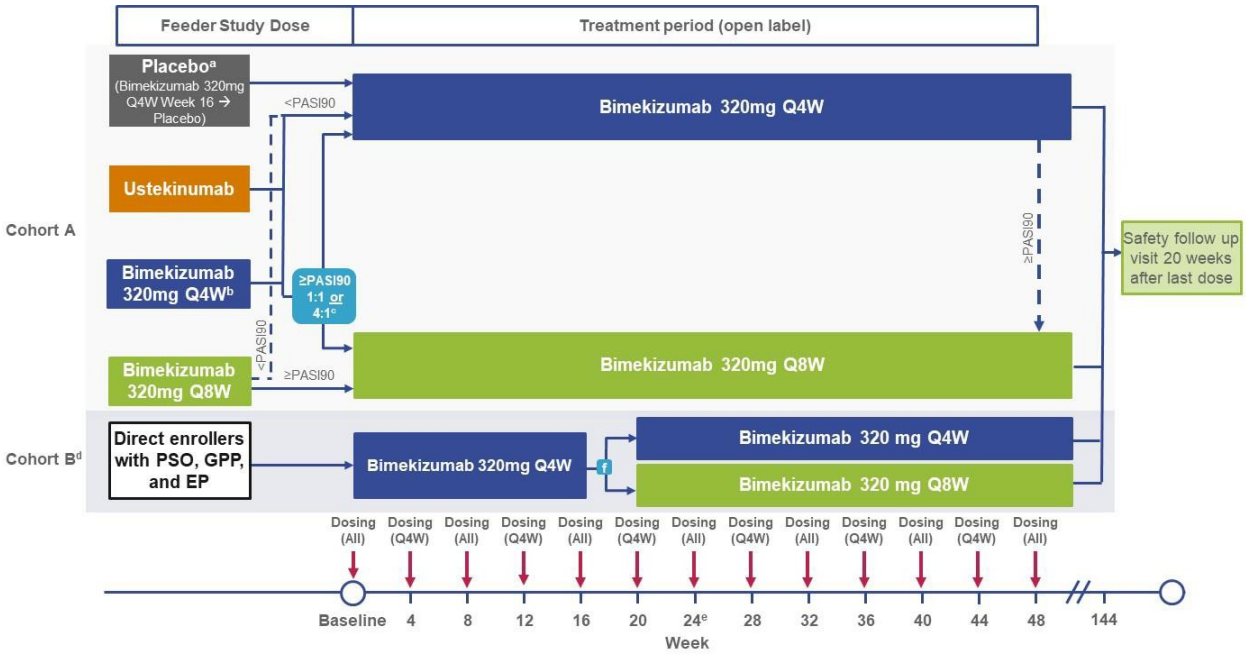
Study population

Subjects eligible for enrollment in Trials PS0008, PS0009, or PS0013 had an Investigator's Global Assessment (IGA) Score ≥3 (moderate), a Psoriasis Area and Severity Index (PASI) score of ≥12, affected body surface area (BSA) ≥10%, and were candidates for systemic therapy and/or phototherapy. To be eligible to roll over to PS0014, subjects must have achieved a PASI50 response by the prespecified timepoint in the feeder trial.

Study design

A schematic diagram for Trial PS0014 (Weeks 0-144) is presented in the figures below. Further details regarding treatment assignment are provided in the footnotes of the schematic.

Figure 1: PS0014 Schematic (Weeks 0-48)



EP=erythrodermic psoriasis; GPP=generalized pustular psoriasis; IGA=Investigator's Global Assessment; IMP=investigational medicinal product; PASI=Psoriasis Area Severity Index; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks

Note: Self-injection was allowed from Week 48 onward.

Note: At Week 28 and all following visits, study participants on continuous treatment with the same IMP for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period are defined as nonresponders and should discontinue IMP.

[a] Subjects on placebo after a Week 16 response (≥PASI90) on bimekizumab 320mg Q4W during the initial Treatment Period of the feeder study may enroll in PS0014.

[b] Subjects on bimekizumab 320mg Q4W who achieved a PASI50 at Week 12 in the escape arm of the feeder study may enroll in PS0014.

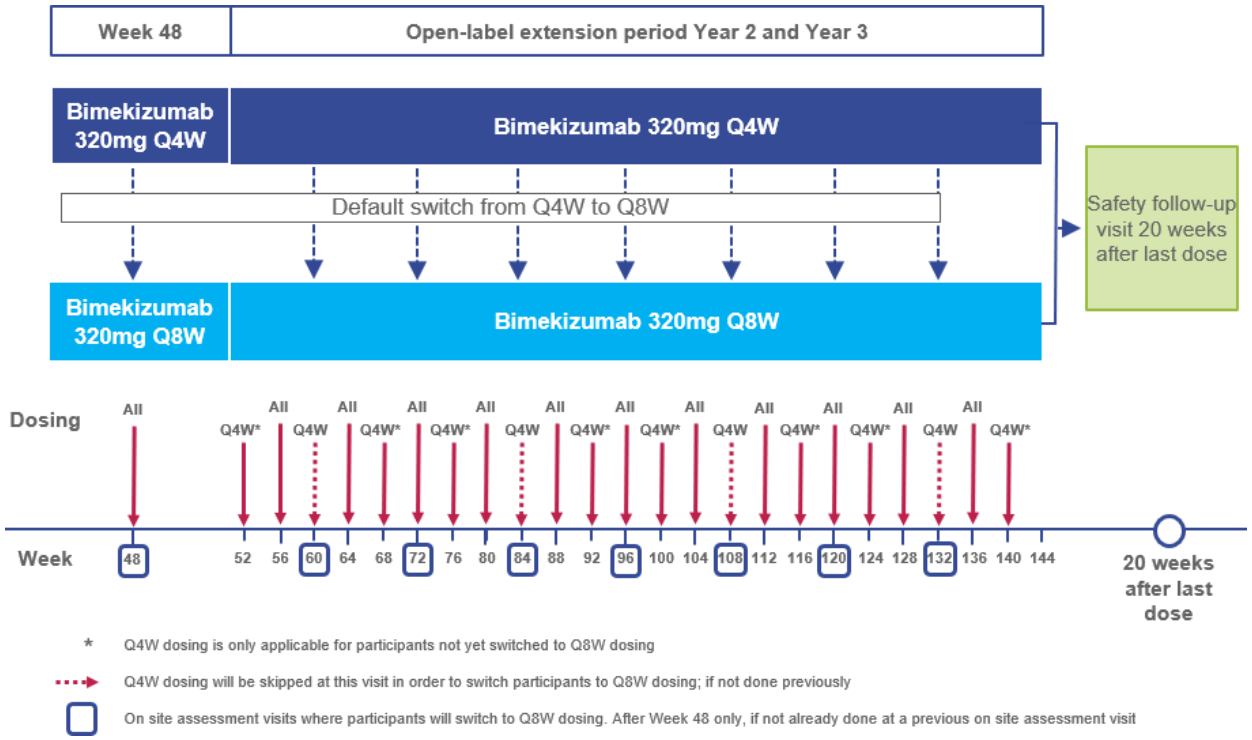
[c] Subjects on ustekinumab or bimekizumab 320mg Q4W in feeder studies who achieved PASI90 were randomized, respectively, 1:1 or 4:1 to bimekizumab 320mg Q4W or 320mg Q8W.

[d] At Week 24, if PASI90 is achieved, Investigator may change the dosing interval from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W (optional).

[e] At Week 48, for subjects receiving bimekizumab 320mg Q4W, if PASI90 is achieved, the subjects' dosing interval will change from 320mg Q4W to 320mg Q8W (default) unless, based on medical judgement, the Investigator decides differently

[f] For Cohort B (which was included in Japan only), subjects with plaque PSO receive bimekizumab 320mg Q4W until Week 16 and 320mg Q8W thereafter through Week 40. At Week 48, if PASI90 is not achieved, the study participant's dosing interval changes from 320mg Q8W to 320mg Q4W through to the end of the study (Week 144). Subjects with GPP and EP who achieve an IGA response of 0 or 1 at Week 16 change from bimekizumab 320mg Q4W to 320mg Q8W through Week 40. At Week 48, for subjects with GPP and EP receiving bimekizumab 320mg Q8W, if IGA response of 0 or 1 is not achieved, the subject's dosing interval changes to 320mg Q4W through to the end of the study (Week 144).

Figure 2: PS0014 Schematic (Weeks 48-144)



Q4W=every 4 weeks; Q8W=every 8 weeks
Note: Self-injection is allowed from Week 48 onward.
Note: The subject's dosing interval will change from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W at Week 48 or at the next scheduled clinic visit (i.e., Week 60, Week 72, Week 84, Week 96, Week 108, Week 120, or Week 132) if the subject has already completed the Week 48 visit prior to implementation of Protocol Amendment #3.

Trial PS0014 also includes a second, 48- week, open-label extension (OLE2) period in the US and Canada. This Period begins after Week 144 of PS0014. This period is ongoing and no data from the OLE2 Period are included in this Safety Update.

Trial PS0015: new active comparator-controlled trial

This is an ongoing phase 3b, multicenter, randomized, double-blind, active comparator-controlled, parallel-group trial designed to compare the efficacy and safety of bimekizumab to secukinumab. The trial enrolled 743 adult subjects with moderate to severe plaque psoriasis.

Study population

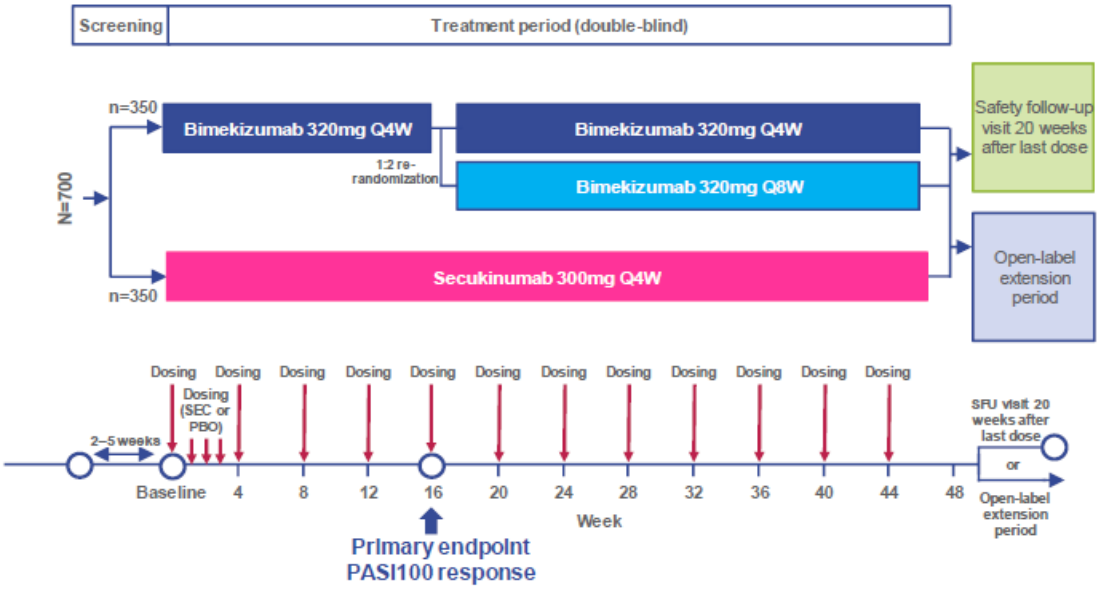
The inclusion criteria were the same as the other phase 3 trials. Eligible subjects had an Investigator's Global Assessment (IGA) Score ≥3 (moderate), a Psoriasis Area and Severity Index (PASI) score of ≥12, affected body surface area (BSA) ≥10%, and were candidates for systemic therapy and/or phototherapy.

Study design

Trial PS0015 included a Screening Period of 2-5 weeks, followed by a 48-week Double-Blind Treatment Period. The Double-Blind Treatment Period was comprised of an Initial Treatment Period (Weeks 0-16) and a Maintenance Treatment Period (Weeks 16-48). After Week 48, subjects entered the Open-Label Extension (OLE) Period (Weeks 48-144). PS0015 was blinded and ongoing at the time of the clinical cutoff dates for the initial BLA submission and the 120-Day safety update, therefore no data from this trial were available during review of the initial BLA. In the US and Canada, an additional 48-week OLE treatment period (OLE2 Period) was added to PS0015 during which eligible subjects could continue or reinitiate bimekizumab treatment for 40 weeks (from Week 144/OLE2 Baseline to OLE2 Week 48). This will be followed by a second Safety Follow-up (SFU) Period of 20 weeks after the final dose of bimekizumab. The OLE2 period is ongoing and no data from the OLE2 Period are included in this safety update.

In the Initial Treatment Period of PS0015, subjects were randomized 1:1 to treatment with bimekizumab 320 mg Q4W or secukinumab. For the Double-Blind Treatment Period, at Week 16 subjects in the bimekizumab arm were rerandomized 1:2 to bimekizumab 320 mg Q4W or 320 mg Q8W. Subjects in the secukinumab arm continued treatment with secukinumab. At the beginning of the OLE period, subjects were assigned to treatment with bimekizumab 320 mg Q4W or Q8W based on whether they had achieved PASI90 response (i.e., a 90% or greater improvement from baseline on their PASI score). Further details regarding treatment assignment are provided in the footnotes of the schematic. A Schematic Diagram for Trial PS0015 (Weeks 0-144) is presented in the figures below:

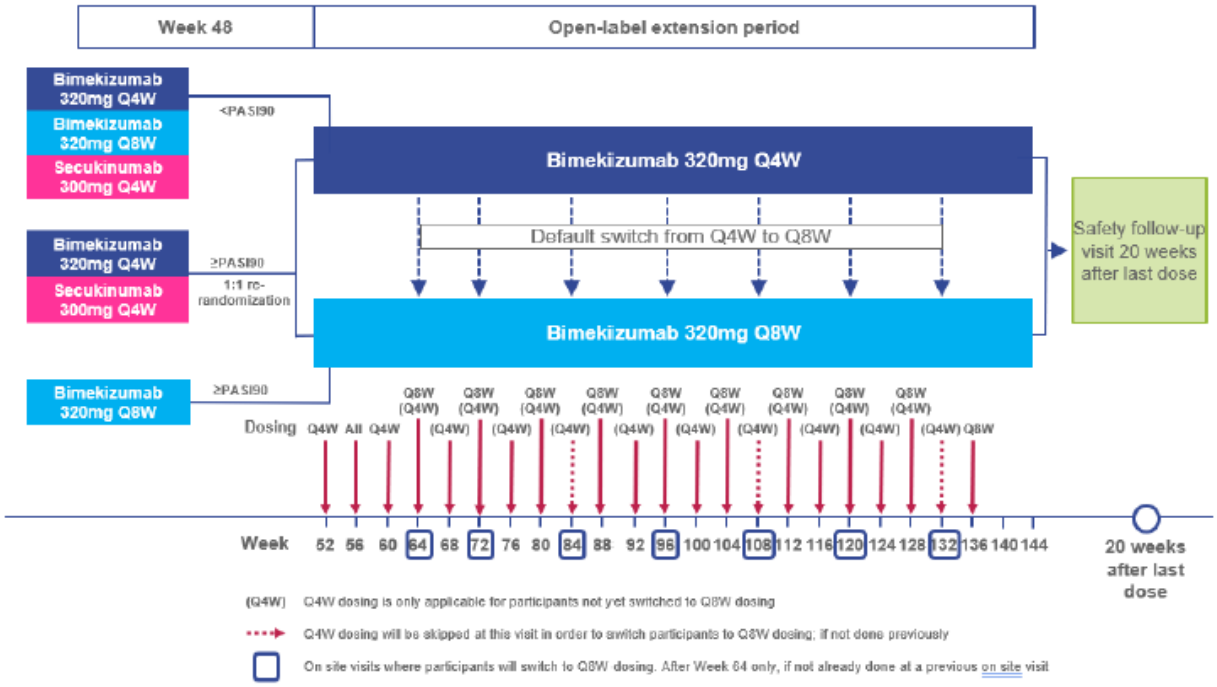
Figure 3: PS0015 Schematic (Screening- Week 48)



IGA=Investigator's Global Assessment; IMP=investigational medicinal product; PASI100=Psoriasis Area Severity

Index complete response; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks; SEC=Secukinumab; FU=Safety Follow-up
Note: Subjects in the bimekizumab 320mg treatment arm during the Initial Treatment Period who reached Week 16 prior to implementation of Protocol Amendment 1 continued to receive bimekizumab 320mg Q4W during the Maintenance Treatment Period. After implementation of Protocol Amendment 1, study participants in the bimekizumab 320mg treatment arm during the Initial Treatment Period were re-randomized 1:2 at Week 16 to receive bimekizumab 320mg Q4W or bimekizumab 320mg Q8W.
Note: At Week 28 and all following visits, study participants on continuous treatment for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period were defined as nonresponders and should have discontinued IMP.

Figure 4: PS0015 Schematic (Weeks 48-144)



PASI=Psoriasis Area Severity Index; PASI90=90% improvement in the PASI score; Q4W=every 4 weeks; Q8W=every 8 weeks
Note: The study participant's dosing interval will change from bimekizumab 320mg Q4W to bimekizumab 320mg Q8W at Week 64, or at the next scheduled clinic visit (i.e., Week 72, Week 84, Week 96, Week 108, Week 120, or Week 132) if the study participant has already completed the Week 64 visit prior to implementation of Protocol Amendment #5.1.

Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022, for a discussion of the approach to the review of safety data from the initial BLA submission.

8.2.2. Review of the Safety Database

Overall Exposure

The safety update provided additional safety data for 1343 subjects who were enrolled in Trial PS0014. Of these subjects, a total of 1108 had completed ≥96 weeks, 473 had completed ≥112 weeks, and 122 had completed ≥128 weeks of treatment in PS0014. When exposure of these subjects during the phase 3 feeder trials is added, a total of 1010 subjects had completed ≥128 weeks, 850 subjects had completed ≥144 weeks, 561 subjects had completed ≥160 weeks, and 67 subjects had completed ≥176 weeks of treatment with bimekizumab in the phase 3 Trials PS0008, PS009, and PS0013 and OLE Trial PS0014. A more detailed summary of exposure is presented in Tables 16 and 17 in Appendix 15.3 of this review.

The resubmission contained new data from 691 subjects from Trial PS0015 for whom safety data was not available during review of the initial BLA. A total of 558 subjects completed 144 weeks of treatment in Trial PS0015.

Safety data from Trial PS0014 and Trial PS0015 were analyzed according to the treatment that subjects actually received (not treatment to which they were assigned).

In the SUR, the Applicant updated the overall summary of exposure to bimekizumab in the development program. In the 120 Day SUR submitted during review of the original BLA, the phase 2/3 population included 1789 subjects with 2424.7 subject-years of exposure and the phase 3 population with psoriasis (PsO) included 1495 subjects with 2055.7 subject-years of exposure. The resubmission includes data from 691 new subjects from PS0015. The updated exposure for the phase 2/3 PsO population includes 2480 subjects with 5830.4 subject-years of exposure and the phase 3 PsO population includes 2186 subjects with 5461.4 subject-years of exposure. This represents 3405.7 additional subject-years of exposure in the resubmission safety update.

Relevant characteristics of the safety population:
The demographics of the study population in Trial PS0015 were similar to the demographics of the overall phase 3 population. The majority of subjects in Trial PS0015 were White (93.5%) and male (65.4%). The mean age was 45 years and a total of 77 (10.4%) subjects were 65 years of age and older. The demographic characteristics were comparable across treatment groups. Refer to Section 8.1.4 of the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for a demographic summary of the phase 3 population from the initial BLA submission.

Adequacy of the safety database:

In general, the total subject exposure to bimekizumab, 320 mg Q4W or Q8W for the treatment of moderate to severe plaque psoriasis presented in the initial BLA and the resubmission

provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. The total exposures for up to 2 years and beyond as described above are sufficient to characterize the safety of the product over longer treatment periods. However, a safety database of this size provides limited ability to detect rare adverse events.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data provided in the resubmission is adequate to further characterize the safety of bimekizumab for the treatment of moderate to severe plaque psoriasis. The resubmission provided summaries using pooled data from Pool S2-3b. In addition, the Applicant provided separate safety analyses for Trials PS0014 and PS0015 in response to an information request.

Categorization of Adverse Events

The definition and categorization of adverse events (AEs), including treatment-emergent AEs (TEAEs), serious AEs (SAEs) and AESIs for the resubmission was the same as for the initial BLA submission. AESIs are defined in Section 8.2.1 and discussed in more detail in Section 8.2.5 of this review.

Refer to the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for a discussion of the categorization of AEs during the development program.

Routine Clinical Tests

The safety assessments included in the safety update are the same as those reviewed under the initial BLA. The Applicant's safety assessments included clinical evaluation of AEs, SAEs, vital signs, physical examinations, clinical laboratory evaluation (chemistry, hematology, and urinalysis), and ECGs. Safety assessments also included pregnancy testing at Screening and periodically throughout the trials. Investigators assessed subjects for suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) in all trials, the Hospital Anxiety and Depression Scale (HADS) during the phase 2 trials, and the Patients' Health Questionnaire 9 (PHQ-9) during the phase 3 trials. Subjects were tested at Screening for tuberculosis (TB) and were reassessed periodically using a TB risk assessment questionnaire. The schedules of safety assessments were similar among the trials and are described in detail in Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022).

8.2.4. Safety Results

Deaths

As of the 120-day safety update submitted with the initial BLA, a total of 6 deaths (6/1789; 0.3%; exposure-adjusted incidence rate [EAIR] 0.2/100 subject-years) had been reported during the development program for bimekizumab for psoriasis. In the safety update provided with the BLA resubmission, the Applicant reported 17 additional deaths, for a total of 23 (23/2480; 0.9%, EAIR 1.4/100 subject-years) in the development program.

Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022) for narratives for the 6 subjects with fatal TEAEs evaluated during review of the initial BLA. This review will focus on the new deaths reported in the safety update provided with the BLA resubmission.

Narratives for subjects who experienced fatal AEs related to adjudicated MACE and SI/B events are presented in Sections 8.2.5.6 and 8.2.5.1, respectively. The remaining narratives are presented below and include four cases of death related to coronavirus (COVID-19) infection. The investigator and the Applicant considered all the fatal events described below as not related to treatment with bimekizumab.

Trial PS0014

- A 58-year-old (y/o) male (Subject PS0014-(b) (6)) with a history of (h/o) type 2 diabetes mellitus and overweight who was treated with bimekizumab (BKZ) 320 mg Q4W experienced a fatal AE of SARS-CoV-2 infection. He received his first dose of COVID-19 vaccine 3-4 days prior to hospitalization for SARS-CoV-2 infection. The event occurred 1107 days after his first dose of BKZ and 44 days after his most recent dose.

- A 45 y/o female (Subject PS0014-(b) (6)) with a h/o morbid obesity who was treated with BKZ 320 mg Q8W experienced a fatal AE of SARS-CoV-2 infection. The subject was not vaccinated against COVID-19. The event occurred 1025 days after her first dose of BKZ and 41 days after her most recent dose.

- A 63 y/o male (Subject PS0014-(b) (6)) with a h/o hypertension, type 2 diabetes mellitus and gastrointestinal (GI) bleeding who was treated with BKZ 320 mg Q4W had a fatal AE of hypovolemic shock. The subject also had multiple AEs for iron deficiency anemia which were attributed to gastrointestinal (GI) bleeding from arteriovenous malformations noted on an upper endoscopy. The fatal event occurred 629 days after his first dose of BKZ and 69 days after his most recent dose.

- A 76 y/o male (Subject PS0014-(b) (6)) with a non-contributory history who was treated with BKZ 320 mg Q4W had a fatal AE of brain neoplasm. The event occurred approximately 2 years and 7 months after his first dose and 22 days since the most

recent dose of BKZ. Per the Applicant, the subject refused treatment for his brain tumor. A role for immunosuppression resulting from bimekizumab cannot be excluded.

Trial PS0015

- A 57 y/o male (Subject PS0015 (b) (6)) with a pertinent h/o of type 2 diabetes mellitus and obesity who was treated with BKZ 320 mg Q8W had a fatal AE of SARS-CoV-2 infection. The subject was not vaccinated against COVID-19. The subject also had two separate SAEs of soft tissue infection of the left knee (Day 307 while receiving secukinumab and Day 448 while receiving BKZ 320 mg Q4W) and erysipelas of the lower left leg (Day 669 while receiving BKZ 320 mg Q8W). These SAEs resolved with antibiotic treatment and the subject continued in the trial. The fatal event occurred 704 days after the first dose of secukinumab, 354 days after his first dose of BKZ and 39 days after his most recent dose.

- A 63 y/o female (Subject PS0015 (b) (6)) with a h/o myocardial infarction, transient ischemic attack, hypertension, type 2 diabetes mellitus, tobacco use (33-year h/o smoking), and morbid obesity who was treated with BKZ 320 mg Q8W had a fatal AE of SARS-CoV-2 infection. The subject was not vaccinated against COVID-19. The fatal event occurred 848 days after her first dose of secukinumab, 512 days after her first dose of BKZ and 8 days after her most recent dose.

- A 72 y/o male (Subject PS0015- (b) (6)) with a pertinent h/o attention deficit/hyperactivity disorder and depression who was treated with BKZ 320 mg Q8W had a fatal AE of road traffic accident (Verbatim term- Trauma-pedestrian hit by car). An autopsy was performed, and the death was attributed to multiple blunt force trauma injuries. The event occurred 129 days after his first dose of BKZ and 17 days after his most recent dose. Further information regarding this subject was requested by consultants from the Division of Psychiatry (DP). The subject's eC-SSRS and PHQ-9 screenings during the trial were not indicative of SI/B. The AE was reportedly adjudicated by the Neuropsychiatric Adjudication Committee as non-suicidal. However, a report from the Neuropsychiatric Adjudication Committee could not be located by the Applicant. Although the investigator and the Applicant considered the death not related to treatment with BKZ, the reviewer from DP commented, "Without further details, there cannot be certainty that this death was non-psychiatric in nature."

- A 65 y/o female (Subject PS0015- (b) (6)) with a h/o tobacco use (1/2 pack per day for 21 years) who was treated with BKZ 320 mg Q4W had a fatal AE of hepatic pain (verbatim term: liver pain). This AE was not associated with elevations in liver enzymes

or bilirubin. Per the investigator, the death was suspected to be due to pancreatic cancer with metastasis to the liver. However, no autopsy was reportedly performed. In addition, the Applicant provided no imaging or other test results to support a diagnosis of pancreatic cancer. The event occurred 501 days after her first dose of secukinumab, 157 days after her first dose of BKZ, and 55 days after her most recent dose. Although the investigator and the Applicant considered the death not related to treatment with BKZ, based on the paucity of information provided, the cause of death appears to be inconclusive. As such, the relationship to treatment cannot be assessed.

The deaths resulting from SARS-CoV-2 infection occurred in subjects with risk factors for severe coronavirus infection and who were unvaccinated or inadequately vaccinated. However, treatment with biologic immunomodulators, including BKZ, are known to increase the risk of infection due to immunosuppression. As such, a contributory role of BKZ in these events cannot be excluded.

Serious Adverse Events

Serious TEAEs (SAEs) related to adjudicated SI/B, IBD, and MACE are discussed in Sections 8.2.5.1, 8.2.5.2. and 8.2.5.6 of this review, respectively. Otherwise, SAEs reported in Trials PS0015 and PS0014 are summarized below.

Trial PS0015

During the Initial Treatment Period (Weeks 0-16) of Trial PS0015, serious TEAEs (SAEs) were reported in 10/373 (2.7%) of subjects treated with bimekizumab 320 mg Q4W and 6/370 (1.6%) of subjects treated with secukinumab. All SAEs were reported by single subjects. The treatment emergent SAEs for the Initial Treatment Period of Trial PS0015 are presented in the table below.

Table 2: Summary of Serious TEAEs- Initial Treatment Period Trial PS0015

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)
Gastrointestinal disorders	2 (0.5)	0 (0.0)
Colitis ulcerative	1 (0.3)	0 (0.0)
Inguinal hernia	1 (0.3)	0 (0.0)
Infections and infestations	1 (0.3)	1 (0.3)
Atypical pneumonia	0 (0.0)	1 (0.3)
Dengue fever	1 (0.3)	0 (0.0)
Injury, poisoning and procedural complications	2 (0.5)	0 (0.0)
Cervical vertebral fracture	1 (0.3)	0 (0.0)
Laceration	1 (0.3)	0 (0.0)

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)
Road traffic accident	1 (0.3)	0 (0.0)
Thoracic vertebral fracture	1 (0.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.3)	2 (0.5)
Arthralgia	0 (0.0)	1 (0.3)
Osteoarthritis	1 (0.3)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0 (0.0)
Malignant melanoma in situ	1 (0.3)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (0.3)
Transient ischemic attack	0 (0.0)	1 (0.3)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.3)
Pregnancy on oral contraceptive	0 (0.0)	1 (0.3)
Psychiatric disorders	1 (0.3)	0 (0.0)
Suicide attempt	1 (0.3)	0 (0.0)
Reproductive system and breast disorders	1 (0.3)	0 (0.0)
Uterine polyp	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)
Idiopathic pulmonary fibrosis	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	0 (0.0)
Psoriasis	1 (0.3)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "Bimekizumab 320mg Q4W" and SAFFL = "Y" (Bimekizumab 320mg Q4W); TRT01A = "Secukinumab 300mg Q4W" and SAFFL = "Y" (Secukinumab 300mg Q4W); TRTEMFL = "Y" and ANL02FL = "Y" and AESER = "Y" (Adverse Events).

Selected narratives from PS0015:

- A 49 y/o male (Subject PS0015-(b) (6)) with a h/o obesity and tobacco use (22-year h/o smoking) treated with bimekizumab 320 mg Q8W developed an SAE of pulmonary embolism. The subject denied recent long travels, surgeries, or any ongoing immobility. The SAE occurred 607 days after the first and 47 days after the most recent dose of bimekizumab. The event was severe in intensity and was resolved after 2 days. The subject continued treatment with bimekizumab in the trial. The investigator and the Applicant considered the SAE not related to treatment with bimekizumab.

During the Maintenance Treatment Period (Weeks 16-48) of Trial PS0015, SAEs were reported in 6/147 (4.1%) of subjects treated with bimekizumab 320 mg Q4W, 10/215 (4.7%) of subjects treated with bimekizumab 320 mg Q8W, and 19/254 (5.4%) of subjects treated with secukinumab. SAE PTs of Appendicitis were reported in 2 subjects treated with bimekizumab 320 mg Q8W and Atrial fibrillation were reported in 2 subjects treated with secukinumab. Otherwise, each SAE PT was reported in single subjects. SAEs reported during the Maintenance

Treatment Period of Trial PS0015 are presented in the table below.

Table 3: Summary of Serious TEAEs- Maintenance Treatment Period PS0015

System Organ Class - Preferred Term	Bimekizumab 320mg Q8W (N=215) n (%)	Bimekizumab 320 mg Q4W (N=147) n (%)	Secukinumab 300 mg Q4W (N=354) n (%)
Cardiac disorders	1 (0.5)	1 (0.7)	4 (1.1)
Acute myocardial infarction	0 (0.0)	0 (0.0)	1 (0.3)
Atrial fibrillation	1 (0.5)	0 (0.0)	2 (0.6)
Coronary artery disease	0 (0.0)	0 (0.0)	1 (0.3)
Supraventricular tachycardia	0 (0.0)	1 (0.7)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	2 (1.4)	2 (0.6)
Abdominal pain	0 (0.0)	0 (0.0)	1 (0.3)
Diverticulum oesophageal	0 (0.0)	1 (0.7)	0 (0.0)
Hiatus hernia	0 (0.0)	1 (0.7)	0 (0.0)
Pancreatic fistula	0 (0.0)	0 (0.0)	1 (0.3)
Pancreatitis	0 (0.0)	0 (0.0)	1 (0.3)
Pancreatitis acute	0 (0.0)	0 (0.0)	1 (0.3)
General disorders and administration site conditions	1 (0.5)	0 (0.0)	1 (0.3)
Non-cardiac chest pain	1 (0.5)	0 (0.0)	1 (0.3)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (0.3)
Bile duct stone	0 (0.0)	0 (0.0)	1 (0.3)
Infections and infestations	6 (2.8)	1 (0.7)	7 (2.0)
Appendicitis	2 (0.9)	0 (0.0)	0 (0.0)
Extradural abscess	1 (0.5)	0 (0.0)	0 (0.0)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (0.3)
Latent tuberculosis	1 (0.5)	0 (0.0)	0 (0.0)
Localised infection	1 (0.5)	0 (0.0)	0 (0.0)
Peritoneal abscess	0 (0.0)	0 (0.0)	1 (0.3)
Pneumonia	0 (0.0)	0 (0.0)	1 (0.3)
Pyelonephritis	0 (0.0)	1 (0.7)	0 (0.0)
Respiratory tract infection	0 (0.0)	0 (0.0)	1 (0.3)
Soft tissue infection	0 (0.0)	0 (0.0)	1 (0.3)
Tooth abscess	1 (0.5)	0 (0.0)	1 (0.3)
Urosepsis	0 (0.0)	0 (0.0)	1 (0.3)
Injury, poisoning and procedural complications	1 (0.5)	0 (0.0)	0 (0.0)
Road traffic accident	1 (0.5)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	0 (0.0)	1 (0.3)
Basal cell carcinoma	0 (0.0)	0 (0.0)	1 (0.3)
Nervous system disorders	1 (0.5)	0 (0.0)	0 (0.0)
IIIrd nerve paralysis	1 (0.5)	0 (0.0)	0 (0.0)

System Organ Class - Preferred Term	Bimekizumab 320mg Q8W (N=215) n (%)	Bimekizumab 320 mg Q4W (N=147) n (%)	Secukinumab 300 mg Q4W (N=354) n (%)
Renal and urinary disorders	0 (0.0)	1 (0.7)	0 (0.0)
Ureterolithiasis	0 (0.0)	1 (0.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.7)	1 (0.3)
Asphyxia	0 (0.0)	0 (0.0)	1 (0.3)
Aspiration	0 (0.0)	0 (0.0)	1 (0.3)
Pleurisy	0 (0.0)	1 (0.7)	0 (0.0)
Skin and subcutaneous tissue disorders	0 (0.0)	0 (0.0)	1 (0.3)
Dermal cyst	0 (0.0)	0 (0.0)	1 (0.3)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.3)
Thromboangiitis obliterans	0 (0.0)	0 (0.0)	1 (0.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Bimekizumab 320mg Q8W" and SAFFL = "Y" (Bimekizumab 320mg Q8W); TRT02A = "Bimekizumab 320mg Q4W" and SAFFL = "Y" (Bimekizumab 320 mg Q4W); TRT02A = "Secukinumab 300mg Q4W" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRTEMFL = "Y" and ANL03FL = "Y" and AESER = "Y" (Adverse Events).

During the OLE Period (Weeks 48-144) of Trial PS0015, 10% (64/654) of subjects treated with either dosage of bimekizumab developed SAEs. The most common SAEs were reported in the System-Organ Classes (SOCs) of Infections and infestations (17/654, 2.6%), Musculoskeletal and connective tissue disorders (11/654, 1.7%), Cardiac disorders (10/654, 1.5%), and Neoplasms benign, malignant and unspecified (incl cysts and polyps) (9/654, 1.4%). For the safety analyses for the OLE period, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated with bimekizumab. Because subjects switched dosing regimens during this period of the trial, it is difficult to definitively determine dose-response based on these data.

Table 4: Summary of Serious TEAEs PS0015 -OLE

Summary of Serious TEAEs

System Organ Class - Preferred Term	**BKZ Q4W (N=294) n (%)**	**BKZ Q8W (N=626) n (%)**	**BKZ Total (N=654) n (%)**
Cardiac disorders	**3 (1.0)**	**7 (1.1)**	**10 (1.5)**
Acute coronary syndrome	1 (0.3)	0 (0.0)	1 (0.2)
Arteriosclerosis coronary artery	0 (0.0)	1 (0.2)	1 (0.2)
Atrial fibrillation	2 (0.7)	1 (0.2)	3 (0.5)
Atrial flutter	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac arrest	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac failure congestive	0 (0.0)	2 (0.3)	2 (0.3)
Coronary artery disease	1 (0.3)	0 (0.0)	1 (0.2)
Myocardial infarction	0 (0.0)	1 (0.2)	1 (0.2)
Pericardial effusion	0 (0.0)	1 (0.2)	1 (0.2)
Ear and labyrinth disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Otosclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Endocrine disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Endocrine disorder	0 (0.0)	1 (0.2)	1 (0.2)
Gastrointestinal disorders	**1 (0.3)**	**3 (0.5)**	**4 (0.6)**
Colitis ulcerative	0 (0.0)	1 (0.2)	1 (0.2)
Hemorrhoidal haemorrhage	0 (0.0)	1 (0.2)	1 (0.2)
Ileus	0 (0.0)	1 (0.2)	1 (0.2)
Intestinal obstruction	1 (0.3)	0 (0.0)	1 (0.2)
Hepatobiliary disorders	**1 (0.3)**	**3 (0.5)**	**4 (0.6)**
Bile duct stone	0 (0.0)	1 (0.2)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)	1 (0.2)
Cholecystitis acute	0 (0.0)	1 (0.2)	1 (0.2)
Hepatic pain	1 (0.3)	0 (0.0)	1 (0.2)
Infections and infestations	**5 (1.7)**	**13 (2.1)**	**17 (2.6)**
Anal abscess	1 (0.3)	1 (0.2)	2 (0.3)
Candida sepsis	1 (0.3)	0 (0.0)	1 (0.2)
Corona virus infection	0 (0.0)	5 (0.8)	5 (0.8)
Erysipelas	0 (0.0)	2 (0.3)	2 (0.3)
Otitis externa	1 (0.3)	0 (0.0)	1 (0.2)
Pneumonia	0 (0.0)	1 (0.2)	1 (0.2)
Postoperative abscess	0 (0.0)	1 (0.2)	1 (0.2)
Pyelonephritis	1 (0.3)	0 (0.0)	1 (0.2)
Pyelonephritis acute	1 (0.3)	1 (0.2)	2 (0.3)
Rectal abscess	0 (0.0)	1 (0.2)	1 (0.2)
Soft tissue infection	1 (0.3)	0 (0.0)	1 (0.2)
Staphylococcal bacteremia	0 (0.0)	1 (0.2)	1 (0.2)
Staphylococcal infection	0 (0.0)	1 (0.2)	1 (0.2)
Staphylococcal skin infection	0 (0.0)	1 (0.2)	1 (0.2)
Tonsillitis	0 (0.0)	1 (0.2)	1 (0.2)
Urinary tract infection	0 (0.0)	1 (0.2)	1 (0.2)
Injury, poisoning and procedural complications	**0 (0.0)**	**6 (1.0)**	**6 (0.9)**
Ankle fracture	0 (0.0)	1 (0.2)	1 (0.2)
Joint dislocation	0 (0.0)	1 (0.2)	1 (0.2)
Meniscus injury	0 (0.0)	1 (0.2)	1 (0.2)
Multiple fractures	0 (0.0)	1 (0.2)	1 (0.2)
Pneumothorax traumatic	0 (0.0)	1 (0.2)	1 (0.2)
Rib fracture	0 (0.0)	1 (0.2)	1 (0.2)
Road traffic accident	0 (0.0)	1 (0.2)	1 (0.2)
Skin abrasion	0 (0.0)	1 (0.2)	1 (0.2)
Spinal fracture	0 (0.0)	1 (0.2)	1 (0.2)
Metabolism and nutrition disorders	**0 (0.0)**	**2 (0.3)**	**2 (0.3)**
Dehydration	0 (0.0)	1 (0.2)	1 (0.2)
Diabetic ketoacidosis	0 (0.0)	1 (0.2)	1 (0.2)
Musculoskeletal and connective tissue disorders	**0 (0.0)**	**11 (1.8)**	**11 (1.7)**
Arthralgia	0 (0.0)	1 (0.2)	1 (0.2)
Chondropathy	0 (0.0)	1 (0.2)	1 (0.2)
Intervertebral disc disorder	0 (0.0)	1 (0.2)	1 (0.2)
Intervertebral disc protrusion	0 (0.0)	1 (0.2)	1 (0.2)
Osteoarthritis	0 (0.0)	4 (0.6)	4 (0.6)
Osteonecrosis of jaw	0 (0.0)	1 (0.2)	1 (0.2)

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Rotator cuff syndrome	0 (0.0)	2 (0.3)	2 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**8 (1.3)**	**9 (1.4)**
Angiofibroma	0 (0.0)	1 (0.2)	1 (0.2)
Basal cell carcinoma	0 (0.0)	2 (0.3)	2 (0.3)
Bladder cancer stage iii	0 (0.0)	1 (0.2)	1 (0.2)
Hodgkin's disease nodular sclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Lentigo maligna	0 (0.0)	1 (0.2)	1 (0.2)
Malignant melanoma in situ	1 (0.3)	0 (0.0)	1 (0.2)
Renal cell carcinoma	0 (0.0)	1 (0.2)	1 (0.2)
Uterine leiomyoma	0 (0.0)	1 (0.2)	1 (0.2)
Nervous system disorders	**0 (0.0)**	**3 (0.5)**	**3 (0.5)**
Cerebral infarction	0 (0.0)	1 (0.2)	1 (0.2)
Cerebrovascular accident	0 (0.0)	1 (0.2)	1 (0.2)
Relapsing-remitting multiple sclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Pregnancy on contraceptive	0 (0.0)	1 (0.2)	1 (0.2)
Psychiatric disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Suicide attempt	0 (0.0)	1 (0.2)	1 (0.2)
Renal and urinary disorders	**2 (0.7)**	**2 (0.3)**	**4 (0.6)**
Acute kidney injury	1 (0.3)	0 (0.0)	1 (0.2)
Nephrolithiasis	1 (0.3)	2 (0.3)	3 (0.5)
Obstructive nephropathy	1 (0.3)	0 (0.0)	1 (0.2)
Reproductive system and breast disorders	**0 (0.0)**	**2 (0.3)**	**2 (0.3)**
Endometriosis	0 (0.0)	1 (0.2)	1 (0.2)
Uterine polyp	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**0 (0.0)**	**2 (0.3)**	**2 (0.3)**
Pneumothorax	0 (0.0)	1 (0.2)	1 (0.2)
Pulmonary embolism	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory failure	0 (0.0)	1 (0.2)	1 (0.2)
Skin and subcutaneous tissue disorders	**0 (0.0)**	**2 (0.3)**	**2 (0.3)**
Eczema	0 (0.0)	1 (0.2)	1 (0.2)
Erythrodermic psoriasis	0 (0.0)	1 (0.2)	1 (0.2)
Surgical and medical procedures	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Abortion induced	0 (0.0)	1 (0.2)	1 (0.2)
Vascular disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Aortic aneurysm	0 (0.0)	1 (0.2)	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTIAN = 5 to 5 (BKZ Q4W); TRTIAN = 6 to 6 (BKZ Q8W); TRTIAN = 7 to 7 (BKZ Total); TRTEMFL = "Y" and ANL05FL = "Y" and ASER = "Y" (Adverse Events).

OLE Trial PS0014

In OLE Trial PS0014, 11% of subjects who received bimekizumab developed an SAE. For the safety analyses for Trial PS0014, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated with bimekizumab. Because subjects switched dosing regimens during this trial, it is difficult to definitively determine dose-response based on these data. The most common system-organ

classes (SOCs) in which serious adverse events (SAEs) were reported in the combined bimekizumab groups were Infections and Infestations (30/1353; 2.2%), Cardiac Disorders (20/1353; 1.5%), Neoplasms benign, malignant, and unspecified (incl cysts and polyps) (19; 1.4%), Injury, poisoning and procedural complications (19/1353; 1.4%), and Gastrointestinal disorders (15/1353; 1.1%). The most common infection was SARS-CoV-2 infection (9/1353; 0.7%); the most common cardiac disorders were angina pectoris (4/1353; 0.3%) and cardiac arrest (3/1353; 0.2%). The reported neoplasms were common malignancies: colon cancer (4/1353; 0.3%) and breast cancer (2/1353; 0.1%).[1] Refer to Table 21 in Appendix 15.3 Additional Clinical Analyses for the summary of treatment emergent SAEs in Trial PS0014. Refer to Section 8.2.5 for additional analyses and narratives related to infection, MACE and malignancies.

Selected narratives from PS0014

- 65-year-old Asian male (PS0014-(b) (6)) with a history of obesity (BMI 32 kg/m^2), deep venous thrombosis (DVT), impaired glucose tolerance and decreased mobility due to "gonarthosis" developed a DVT 450 days after his first dose of bimekizumab 320 Q4 and 2 days after the most recent dose. On Day 465 after his first dose of bimekizumab 320 Q4 and 17 days after his most recent dose he developed a pulmonary embolism. The deep vein thrombosis, and pulmonary embolism were considered not related by the Investigator and Applicant and no action was taken with study drug.
- 65-year-old White male (PS0014-(b) (6)) with a history of basal cell carcinoma experienced an SAE of malignant melanoma, 944 days after the first injection of bimekizumab 320 mgQ8. The event was deemed moderate in intensity, not resolved, and not related to study drug by the Investigator and Applicant. The event occurred after the last dose of bimekizumab, so no action taken with study drug.
- 29-year-old white male (PS0014-(b) (6)) with a family history of diverticulitis, obesity (BMI of 32 kg/m^2), gastroesophageal reflux disease, psoriatic arthritis and tobacco use developed abdominal pain and was diagnosed with diverticulitis on Day 488 with an acute exacerbation on Day 1019 and perforation on Day 1024 after his first dose of Bimekizumab 320mg Q4W. The SAEs of diverticulitis, acute diverticulitis and diverticular perforation were deemed as not related and the drug was interrupted.

All of these subjects had risk factors for their respective SAEs. Given the confounding factors, a contribution from exposure to bimekizumab cannot be assessed.

Dropouts and/or Discontinuations Due to Adverse Effects

[1] The review team could not replicate the analyses provided by the Applicant. Data scientists with OCS provided this analysis. For all discrepancies, the Analysis Studio table counts are greater than or equal to the Applicant counts.

Subjects who discontinued treatment because of SI/B TEAEs are described in more detail in Section 8.2.5.1 of this review. Otherwise, TEAEs leading to discontinuation reported in Trials PS0015 and PS0014 are summarized below.

Trial PS0014

During the Initial Treatment Period (Weeks 0-16) of Trial PS0014, TEAEs leading to discontinuation were reported in 9/373 (2.4%) of subjects in the bimekizumab group and 4/370 (1.1%) of subjects in the secukinumab group. Each of the PTs for TEAEs leading to discontinuation were reported in single subjects. These TEAEs are presented in the table below.

Table 5: Summary of TEAEs Leading to Discontinuation-Initial Treatment Period Trial PS0015

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)
Endocrine disorders	1 (0.3)	0 (0.0)
Endocrine disorder	1 (0.3)	0 (0.0)
Eye disorders	0 (0.0)	1 (0.3)
Vision blurred	0 (0.0)	1 (0.3)
Gastrointestinal disorders	2 (0.5)	0 (0.0)
Colitis ulcerative	1 (0.3)	0 (0.0)
Large intestine polyp	1 (0.3)	0 (0.0)
General disorders and administration site conditions	1 (0.3)	0 (0.0)
Fatigue	1 (0.3)	0 (0.0)
Hepatobiliary disorders	1 (0.3)	0 (0.0)
Drug-induced liver injury	1 (0.3)	0 (0.0)
Investigations	1 (0.3)	0 (0.0)
Hepatic enzyme increased	1 (0.3)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	1 (0.3)
Hyperkaliemia	0 (0.0)	1 (0.3)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3)	0 (0.0)
Malignant melanoma in situ	1 (0.3)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	1 (0.3)
Pregnancy on oral contraceptive	0 (0.0)	1 (0.3)
Psychiatric disorders	1 (0.3)	0 (0.0)
Suicide attempt	1 (0.3)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (0.3)
Idiopathic pulmonary fibrosis	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.3)	0 (0.0)
Eczema	1 (0.3)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)

Filters: TRT01A = "Bimekizumab 320mg Q4W" and SAFFL = "Y" (Bimekizumab 320mg Q4W); TRT01A = "Secukinumab 300mg Q4W" and SAFFL = "Y" (Secukinumab 300mg Q4W); TRTEMFL = "Y" and ANL02FL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

During the Maintenance Treatment Period (Weeks 16-48) of Trial PS0015, TEAEs leading to discontinuation were reported in 3/147 (2.0%) of subjects treated with bimekizumab 320 mg Q4W, 2/215 (0.9%) of subjects treated with bimekizumab 320 mg Q8W, and 5/354 (1.4%) of subjects treated with secukinumab. Each of the PTs for TEAEs leading to discontinuation were reported in single subjects. These TEAEs are presented in the table below.

Table 6: Summary of TEAEs Leading to Discontinuation- Maintenance Treatment Period PS0015

System Organ Class - Preferred Term	Bimekizumab 320mg Q8W (N=215) n (%)	Bimekizumab 320 mg Q4W (N=147) n (%)	Secukinumab 300 mg Q4W (N=354) n (%)
Gastrointestinal disorders	0 (0.0)	1 (0.7)	2 (0.6)
Diarrhoea	0 (0.0)	0 (0.0)	1 (0.3)
Diverticulum oesophageal	0 (0.0)	1 (0.7)	0 (0.0)
Pancreatic fistula	0 (0.0)	0 (0.0)	1 (0.3)
Infections and infestations	0 (0.0)	2 (1.4)	0 (0.0)
Latent tuberculosis	0 (0.0)	1 (0.7)	0 (0.0)
Skin candida	0 (0.0)	1 (0.7)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.5)	0 (0.0)	0 (0.0)
Road traffic accident	1 (0.5)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.3)
Arthralgia	0 (0.0)	0 (0.0)	1 (0.3)
Psoriatic arthropathy	0 (0.0)	0 (0.0)	1 (0.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (0.3)
Asphyxia	0 (0.0)	0 (0.0)	1 (0.3)
Aspiration	0 (0.0)	0 (0.0)	1 (0.3)
Skin and subcutaneous tissue disorders	1 (0.5)	0 (0.0)	1 (0.3)
Eczema nummular	1 (0.5)	0 (0.0)	0 (0.0)
Seborrhoeic dermatitis	0 (0.0)	0 (0.0)	1 (0.3)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Bimekizumab 320mg Q8W" and SAFFL = "Y" (Bimekizumab 320mg Q8W); TRT02A = "Bimekizumab 320mg Q4W" and SAFFL = "Y" (Bimekizumab 320 mg Q4W); TRT02A = "Secukinumab 300mg Q4W" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRTEMFL = "Y" and ANL03FL = "Y" and AEACN = "DRUG WITHDRAWN" (Adverse Events).

During the OLE Period (Weeks 48-144) of PS0015, 5% of subjects who received any dose of

bimekizumab developed an adverse event that led to discontinuation. For the safety analyses for the OLE period, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated with bimekizumab. Because subjects switched dosing regimens during this portion of the trial, it is difficult to definitively determine dose-response based on these data. These TEAEs are presented in the table below.

Table 7: Summary of TEAEs Leading to Discontinuation-OLE Treatment Period Trial PS0015

Summary of TEAEs Leading to Discontinuation

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Cardiac disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Cardiac arrest	0 (0.0)	1 (0.2)	1 (0.2)
Endocrine disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Endocrine disorder	0 (0.0)	1 (0.2)	1 (0.2)
Gastrointestinal disorders	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Colitis ulcerative	0 (0.0)	1 (0.2)	1 (0.2)
General disorders and administration site conditions	**1 (0.3)**	**1 (0.2)**	**2 (0.3)**
Asthenia	1 (0.3)	1 (0.2)	2 (0.3)
Hepatobiliary disorders	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**
Hepatic pain	1 (0.3)	0 (0.0)	1 (0.2)
Infections and infestations	**4 (1.4)**	**11 (1.8)**	**15 (2.3)**
Bacterial rhinitis	0 (0.0)	1 (0.2)	1 (0.2)
Corona virus infection	0 (0.0)	3 (0.5)	3 (0.5)
Eczema infected	1 (0.3)	0 (0.0)	1 (0.2)
Gastrointestinal candidiasis	0 (0.0)	3 (0.5)	3 (0.5)
Oral candidiasis	2 (0.7)	1 (0.2)	3 (0.5)
Oral fungal infection	0 (0.0)	1 (0.2)	1 (0.2)
Oropharyngeal candidiasis	0 (0.0)	1 (0.2)	1 (0.2)
Staphylococcal skin infection	0 (0.0)	1 (0.2)	1 (0.2)
Urinary tract infection	1 (0.3)	0 (0.0)	1 (0.2)
Investigations	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**
Alanine aminotransferase increased	1 (0.3)	0 (0.0)	1 (0.2)
Gamma-glutamyl transferase increased	1 (0.3)	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	**1 (0.3)**	**1 (0.2)**	**2 (0.3)**
Arthralgia	1 (0.3)	0 (0.0)	1 (0.2)
Myalgia	1 (0.3)	0 (0.0)	1 (0.2)
Psoriatic arthropathy	0 (0.0)	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**1 (0.3)**	**2 (0.3)**	**3 (0.5)**
Bladder cancer stage iii	0 (0.0)	1 (0.2)	1 (0.2)
Hodgkin's disease nodular sclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Malignant melanoma in situ	1 (0.3)	0 (0.0)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Pregnancy on contraceptive	0 (0.0)	1 (0.2)	1 (0.2)
Psychiatric disorders	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**
Insomnia	1 (0.3)	0 (0.0)	1 (0.2)
Renal and urinary disorders	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**
Obstructive nephropathy	1 (0.3)	0 (0.0)	1 (0.2)

Summary of TEAEs Leading to Discontinuation

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Respiratory, thoracic and mediastinal disorders	**1 (0.3)**	**0 (0.0)**	**1 (0.2)**
Oropharyngeal pain	1 (0.3)	0 (0.0)	1 (0.2)
Skin and subcutaneous tissue disorders	**1 (0.3)**	**5 (0.8)**	**6 (0.9)**
Alopecia	0 (0.0)	1 (0.2)	1 (0.2)
Dyshidrotic eczema	1 (0.3)	0 (0.0)	1 (0.2)
Eczema	0 (0.0)	2 (0.3)	2 (0.3)
Psoriasis	0 (0.0)	1 (0.2)	1 (0.2)
Vitiligo	0 (0.0)	1 (0.2)	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTIAN = 5 to 5 (BKZ Q4W); TRTIAN = 6 to 6 (BKZ Q8W); TRTIAN = 7 to 7 (BKZ Total); TRTEMFL = "Y" and ANL05FL = "Y" and AEDROP = "Y" (Adverse Events).

During the OLE Trial PS0014, 5% of subjects who received bimekizumab developed AEs which led to discontinuation. For the safety analyses for Trial PS0014, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated with bimekizumab. Because subjects switched dosing regimens during this trial, it is difficult to definitively determine dose-response based on these data. These TEAEs are presented in Table 22 in Appendix 15.3.

Significant Adverse Events

Refer to Section 8.2.5 of this review for a discussion of the Adverse Events of Special Interest (AESI).

Treatment Emergent Adverse Events and Adverse Reactions

Adverse reactions (ARs) identified during review of the initial BLA for the placebo-controlled period (Pool S1) are presented in the table below:

Table 8: Adverse Reactions Occurring in **≥1%** of Subjects with Plaque Psoriasis in the bimekizumab Group and More Frequently Than in the Placebo Group in the Placebo-Controlled Trials

	BIMEKIZUMAB N=670 n, %	Placebo N=169 n, %
URI[a]	102 (15)	24 (14)
Oral Candidiasis[b]	61 (9)	0 (0)
Headache	22 (3)	0 (0)
Injection Site Reactions[c]	19 (3)	2 (1)
Tinea Infections[d]	18 (3)	1 (1)
Gastroenteritis[e]	12 (2)	0 (0)
Herpes Simplex Infections[f]	9 (1)	0 (0)

	BIMEKIZUMAB N=670 n, %	Placebo N=169 n, %
Acne	8 (1)	0 (0)
Folliculitis	8 (1)	0 (0)
Other Candida Infections[g]	7 (1)	1 (1)
Fatigue	7 (1)	0 (0)

[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Oral Candidiasis includes oral candidiasis, oropharyngeal candidiasis, oral fungal infection, fungal pharyngitis, and oropharyngitis fungal
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes Enterovirus infection, gastroenteritis, gastroenteritis bacterial, and gastroenteritis viral
[f] Herpes Simplex Infections include herpes simplex and oral herpes
[g] Other Candida Infections include, vulvovaginal candidiasis, vulvovaginal mycotic infection, skin candida, and genital candidiasis.
Source: Reviewer's table, BLA 761151 Unireview dated May 11, 2022

(b) (4) The review team compared exposure-adjusted incidence rates (EAIRs) of ARs identified during the review of the initial BLA with data in the resubmission to determine whether the frequency of these ARs were increased with increased duration of treatment with bimekizumab. For the safety analyses from both pools, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated with bimekizumab. This analysis is presented in the table below:

Table 9: Comparison of Adverse Reactions between Initial BLA and Resubmission

	120 Day Safety Update- Original BLA Submission		Pool S2-3b- BLA Resubmission	
	Phase 3 BKZ 320mg Q4W N=1456 100 subject yrs=15.45 n (%) EAIR (95% CI)	Phase 3 BKZ 320 mg Q8W N=640 100 subject-yrs=5.13 n (%) EAIR (95% CI)	Phase 3 BKZ 320mg Q4W N=2025 100 subject yrs=24.31 n (%) EAIR (95% CI)	Phase 3 BKZ 320 mg Q8W N=1935 100 subject-yrs=30.35 n (%) EAIR (95% CI)
Upper Respiratory Infections[a]	565 (38.8) 51.3 (47.2, 55.7)	208 (32.5) 54.5 (47.4, 62.4)	742 (36.6) 44.5 (41.4, 47.8)	471 (24.3) 20.3 (18.5, 22.2)
Oral Candidiasis[b]	288 (19.8) 21.7 (19.2, 24.3)	66 (10.3) 14.1 (10.9, 17.9)	402 (19.9) 19.6 (17.7, 21.6)	234 (12.1) 8.6 (7.5, 9.8)
Headache	57 (3.9)	11 (1.7)	77 (3.8)	67 (3.5)

	120 Day Safety Update- Original BLA Submission		Pool S2-3b- BLA Resubmission	
	Phase 3 BKZ 320mg Q4W N=1456 100 subject yrs=15.45 n (%) EAIR (95% CI)	Phase 3 BKZ 320 mg Q8W N=640 100 subject-yrs=5.13 n (%) EAIR (95% CI)	Phase 3 BKZ 320mg Q4W N=2025 100 subject yrs=24.31 n (%) EAIR (95% CI)	Phase 3 BKZ 320 mg Q8W N=1935 100 subject-yrs=30.35 n (%) EAIR (95% CI)
	3.8 (2.9, 4.9)	2.2 (1.1, 3.9)	3.3 (2.6, 4.1)	2.3 (1.7, 2.9)
Injection Site Reactions[c]	40 (2.7) 2.6 (1.9, 3.6)	8 (1.3) 1.6 (0.7, 3.1)	60 (3.0) 2.5 (1.9, 3.2)	28 (1.4) 0.9 (0.6, 1.3)
Tinea Infections[d]	61 (4.2) 4.1 (3.1, 5.2)	20 (3.1) 4.0 (2.4, 6.2)	93 (4.6) 4.0 (3.2, 4.9)	84 (4.3) 2.9 (2.3, 3.5)
Gastroenteritis[e]	41 (2.8) 2.7 (1.9, 3.7)	14 (2.2) 2.8 (1.5, 4.7)	55 (2.7) 2.3 (1.7, 3.0)	25 (1.3) 0.8 (0.5, 1.2)
Herpes Simplex Infections[f]	40 (2.7) 2.6 (1.9, 3.6)	8 (1.3) 1.6 (0.7, 3.1)	54 (2.7) 2.3 (1.7, 3.0)	31 (1.6) 1.0 (0.7, 1.5)
Acne	19 (1.3) 1.2 (0.8, 1.9)	3 (0.5) 0.6 (0.1, 1.7)	27 (1.3) 1.1 (0.7, 1.6)	12 (0.6) 0.4 (0.2, 0.7)
Folliculitis	56 (3.8) 3.7 (2.8, 4.8)	12 (1.9) 2.4 (1.2, 4.1)	82 (4.0) 3.5 (2.8, 4.3)	40 (2.1) 1.3 (1.0, 1.8)
Other Candida Infections[g]	33 (2.3) 2.2 (1.5, 3.1)	5 (0.8) 1.0 (0.3, 2.3)	55 (2.7) 2.3 (1.7, 3.0)	44 (2.3) 1.5 (1.1, 2.0)
Fatigue	20 (1.4) 1.3 (0.8, 2.0)	5 (0.8) 1.0 (0.3, 2.3)	29 (1.4) 1.2 (0.8, 1.7)	16 (0.8) 0.5 (0.3, 0.9)

Abbreviations: BKZ=bimekizumab; Uste=ustekinumab; CI=confidence interval, Q4W=every four weeks, Q8W=every eight weeks, TEAE=treatment-emergent adverse event, yrs=years, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
120 Day Safety Update- Original Submission includes data from Initial, Maintenance, and OLE Periods of Trials PS0008, PS0009, PS0013, and PS0014.
Pool S2-3b of Resubmission includes data from Initial, Maintenance, and OLE Periods of Trials PS0008, PS0009, PS0013, PS0014, and PS0015.
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Oral Candidiasis includes oral candidiasis, oropharyngeal candidiasis, oral fungal infection, fungal pharyngitis, and oropharyngitis fungal
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes Enterovirus infection, gastroenteritis, gastroenteritis bacterial, and gastroenteritis viral
[f] Herpes Simplex Infections include herpes simplex and oral herpes
[g] Other Candida Infections include, vulvovaginal candidiasis, vulvovaginal mycotic infection, skin candida, and genital candidiasis.
Source: Reviewer's Table with data from Applicant's Tables 5.2.2 in 120 DSU, and Table 5.2.2a in Applicant's Safety Update for Pool S2-3b

Overall, based on the EAIRs, the frequency of ARs did not increase with increased duration of treatment with bimekizumab. As stated above, the dosing regimen to which the AR was attributed was based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Because subjects switched dosing regimens during the trials, it is difficult to definitively determine dose-response based on these data.

The review team also evaluated TEAEs based on data from Trials PS0015 and OLE Trial PS0014 separately. TEAEs related to adjudicated SI/B events are discussed in Section 8.2.5.1 of this review.

Trial PS0015

Because Trial PS0015 had an active control (secukinumab) and no placebo arm, no new imbalances in TEAEs could be identified. Adverse reactions identified during the placebo-controlled period of Trials PS0009 and PS0013 and proposed for inclusion in labeling were similar to the TEAEs identified during Trial PS0015. Summaries of TEAEs reported in 1% or more subjects for the Initial and Maintenance Treatment Periods of Trial PS0015 are presented in the tables below.

Table 10: Summary of TEAEs Reported in **≥1%** of Subjects in the Initial Treatment Period- Trial PS0015

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)
Blood and lymphatic system disorders	7 (1.9)	8 (2.2)
Cardiac disorders	3 (0.8)	4 (1.1)
Eye disorders	7 (1.9)	5 (1.4)
Gastrointestinal disorders	33 (8.8)	31 (8.4)
Abdominal pain	4 (1.1)	2 (0.5)
Abdominal pain upper	5 (1.3)	3 (0.8)
Diarrhea	1 (0.3)	6 (1.6)
Gastroesophageal reflux disease	5 (1.3)	3 (0.8)
Nausea	4 (1.1)	5 (1.4)
Vomiting	2 (0.5)	4 (1.1)
General disorders and administration site conditions	21 (5.6)	22 (5.9)
Fatigue	4 (1.1)	3 (0.8)
Injection site erythema	4 (1.1)	0 (0.0)
Infections and infestations	161 (43.2)	118 (31.9)
Bronchitis	4 (1.1)	2 (0.5)
Conjunctivitis	5 (1.3)	1 (0.3)
Ear infection	4 (1.1)	0 (0.0)
Folliculitis	8 (2.1)	1 (0.3)

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)
Fungal skin infection	4 (1.1)	1 (0.3)
Gastroenteritis	4 (1.1)	2 (0.5)
Hordeolum	4 (1.1)	1 (0.3)
Impetigo	4 (1.1)	0 (0.0)
Influenza	0 (0.0)	5 (1.4)
Nasopharyngitis	47 (12.6)	54 (14.6)
Oral candidiasis	39 (10.5)	4 (1.1)
Oral herpes	4 (1.1)	5 (1.4)
Pharyngitis	13 (3.5)	7 (1.9)
Rhinitis	6 (1.6)	4 (1.1)
Upper respiratory tract infection	16 (4.3)	17 (4.6)
Urinary tract infection	6 (1.6)	7 (1.9)
Viral upper respiratory tract infection	6 (1.6)	6 (1.6)
Injury, poisoning and procedural complications	23 (6.2)	15 (4.1)
Investigations	31 (8.3)	19 (5.1)
Blood pressure increased	5 (1.3)	1 (0.3)
Gamma-glutamyl transferase increased	4 (1.1)	0 (0.0)
Metabolism and nutrition disorders	10 (2.7)	14 (3.8)
Hypertriglyceridemia	1 (0.3)	4 (1.1)
Musculoskeletal and connective tissue disorders	24 (6.4)	26 (7.0)
Arthralgia	5 (1.3)	7 (1.9)
Back pain	5 (1.3)	5 (1.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	6 (1.6)	2 (0.5)
Nervous system disorders	27 (7.2)	22 (5.9)
Headache	10 (2.7)	10 (2.7)
Psychiatric disorders	8 (2.1)	7 (1.9)
Renal and urinary disorders	5 (1.3)	5 (1.4)
Reproductive system and breast disorders	1 (0.3)	7 (1.9)
Respiratory, thoracic and mediastinal disorders	22 (5.9)	18 (4.9)
Cough	2 (0.5)	4 (1.1)
Oropharyngeal pain	12 (3.2)	5 (1.4)
Skin and subcutaneous tissue disorders	40 (10.7)	40 (10.8)
Dermatitis contact	4 (1.1)	1 (0.3)
Eczema	5 (1.3)	1 (0.3)
Pruritus	5 (1.3)	9 (2.4)
Psoriasis	5 (1.3)	2 (0.5)
Seborrheic dermatitis	3 (0.8)	5 (1.4)
Vascular disorders	11 (2.9)	6 (1.6)
Hypertension	8 (2.1)	4 (1.1)

Source: OCS Analysis Studio, Safety Explorer.

System Organ Class - Preferred Term	Bimekizumab 320mg Q4W (N=373) n (%)	Secukinumab 300mg Q4W (N=370) n (%)

Filters: TRT01A = "Bimekizumab 320mg Q4W" and SAFFL = "Y" (Bimekizumab 320mg Q4W); TRT01A = "Secukinumab 300mg Q4W" and SAFFL = "Y" (Secukinumab 300mg Q4W); TRTEMFL = "Y" and ANL02FL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

Table 11: Summary of TEAEs **≥1%** in the Maintenance Period- PS0015

System Organ Class - Preferred Term	Bimekizumab 320mg Q8W (N=215) n (%)	Bimekizumab 320 mg Q4W (N=147) n (%)	Secukinumab 300 mg Q4W (N=354) n (%)
Blood and lymphatic system disorders	1 (0.5)	3 (2.0)	3 (0.8)
Lymphadenopathy	1 (0.5)	2 (1.4)	0 (0.0)
Cardiac disorders	4 (1.9)	3 (2.0)	4 (1.1)
Ear and labyrinth disorders	1 (0.5)	6 (4.1)	6 (1.7)
Eye disorders	9 (4.2)	7 (4.8)	10 (2.8)
Blepharitis	2 (0.9)	3 (2.0)	3 (0.8)
Chalazion	4 (1.9)	0 (0.0)	1 (0.3)
Dry eye	0 (0.0)	2 (1.4)	1 (0.3)
Gastrointestinal disorders	22 (10.2)	13 (8.8)	36 (10.2)
Abdominal pain	4 (1.9)	0 (0.0)	3 (0.8)
Dental caries	1 (0.5)	2 (1.4)	4 (1.1)
Diarrhea	2 (0.9)	3 (2.0)	7 (2.0)
Gastroesophageal reflux disease	2 (0.9)	0 (0.0)	4 (1.1)
Hemorrhoids	0 (0.0)	2 (1.4)	0 (0.0)
Hiatus hernia	0 (0.0)	2 (1.4)	1 (0.3)
Nausea	0 (0.0)	1 (0.7)	4 (1.1)
Toothache	3 (1.4)	0 (0.0)	1 (0.3)
General disorders and administration site conditions	15 (7.0)	7 (4.8)	16 (4.5)
Asthenia	3 (1.4)	1 (0.7)	0 (0.0)
Pyrexia	3 (1.4)	1 (0.7)	1 (0.3)
Hepatobiliary disorders	2 (0.9)	0 (0.0)	4 (1.1)
Immune system disorders	0 (0.0)	2 (1.4)	2 (0.6)
Infections and infestations	120 (55.8)	85 (57.8)	165 (46.6)
Angular cheilitis	1 (0.5)	2 (1.4)	0 (0.0)
Appendicitis	3 (1.4)	0 (0.0)	0 (0.0)
Bronchitis	1 (0.5)	2 (1.4)	7 (2.0)
Conjunctivitis	7 (3.3)	5 (3.4)	4 (1.1)
Cystitis	0 (0.0)	0 (0.0)	4 (1.1)
Ear infection bacterial	0 (0.0)	2 (1.4)	1 (0.3)
Folliculitis	3 (1.4)	1 (0.7)	3 (0.8)
Fungal skin infection	3 (1.4)	0 (0.0)	3 (0.8)

System Organ Class - Preferred Term	Bimekizumab 320mg Q8W (N=215) n (%)	Bimekizumab 320 mg Q4W (N=147) n (%)	Secukinumab 300 mg Q4W (N=354) n (%)
Furuncle	1 (0.5)	2 (1.4)	1 (0.3)
Gastroenteritis	1 (0.5)	2 (1.4)	1 (0.3)
Gastroenteritis viral	0 (0.0)	4 (2.7)	1 (0.3)
Herpes zoster	2 (0.9)	0 (0.0)	4 (1.1)
Hordeolum	3 (1.4)	5 (3.4)	3 (0.8)
Impetigo	2 (0.9)	3 (2.0)	1 (0.3)
Influenza	4 (1.9)	0 (0.0)	7 (2.0)
Latent tuberculosis	1 (0.5)	4 (2.7)	5 (1.4)
Nasopharyngitis	33 (15.3)	20 (13.6)	67 (18.9)
Oral candidiasis	36 (16.7)	19 (12.9)	10 (2.8)
Oral fungal infection	1 (0.5)	3 (2.0)	1 (0.3)
Oral herpes	6 (2.8)	3 (2.0)	4 (1.1)
Otitis externa	2 (0.9)	1 (0.7)	4 (1.1)
Otitis media	4 (1.9)	2 (1.4)	3 (0.8)
Pharyngitis	9 (4.2)	2 (1.4)	3 (0.8)
Pharyngitis streptococcal	0 (0.0)	2 (1.4)	1 (0.3)
Rhinitis	3 (1.4)	2 (1.4)	4 (1.1)
Sinusitis	1 (0.5)	7 (4.8)	4 (1.1)
Tinea pedis	7 (3.3)	2 (1.4)	3 (0.8)
Tonsillitis	2 (0.9)	1 (0.7)	9 (2.5)
Tooth abscess	5 (2.3)	2 (1.4)	4 (1.1)
Upper respiratory tract infection	21 (9.8)	8 (5.4)	20 (5.6)
Urinary tract infection	10 (4.7)	11 (7.5)	19 (5.4)
Injury, poisoning and procedural complications	12 (5.6)	7 (4.8)	23 (6.5)
Joint injury	4 (1.9)	1 (0.7)	0 (0.0)
Investigations	17 (7.9)	11 (7.5)	26 (7.3)
Blood pressure increased	1 (0.5)	2 (1.4)	2 (0.6)
False positive tuberculosis test	1 (0.5)	2 (1.4)	4 (1.1)
Gamma-glutamyl transferase increased	4 (1.9)	0 (0.0)	1 (0.3)
Hepatic enzyme increased	2 (0.9)	2 (1.4)	3 (0.8)
Metabolism and nutrition disorders	8 (3.7)	10 (6.8)	16 (4.5)
Hypertriglyceridemia	1 (0.5)	3 (2.0)	2 (0.6)
Musculoskeletal and connective tissue disorders	22 (10.2)	11 (7.5)	29 (8.2)
Arthralgia	7 (3.3)	4 (2.7)	4 (1.1)
Back pain	7 (3.3)	1 (0.7)	11 (3.1)
Bursitis	3 (1.4)	0 (0.0)	0 (0.0)
Muscle spasms	0 (0.0)	2 (1.4)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (1.4)	7 (4.8)	8 (2.3)
Skin papilloma	1 (0.5)	2 (1.4)	0 (0.0)
Nervous system disorders	13 (6.0)	3 (2.0)	18 (5.1)

System Organ Class - Preferred Term	Bimekizumab 320mg Q8W (N=215) n (%)	Bimekizumab 320 mg Q4W (N=147) n (%)	Secukinumab 300 mg Q4W (N=354) n (%)
Headache	4 (1.9)	2 (1.4)	9 (2.5)
Psychiatric disorders	5 (2.3)	3 (2.0)	5 (1.4)
Renal and urinary disorders	8 (3.7)	4 (2.7)	6 (1.7)
Nephrolithiasis	2 (0.9)	2 (1.4)	1 (0.3)
Reproductive system and breast disorders	4 (1.9)	2 (1.4)	4 (1.1)
Respiratory, thoracic and mediastinal disorders	12 (5.6)	13 (8.8)	26 (7.3)
Cough	3 (1.4)	2 (1.4)	8 (2.3)
Oropharyngeal pain	4 (1.9)	3 (2.0)	6 (1.7)
Skin and subcutaneous tissue disorders	19 (8.8)	28 (19.0)	50 (14.1)
Actinic keratosis	3 (1.4)	0 (0.0)	2 (0.6)
Alopecia	1 (0.5)	0 (0.0)	4 (1.1)
Dermatitis contact	1 (0.5)	3 (2.0)	9 (2.5)
Pruritus	0 (0.0)	3 (2.0)	4 (1.1)
Pruritus generalized	3 (1.4)	2 (1.4)	2 (0.6)
Psoriasis	1 (0.5)	2 (1.4)	14 (4.0)
Seborrheic dermatitis	3 (1.4)	4 (2.7)	4 (1.1)
Vascular disorders	5 (2.3)	6 (4.1)	7 (2.0)
Hypertension	3 (1.4)	3 (2.0)	5 (1.4)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT02A = "Bimekizumab 320mg Q8W" and SAFFL = "Y" (Bimekizumab 320mg Q8W); TRT02A = "Bimekizumab 320mg Q4W" and SAFFL = "Y" (Bimekizumab 320 mg Q4W); TRT02A = "Secukinumab 300mg Q4W" and SAFFL = "Y" (Secukinumab 300 mg Q4W); TRTEMFL = "Y" and ANL03FL = "Y" (Adverse Events).
Percent Threshold: Any Column ≥ 1%.

During the OLE period of PS0015, 85% of subjects who received bimekizumab experienced a TEAE. For the safety analyses for the OLE period, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated with bimekizumab. Because subjects may have switched dosing regimens during this portion of the trial, it is difficult to definitively determine dose-response based on these data. Refer to Table 23 in Appendix 15.3 for TEAEs reported during the OLE period of Trial PS0015.

PS0014

During the OLE Trial PS0014, 85% of subjects who received bimekizumab experienced a TEAE. Adverse reactions reported during the placebo-controlled period of Trials PS0009 and PS0013 and planned for inclusion in labeling were similar to TEAEs reported in Trial PS0014. For the safety analyses for Trial PS0014, subjects were included in the bimekizumab group based on the dosing regimen to which the subject was assigned most recently prior to the date of the event. Therefore, the number of subjects in each group exceeds the total number of subjects treated

with bimekizumab. Because subjects may have switched dosing regimens during Trial PS0014, it is difficult to definitively determine dose-response based on these data. Refer to Table 24 in Appendix 15.3 for TEAEs reported during the OLE period of Trial PS0014.

Laboratory Findings

During the development program for bimekizumab, evaluation of systemic safety included assessment of clinical laboratory data, which included hematology, serum chemistry, and urinalysis. Liver biochemistries and leukopenia, including neutropenia, will be discussed in Section 8.2.5 of this review. Excluding these parameters, the incidence rate for abnormalities in hematology and chemistry parameters were similar to those observed during review of the initial BLA. Other than liver biochemical abnormalities and neutropenia, the review team identified no clinically meaningful changes to laboratory parameters in the safety update.

Vital Signs

The safety update included data from Trials PS0014 and PS0015 related to the assessment of vital signs. Overall, there were no clinically meaningful differences from data reviewed during the initial BLA. The review team identified no new safety signals related to abnormalities in vital signs associated with treatment with bimekizumab. Refer to Section 8.2.5 under the discussion of Major Adverse Cardiovascular Events (MACE) of this review for a discussion of the AE of hypertension.

Electrocardiograms (ECGs)/QT

In Pool S2-3b, TEAEs under "ECG Investigations" (High Level Term [HLT]) were reported in 11/2480 (0.4%; exposure-adjusted incidence rate [EAIR] 0.2/100 subject-years) compared to 2/1789 (0.1%; EAIR 0.1/100 subject-years). None of the ECG abnormalities were associated with cardiovascular TEAEs. Refer to Section 8.2.5 of this review for a discussion of MACE.

Immunogenicity

The safety update included with the resubmission provided no new information regarding immunogenicity. The immunogenicity of bimekizumab was evaluated during review of the initial BLA. The review team concluded that the presence of anti-drug antibodies and neutralizing antibodies had no clinically meaningful effect on the safety of bimekizumab. The Applicant proposed no changes to labeling regarding immunogenicity.

Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022, for a discussion of the evaluation of immunogenicity during the review of the original BLA.

8.2.5. Analysis of Submission-Specific Safety Issues

During the development program, Adverse Events of Special Interest (AESI) were identified. AESIs were events that were potentially related to the proposed mechanism of action for bimekizumab (immunomodulation via cytokine blockade, specifically IL-17A and IL-17F), class effects associated with other anti-cytokine antibody therapies (including anti-IL-17A), and the specific risks and co-morbidities observed in the target population. The following were identified as AESIs:

- Suicidal Ideation/Behavior (SI/B)
- Inflammatory Bowel Disease
- Hepatotoxicity/DILI
- Infections
- Malignancies
- Major Adverse Cardiovascular Events (MACE)
- Neutropenia
- Hypersensitivity and Injection Site Reactions

The subsections below will focus on AESIs reported in the SUR provided with the resubmission. Refer to the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for information and analysis of these AESIs during review of the initial BLA.

8.2.5.1. Suicidal Ideation and Behavior

In the resubmission, the Applicant included new safety data from Trial PS0015 [a double-blind, active comparator-controlled (secukinumab) and parallel group trial that enrolled 743 subjects] and Trial PS0014 [an open- label extension (OLE) trial that enrolled 1343 subjects]. New safety data included a report of completed suicide in a subject with no prior psychiatric history and three cases of suicide attempt associated with the use of bimekizumab. There were five and nine cases of serious neuropsychiatric adverse events (AEs) in subjects exposed to bimekizumab in Trials PS0015 and PS0014, respectively. These new data prompted a re-evaluation of all relevant data (including data from original BLA submission as well as from resubmission) by the Division of Psychiatry (DP).

The review of the data from the original BLA submission by the DP team, focused on the controlled trials (Review by Shamir N. Kalaria, PharmD, PhD dated December 18, 2020). Because of the low number of cases overall, and the "lack of a clear association between drug initiation/treatment duration and positive eC-SSRS responses", the previous DP consult did not recommend product labeling for SI/B. However, in the context of a completed suicide and suicide attempts, DP team reexamined the data that was evaluated in the previous consult and

new data from the resubmission (Review by Jennifer Reid, MD, and Bernard Fischer, MD, dated June 5, 2023).

It should be noted that all trials for bimekizumab in psoriasis development program included same study population define by inclusion (e.g., disease severity) and exclusion criteria. Subjects with active suicidal ideation, suicidal ideation within the month prior to screening, a history of suicide attempt within the past 5 years prior to screening, or moderately severe to severe major depression (i.e., score of ≥15 on the screening Patient Health Questionnaire-9 [PHQ-9]) were excluded from the trial. Because of the above exclusion criteria, the data from these trials might be limited in their generalizability to inform the risk of SI/B in the population with moderate to severe psoriasis.

Per DP review, in a pool of subjects from the initial treatment period of the placebo/active-controlled phase 3 trials, PS0008, PS0009, and PS0013, there were 18 positive responses on the eC-SSRS (most reporting a passive wish to be dead without active suicidal ideation). Of these, 17 positive responses were in bimekizumab-treated subjects (1.7%) while only 1 was in placebo-treated subjects (0.6%). Of the 17 positive responses in bimekizumab-treated subjects, only 4 were in subjects with a previous psychiatric history.

Table 12: Incidence of SI/B as measured by the eC-SSRS during an Initial Treatment Period of Trials PS0008, PS0009, and PS0013

eC-SSRS				Total Events (yes/no)	
		Maximum: Treatment Phase N (%)		Lifetime N (%)	Maximum: Treatment Phase N (%)
Treatment Arm	Category	SI	SB	SI/B	SI/B
Bimekizumab	0	959 (98.3)	976 (100)	73 (7.5)	17 (1.7)
	1	16 (1.6)	0		
	2	1 (0.1)	0		
	3	0	0		
	4	0	0		
	5	0	0		
Placebo	0	168 (99.4)	169 (100)	12 (7.1)	1 (0.6)
	1	1 (0.6)	0		
	2	0	0		
	3	0	0		
	4	0	0		
	5	0	0		

eC-SSRS = electronic Columbia Suicide Severity Rating Scale; SI = suicidal ideation; SB = suicidal behavior
Analysis using crude pooling of the bimekizumab and placebo arms from Trials PS0008, PS0009, and PS0013 due to the rarity of the event of SI/B.
Source: DP reviewer's table.

In a pool of subjects from the open-label maintenance period of the phase 3 trials, PS0008, PS0009, and PS0013, there were 16 positive responses on the eC-SSRS (most reporting a passive wish to be dead without active suicidal ideation). Of the 16 positive responses in bimekizumab-treated subjects, only 2 were in subjects with a previous psychiatric history.

Table 13: Incidence of SI/B as measured by the eC-SSRS during the Maintenance Period of Trials PS0008, PS0009, and PS0013

eC-SSRS				Total Events (yes/no)	
		Maximum: Treatment Phase N (%)		Lifetime N (%)	Maximum: Treatment Phase N (%)
Treatment Arm	Category	SI	SB	SI/B	SI/B
Bimekizumab	0	1011 (98.4)	1027 (100)	51 (5)	16 (1.6)
	1	13	0		
	2	1	0		
	3	1	0		
	4	1	0		
	5	0	0		

eC-SSRS = electronic Columbia Suicide Severity Rating Scale; SI = suicidal ideation; SB = suicidal behavior
Source: DP reviewer's table.

In the previous consult review, the DP team did not examine the data comparing bimekizumab to active controls. In Trial PS0008, eight subjects randomized to bimekizumab (n=319, 2.6%) reported positive responses to the eC-SSRS (one subject with non-specific active suicidal thoughts, seven with passive wish to be dead) compared to three subjects receiving adalimumab (n=159, 1.9%, one subject with non-specific active suicidal thoughts, two with passive wish to be dead). In trial PS0009, three subjects randomized to bimekizumab (n=321, 0.9%, all three with passive wish to be dead) and three subjects receiving ustekinumab (n=163, 1.8%, one subject with non-specific active suicidal thoughts, two with passive wish to be dead) reported positive responses to the eC-SSRS.

Per DP team, this reevaluation of the original data shows a three-fold increase in positive eC-SSRS responses in bimekizumab group compared to placebo/active group during the controlled portion of trials PS0008, PS0009, and PS0013. This imbalance occurred despite a similar lifetime prevalence of positive eC-SSRS responses in the treatment groups at screening (7.5% in the bimekizumab group, 7.1% in the placebo group). Furthermore, a minority of eC-SSRS positive responses, 22%, were in subjects with a past psychiatric history. During the open-label maintenance periods of these trials, most of the positive eC-SSRS responses were also in subjects without a prior psychiatric history.

<u>eC-SSRS in placebo-controlled trials</u>

- Trial PS0009: during 16-week placebo-controlled period, 4/321 subjects on bimekizumab and 0/83 subjects on placebo experienced SI/B captured by the eC-SSRS instrument.

- Trial PS0013: during a 16-week placebo-controlled period, 8/349 subjects on bimekizumab and 1/86 subjects on placebo experienced SI/B captured by the eC-SSRS instrument.

Pooled analysis of eC-SSRS data from two 16-week, placebo-controlled trials indicated that 12/670 (1.8%) bimekizemab treated subjects and 1/169 (0.6%) placebo-treated subjects reported passive suicidal ideation. The Mantel-Haenszel risk difference for the proportion of subjects who experienced SI/B in these two trials over 16 weeks was 1.19% (-0.34%, 2.72%) and the corresponding Relative Risk was 3.0 (95% confidence interval: 0.39, 22.74). Of note, all subjects who reported a positive SI/B response to the eC-SSRS instrument experienced passive suicidal ideation (i.e., positive response to eC-SSRS question 1: "Wish to be dead or not wake up"). Subjects without prior history of SI/B treated with bimekizumab also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects treated with placebo (1.3% vs. 0.6%). This analysis shows a numerical imbalance suggesting possible increased risk of SI/B associated with bimekizumab relative to placebo over 16 weeks. In the context of the completed suicide, this data appears to support an association between positive eC-SSRS responses and bimekizumab use.

The key features of these cases were summarized in the DP consult as follows: (Review by Jennifer Reid, MD, and Bernard Fischer, MD, dated June 5, 2023).

Completed Suicide
"Subject (b) (6), participating in PS0014, was a 39-year-old white male with no prior psychiatric history (confirmed by subject's wife). He reportedly drank two alcoholic drinks per week and smoked 1 pack per day tobacco. The subject began participation in PS0013 (b) (6) and was randomized to placebo. On (b) (6), he qualified for the escape treatment arm and began bimekizumab 320 mg every 4 weeks. He completed PS0013 on (b) (6) and entered PS0014. He completed suicide on (b) (6), 718 days after starting bimekizumab. An autopsy was not performed. Previous PHQ-9 scores were 0 and eC-SSRS screenings had been negative. The subject had unspecified "financial issues." … At the time of the suicide, the subject was prescribed pantoprazole, the beta blocker nebivolol and a combination of amlodipine, indapamide, and perindopril… While it is impossible to determine whether any of these drugs alone or in combination contributed to the subject's suicide, their adverse reaction profiles do not present a compelling case that the suicide was unrelated to bimekizumab."

The psychiatry team noted that "Determining whether this suicide is related to drug is impossible. Financial difficulties can be a significant driving force for suicide even in the absence of psychiatric or substance use history. We do not know the extent of the reported financial difficulties. The subject had been on bimekizumab for close to 2 years before the suicide and one might have expected an earlier signal of risk on the PHQ-9 or eC-SSRS. However, we know very little about the pharmacodynamics of suicide risk. It is plausible that drugs associated with suicide risk alter the brain such that the patient is more likely to suicide when presented with external stressors. In this scenario, it would not be unusual for a patient to be on drug for an extended time before experiencing an external stressor resulting in suicide. Although the patient was prescribed other medications associated with psychiatric adverse reactions, none of those other drugs is labeled for suicide risk and the subject's rating scales do not show depression or anxiety. Some drug-associated suicides have been hypothesized as related to a lack of drug effect (i.e., the patient becomes despondent that the drug does not work for them). In this case, the subject reached complete skin clearance on bimekizumab."

In addition, psychiatry team stated "The Applicant could not objectively confirm the subject's death, but it seems unlikely his wife would report him as dying by suicide if that were not the case. Even if this report was not accurate, there are imbalances in eC-SSRS data (reviewed above) and suicide attempts (see below) that suggest bimekizumab may be associated with increased SI/B.

Suicide is a rare event and an occurrence in a drug development program in a subject with no prior psychiatric history is an important signal. It is also worth noting that the Applicant instituted close monitoring of mood and SI/B and subjects that developed elevations in the PHQ-9 were terminated from the program early and referred for mental health treatment. It is unknown whether more SI/B events would have been seen if subjects were not terminated early and referred for mental health treatment. We know little of the mechanism of drug-related suicide risk or the relationship between the duration of exposure and risk. We cannot know whether the subject would have completed suicide if he had not been taking bimekizumab. Given the concern for mood and SI/B events in another drug acting on IL-17 (i.e., brodalumab), DP recommends this suicide be considered possibly drug-related and the label reflect a potential risk."

Psychiatric Cases in Trial PS0015

In addition, the consult review from the DP team included tabular summaries of neuropsychiatric SAEs in Trials PS0014 and PS0015. These tables are presented below.

Table 14: Psychiatric Case Summaries from Trial PS0015

Subject ID	Event	Exposure when Event Occurred	Summary	Reviewer Causality Assessment
(b) (6)	Suicide Attempt	BKZ	50 year-old white female with pertinent past psychiatric history of depression, generalized anxiety disorder, posttraumatic stress disorder, multiple electroconvulsive therapy treatments, and two previous suicide attempts (most recent was 6 years prior to study enrollment), which she had not disclosed during screening. Family history of completed suicide. Taking multiple concurrent psychiatric medications at time of attempt. Started study (b) (6) randomized to BKZ. Suicide attempt (b) (6) via overdose of 20 paracetamol. Note, son had died by suicide around the same time of year 3 years earlier. Reported feeling depressed since (b) (6) Pt was terminated from the study and last BKZ dose was (b) (6)	Unclear association. Pt had a past psychiatric history including previous attempts and stressor of son's suicide 3 years ago. However, pt reports low mood coinciding with start of BKZ and had been stable on psychiatric medication on enrollment and no acute stressors.
(b) (6)	Suicide Attempt	BKZ	23 year-old Asian female with past psychiatric history of attention-deficit/ hyperactivity disorder (taking a stimulant).	Unclear association given timing of psychiatric episode.

			On secukinumab during double-blind phase; started open-label BKZ (b) (6) Completed study, final dose of study drug was (b) (6) Suicide attempt (b) (6) Pt attempted to jump out of a window, cited stressors of grandmother's death and being in the U.S. illegally. Pt hospitalized; exhibited psychotic symptoms and diagnosed bipolar mixed with psychosis. She presented tearful and manic at (b) (6) follow-up visit, disclosing via C-SSRS many prior aborted attempts, though unclear if accurate.	
(b) (6)	Possible Suicide Attempts/Elevated PHQ-9	While on blinded secukinumab reported aborted suicide attempts, later determined to be error (with data correction) Continued to report aborted attempts during BKZ open-label	71 year old White male without psychiatric history. While on secukinumab reported aborted suicide attempts, later determined to be a reporting error (with data correction). When switched to BKZ open-label, continued to periodically report aborted suicide attempts that were denied when patient confronted. PHQ-9 elevated on select visits (up to a score of 14) that patient connected to loneliness during pandemic lockdown. Referred for psychiatric evaluation and diagnosed with dysthymia (reported as an AE). Participation in study ongoing. Diagnosed with dysthymia (reported as an AE). Participation in study ongoing.	Suicide attempts appear to be problems with subject reports and do not represent real events. Unclear relationship of dysthymia to BKZ given patient's report of loneliness due to pandemic lockdown.
(b) (6)	Elevated PHQ-9	BKZ	40 year old white female with a history of anxiety and depression. Developed alopecia and reported worsening depression (PHQ-9 up to 15). Discontinued study drug because of alopecia. Referred to mental health provider. During follow-up had plan for alopecia and mood back to baseline.	Unclear relationship to study drug given patient reports mood connected to new alopecia.
(b) (6)	Elevated PHQ-9	Blinded treatment	34-year old woman developed worsening mood with PHQ-9 score of 20. Referred to ER after patient answered yes to eC-SSRS "Do you wish to be dead or not wake up?". Social stressors included loss of job and leaving abusive partner. Pt receiving follow-up at community mental health center. Mood improved and pt continues in study.	Unclear which treatment patient receiving. Significant social stressors.

AE = adverse event, BKZ = bimekizumab, eC-SSRS = electronic Columbia Suicide Severity Rating Scale, ER = emergency room, PHQ-9 = Patient Health Questionnaire, pt = patient.
Source: DP Consult Review

In reference to these cases, the DP team commented that the "The above cases do not demonstrate a clear signal of SI/B risk associated with bimekizumab. Most case are complicated by a past psychiatric history and social stressors. However, there are some concerning aspects of these cases (such as Subject 661-08171 reporting low mood coinciding with starting bimekizumab with the subject ultimately attempting suicide and Subject 954-08267, who did not experience her suicide attempt until discontinuing secukinumab and switching to bimekizumab) that, coupled with a completed suicide in someone with no psychiatric history, can be viewed as consistent with a possible drug-related risk."

Psychiatric Cases in Trial PS0014

Table 15: Psychiatric Case Summaries from Trial PS0014

Subject ID	Event Type	Summary	Causality Assessment
(b) (6)	Suicidal ideation/attempt	41 year-old white male with pertinent past psychiatric history of prior suicide attempt. Started PS0014 (b) (6) Suicide attempt (b) (6). Subject tried to put an end to his life with a knife; presented self to hospital. Pt hospitalized, diagnosed with anxiety disorder (unspecified), accommodation disorder, and unspecified personality disorder. Pt cited stressor of pending divorce from wife. Pt improved with psychotherapy alone and continued in the study.	Unclear relationship to BKZ given history of suicide attempt, marital stressor, diagnosed unspecified personality disorder, and prolonged time since beginning BKZ.
(b) (6)	Adjustment disorder with depressed mood, suicidal ideation	32 year-old white male with past psychiatric history of anxiety, depression, 12 units alcohol use weekly, and recent use of amphetamines, methamphetamines, and cocaine. Concomitant Cannabis sativa use at time of adverse events. Pt started open-label BKZ (b) (6) Elevated PHQ-9 of 15 on (b) (6) and reported suicide attempt on eC-SSRS. Pt referred to mental health and reported unemployment and pending divorce. Mental health eval clarified that the attempted suicide was non-suicidal self-injurious behavior. On (b) (6) pt reported SI with a plan, called help line, and police escorted pt to ER. Pt was terminated from the study and last PHQ-9 was 10.	Possible association, although pt had a number of stressors.
(b) (6)	Bipolar I disorder (exacerbation)	26 year-old white male with pertinent psychiatric history of bipolar disorder. Pt developed manic and psychotic symptoms including dancing in the street, jumping in front of cars, nonsensical rambling speech. He had self-discontinued his bipolar medication (aripiprazole) 6 months prior to the OL study and admitted cannabis use.	Unclear relationship to BKZ given known history of bipolar disorder with mania, self-discontinuation of his medication and concurrent cannabis use.
(b) (6)	Elevated PHQ-9	25 year-old white female with past psychiatric history of depression. PHQ-9 increased from 8 at baseline to 21 in 8 weeks. Details of symptoms contributing to score not provided; eC-SSRS negative on same day.	Unable to assess possible relationship to BKZ given limited detail provided; however, extended time since initial treatment with BKZ in PS0013 is less supportive of a relationship.
(b) (6)	Elevated PHQ-9	57 year old female with a past psychiatric history of alcoholism and depression on duloxetine for sciatica and levothyroxine for hypothyroidism, papillary thyroid cancer. Had PHQ-9 score of 21 on last study day. Met criteria for withdrawal from the study, but no study action taken as it was her last day. Referred to mental health provider and did not meet criteria for MDD, no SI/B. Pt reported mood due to diagnosis of cancer.	Unlikely due to pt attribution of mood to newly diagnosed cancer.

Neuropsychiatric SAEs in Trial PS0014 continued

[redacted]	Elevated PHQ-9	60 year-old female. Received BZK [redacted] until early termination for skin rash [redacted]. At [redacted] visit, PHQ-9 was 25. Met criteria for withdrawal from the study, but no study action taken as she had already terminated the study drug. Denied SI/B and reported high scores on PHQ-9 due to itchiness after d/c BZK. Referred to her primary care physician for further management.	Unlikely due to having discontinued BKZ 1 month previously and pt's attribution of increased score to frustration with increased itchiness.
	Elevated PHQ-9	33 year-old male. Received BKZ [redacted] until early termination for elevated liver enzymes [redacted] On [redacted] pt scored 27 on PHQ-9. Pt reported it was due to termination from the study and increased psoriasis symptoms. Previous PHQ-9 scores were 0 to 1. Pt refused mental health referral and was lost to follow-up.	Unlikely due to having discontinued BKZ several months previously and pt's attribution of increased score to increased symptoms of psoriasis.
	Elevated PHQ-9	47 year-old male. Started BKZ [redacted] PHQ-9 score 20 on [redacted] BKZ interrupted and pt referred to mental health. Pt reported low mood due to death in the family. Subsequent PHQ-9 [redacted] was 0. No diagnosis of MDD and no SI/B. Pt continued the study.	Unlikely due to precipitating event of family death and no further incidents on elevated scores on re-challenge.
	Elevated PHQ-9	35 year-old male. On unknown treatment in Study PS0009 (BKZ vs. placebo/ ustekinumab) starting [redacted] started open-label BKZ [redacted] Elevated PHQ-9 of 20 on [redacted] and pt removed from study. Diagnosed with "acclimatization disfunction (depressive)" (similar to DSM diagnosis of adjustment disorder); reported as resolved [redacted] PHQ-9 of 7.	Unclear without more details; resolved before pt due for next dose.

AE = adverse event, BKZ = bimekizumab, DSM = Diagnostic and Statistical Manual of Mental Disorders, eC-SSRS = electronic Columbia Suicide Severity Rating Scale, MDD = Major Depressive Disorder, PHQ-9 = Patient Health Questionnaire, pt = patient, SI/B = suicidal ideation and behavior.
Source: DP Consult Review

In reference to these cases, the DP team reiterated that "the above cases do not demonstrate a clear signal of SI/B risk associated with bimekizumab. Again, most cases are complicated by a past psychiatric history and social stressors. However, coupled with a completed suicide in someone with no psychiatric history, the narratives from Study PS0015, and the increased rates of positive eC-SSRS responses from the pooled data of Studies PS0008, PS0009 and PS0013, these cases could be viewed as consistent with a possible drug-related risk."

Investigators withdrew three subjects following suicide attempts from Trial PS0014 and from Trial PS0015 [redacted] In addition, investigators withdrew six subjects from clinical trials who received bimekizumab and met the neuropsychiatric withdrawal criteria related to PHQ-9 or C-SSRS. Without withdrawal criteria associated with the development of active suicidal ideation and severe major depression, the number of SI/B events may have been even greater.

Inconsistencies between the PHQ-9 and eC-SSRS

The Applicant emphasized that the result of the single PHQ-9 item on suicide (question 9) is inconsistent with the result of the eC-SSRS. Based on the placebo-controlled trials (PS0009 and PS0013), the incidence of an SI/B event (positive response to eC-SSRS questions 1 through 9)

was 1.3% in the bimekizumab group vs. 0.6% in the placebo group (Risk Difference = 0.75; [95% CI: -0.70, 2.20]). In comparison, the incidence of subjects with a positive response for Question 9 on the PHQ-9 was 0.3% in the bimekizumab group vs. 3.0% in the placebo group (Risk Difference = -2.51; [95% CI: -5.11, 0.09]). Although the Applicant administered the eC-SSRS each visit throughout the study period for both studies PS009 and PS0013, the Applicant did not administer the PHQ-9 at Weeks 1 and 2. Of note, subjects (b) (6) experienced passive suicidal ideation at Week 1 and reported an interrupted suicidal attempt at Week 2, respectively.

The Division of Psychiatry instituted a policy of recommending greater prospective monitoring of SI/B for drugs affecting the central nervous system because events were not adequately captured with commonly employed depression ratings (such as the PHQ-9); see the draft guidance for industry, *Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials* (August 2012). Although it is unclear why the SI/B item of the PHQ-9 would provide inconsistent (or contradictory) results when compared to the eC-SSRS, it is worth noting that the eC-SSRS is a more in-depth rating of SI/B and the PHQ-9 item is "double-barreled" in the sense that it asks about "thoughts that you would be better off dead, or thoughts of hurting yourself in some way" (emphasis added). Regardless of which scale demonstrated an increase of SI/B in a drug arm (i.e., whether the PHQ-9 item or the eC-SSRS scale showed an increase in SI/B in a bimekizumab group), in the context of a completed suicide and three suicide attempts, the Division would be concerned. Per DP, "The lack of finding on the PHQ-9 item does not negate the finding on the eC-SSRS and does not indicate there is no risk."

Cases with Ambiguous Causes of Death

The DP team identified two subjects who received bimekizumab with "ambiguous causes of death." Without additional information, it cannot be determined with certainty that these deaths were "non-psychiatric in nature." One subject was a 42-year-old white male with no known psychiatric history who had risk factors for cardiovascular disease and died of undetermined cause; the other subject was a 72-year-old white male with a psychiatric history of attention deficit hyperactivity disorder (ADHD) and depression (receiving venlafaxine and mixed amphetamine salts), who died of blunt force traumatic injuries after he was struck by a motor vehicle.

eC-SSRS in active-controlled trials over the first 16 weeks after randomization

- Trial PS0008 observed 5/319 subjects on bimekizumab and 3/159 subjects on adalimumab with SI/B captured in the eC-SSRS.
- Trial PS0009 observed 4/321 subjects on bimekizumab and 4/163 subjects on ustekinumab with SI/B captured in the eC-SSRS.
- Trial PS0015 observed 3/373 subjects on bimekizumab and 2/370 subjects on secukinumab with SI/B captured in the eC-SSRS.

The Mantel-Haenszel risk difference for the proportion of subjects who experienced SI/B in these three trials over 16 weeks was -0.29% (-1.41%, 0.84%) and the corresponding Relative Risk was 0.80 (0.34, 1.85). Of note, out of all subjects who reported a positive SI/B response to the eC-SSRS instrument across trials PS0008, PS0009, and PS0015, one bimekizumab-treated subject participating in Trial PS0015 reported an interrupted suicide attempt during the first 16 weeks of treatment. This analysis shows no statistical evidence of increased risk of SI/B associated with bimekizumab relative to active comparators over 16 weeks. Although the analyses did not show a difference in the risk for SI/B between bimekizumab and active comparators, SI/B events are rare, and the available trials were not powered to detect differences in SI/B among active treatments. It may be that all active treatments have a small elevation in risk over placebo with the bimekizumab risk somewhat worse than most treatments. Therefore, although our analysis was able to observe some SI/B difference between bimekizumab and placebo, it did not include enough observations to evaluate whether there is a difference between bimekizumab risk and the SI/B risk with other treatments.

eC-SSRS in active-controlled trials of 1 year (48 to 52 weeks) after randomization

- Trial PS0009 had 52 weeks of controlled follow-up with ustekinumab. During these 52 weeks, 12/321 subjects on bimekizumab and 8/163 subjects on ustekinumab experienced SI/B captured by the eC-SSRS instrument.

- Trial PS0015 had 48 weeks of controlled follow-up with secukinumab. During these 48 weeks, 7/373 subjects on bimekizumab and 4/370 subjects on secukinumab experienced SI/B captured by the eC-SSRS instrument.

The Mantel-Haenszel risk difference for the proportion of subjects who experienced SI/B in these two trials of 1 year (48 to 52 weeks) was 0.07% (-1.74%, 1.88%) and the corresponding Relative Risk was 1.03 (0.51, 2.07). This analysis shows no evidence of increased risk of SI/B associated with bimekizumab relative to active comparators over 1 year.

Although the analyses did not show a difference in the risk for SI/B between bimekizumab and active comparators (Relative Risk = 1.03 (0.51, 2.07) over a 1-year period, SI/B is a rare event, and these trials are not powered or designed to observe a difference between active controls.

Effect of different doses of bimekizumab on SI/B

The trials discussed above (P0008, P0009, P0013, and P0015) were not designed or powered to compare the risk of SI/B between different doses of bimekizumab. For example, Trial P0015

randomized subjects to bimekizumab 320 mg Q4W (or secukinumab) during the first 16 weeks; after 16 weeks subjects on bimekizumab were re-randomized to Q4W or Q8W dosing. Because of the small number of events captured on the eC-SSRS, and because of the design of these trials, it is not possible to conduct a meaningful analysis of the effect of different doses of bimekizumab on SI/B.

The eC-SSRS instrument was also administered in: (1) dose-ranging phase 2 clinical trials PS0010 and PS0016, (2) open label extensions on bimekizumab. Neither of these sources provide useful additional data on the risk associated with bimekizumab relative to placebo or active comparators.

Adverse events of suicidal ideation, suicide attempt, and completed suicide

Neuropsychiatric adverse events

During the first 16 weeks of Trial PS0009, 6/321 subjects on bimekizumab and 0/83 subjects on placebo experienced psychiatric AEs (e.g., most commonly anxiety and depression see below). During the first 16 weeks of Trial PS0013, 6/349 subjects on bimekizumab (e.g., anxiety, stress, bipolar disorder, insomnia, and alcohol abuse) and 0/86 subjects on placebo experienced psychiatric AEs. The Mantel Haenszel risk difference and 95% CIs for psychiatric AEs comparing bimekizumab to placebo in these two trials is 1.79% (0.79%, 2.80%).

Over the first 16 weeks after randomization:

- Trial PS0008 observed 2/319 subjects on bimekizumab (e.g., confusional state and somnambulism) and 1/159 subjects on adalimumab (e.g., anxiety) with psychiatric AEs.
- Trial PS0009 observed 6/321 subjects on bimekizumab (e.g., depression, anxiety, mood swings, attention deficit/hyperactivity disorder, and aggression) and 1/163 subjects on ustekinumab (e.g., depression) with psychiatric AEs.
- Trial PS0015 observed 8/373 subjects on bimekizumab (e.g., anxiety, depression, insomnia, libido decreased, and suicide attempt) and 7/370 subjects on secukinumab (e.g., anxiety, adjustment disorder with anxiety, depressed mood, insomnia, and substance abuse) with psychiatric AEs

The Mantel Haenszel risk difference and 95% CIs for psychiatric AEs comparing bimekizumab to active comparators over 16 weeks in these three trials is 0.45% (-0.69%, 1.60%). The corresponding Relative Risk and 95% CI is 1.38 (0.60, 3.18).

During the full duration (initial phase plus maintenance phase) of Trial PS0009, 11/321 subjects on bimekizumab and 4/163 subjects on ustekinumab experienced psychiatric AEs. In Trial PS0015, 15/373 subjects on bimekizumab and 12/370 subjects on secukinumab experienced psychiatric AEs. The Mantel Haenszel risk difference and 95% CIs for psychiatric AEs comparing bimekizumab to active comparators over the full duration in these two trials is 0.85% (-1.20%, 2.90%). The corresponding Relative Risk and 95% CI is 1.29 (0.69, 2.40).

Serious AEs (SAEs) in the psychiatric disorders system organ class (SOC) in the open-label extension Trial PS0014 included suicidal ideation, bipolar disorder, drug dependence, alcohol withdrawal syndrome and completed suicide. In addition, six subjects had elevated PHQ-9 scores with maximum scores ranging from 20 to 27. During the initial treatment period (Week 0 to 16) of Trial PS0015, SAEs in the psychiatric disorders system organ class (SOC) included a suicide attempt with an elevated PHQ-9 score of 14. In addition, there were two subjects with elevated PHQ-9 scores (15 and 20.)

The Applicant argues that the lack of a signal for other mental health AEs indicates any signal for SI/B is not real. However, SI/B can occur in the absence of mental illness. A substantial portion with SI/B has no prior indication of mental health problem.

Trial discontinuation due to neuropsychiatric withdrawal criteria:

A total of 7 subjects discontinued from clinical trials for plaque psoriasis (PSO) because they met neuropsychiatric potential withdrawal criteria or no longer met the neuropsychiatric enrollment criteria. Of the 7 subjects, 6 subjects were from the bimekizumab treatment group, and 1 subject was from the placebo treatment group; there were no subjects from the active comparator treatment group.

Discontinuation rates are provided for Pool S2-3b, the most comprehensive view of bimekizumab in PSO which included all phase 3 safety data and accounts for 5461.4 subject-years of bimekizumab exposure and 673.4 subject-years of exposure to placebo or active comparators. The exposures result in a discontinuation rate related to neuropsychiatric criteria of 0.11/100 PYs for bimekizumab and 0.15/100 PYs for placebo/active comparator.

Risk of SI/B in other development programs for bimekizumab
In the phase 2/3 program for hidradenitis suppurativa which included 1041 subjects (1296.8 subject-years), the Applicant reports two suicide attempts (0.2%) (exposure-adjusted incidence rate of 0.15/100 PY, or 1.5/1000 PY). While in the development programs for axial spondyloarthritis and ankylosing spondylitis, there was a suicide attempt in Trial AS0010 and one case of suicidal ideation (0.3%) in the maintenance period of Trial AS0011. In addition, there was one suicide attempt in the psoriatic arthritis development program. The Applicant

provides the following summary of completed suicides and suicide attempts. The majority of these subjects had a history of a psychiatric disorder. (SDN 80 dated April 25, 2023 -UCB Response to FDA Information Request dated April 21, 2023).

Table 16: Summary of adjudicated completed suicide and suicide attempts across indications

Category Event type	PSO Phase 2/3 BKZ Total N=2480 100 participant-yrs=58.30 n (%) [#] EAIR	PsA Phase 2/3 BKZ Total N=1413 100 participant-yrs=26.64 n (%) [#] EAIR	axSpA Phase 2/3 BKZ Total N=928 100 participant-yrs=22.41 n (%) [#] EAIR	HS Phase 2/3 BKZ Total N=1041 100 participant-yrs=12.97 n (%) [#] EAIR
Completed suicide	1 (<0.1) [1] 0.02	0	0	0
Suicide attempt	2 (<0.1) [2] 0.03	1 (<0.1) [1] 0.04	1 (0.1) [1] 0.04	2 (0.2) [2] 0.15

axSpA=axial spondyloarthritis; BKZ=bimekizumab; EAIR=exposure-adjusted incidence rate; HS=hidradenitis suppurativa; PsA=psoriatic arthritis; PSO=psoriasis; TEAE=treatment-emergent adverse event
Note: n=number of study participants reporting at least one TEAE within the event type classification.
Note: there were 3 suicide attempts in the PSO development program. One suicide attempt is not included in the table above.
Note: EAIR=Incidence of new cases per 100 study participant-years.

The DP review commented "Drug-related SI/B risk is poorly understood, and the influence of the underlying disorder may or may not impact this risk. A clear signal of increased SI/B risk across disorders would be concerning, but a lack of a clear signal in other disorders does not indicate there is no risk in plaque psoriasis."

Postmarketing Data from Other Countries

The Applicant reported that there was no signal for completed suicides or suicide attempts from postmarketing data in jurisdictions where bimekizumab is currently marketed. The DP review states "Postmarketing data has inherent limitations. In general, death by suicide and suicide attempt are underreported. Dermatologists may be unlikely to report SI/B adverse events in a postmarket setting, particularly for patients with previous psychiatric history."

The totality of the data including the completed suicide, suicide attempts, neuropsychiatric AEs cases and eC-SSRS responses supported a safety signal for SI/B associated with bimekizumab use.

Teleconference held on May 3, 2023, and May 10, 2023.

The Agency communicated this new safety concern to the Applicant during a teleconference held on May 3, 2023. Further discussion of the risk of SI/B with bimekizumab use occurred on May 10, 2023. Some of the arguments advanced by the Applicant (bolded and summarized from SDN 86 dated May 12, 2023) and the response to these statements by the psychiatric consultant, Bernard Fischer, MD are summarized below.

1. The population for phase 3 trials reflected the population of patients with psoriasis in the real-world and some events of SI/B are expected due to the elevated background rate in this population
   DP response: The population for the phase 3 trials did not include subjects with what may be highest risk factors for SI/B. Whether the bimekizumab program reflects a higher rate of SI/B than the general population with psoriasis depends how one views the data.
   Exclusion criteria were:
   - Presence of active suicidal ideation or positive suicidal behavior using the "Screening" version of the eC-SSRS and with either of the following criteria:
     - history of suicide attempt within the past 5 years prior to screening
     - suicidal ideation in the past month prior to screening as indicated as a positive response to either Question 4 or 5 of the "Screening" version of the eC-SSRS
   - Moderately severe major depression or severe major depression indicated by a score of ≥15 using the screening PHQ-9
   - Medication used to treat depression should be stable for 8 weeks prior to baseline

2. There is no signal for SI/B in other jurisdictions from postmarketing exposure of 4,840 patient year (PY).
   DP response: There is no substantial difference in the patient years (PY) of exposure postmarketing and the PY from the development program (in fact, there is more experience in the development program). Given there is much closer monitoring and reporting in the development program, the difference in signal in the development program versus the postmarketing data is not surprising.

3. The lack of a safety signals regarding other neuropsychiatric events (e.g., MDD, anxiety) argues against an association of SI/B and bimekizumab.
   DP response: It is a common misconception that SI/B can only occur in the context of a mental illness. A substantial portion of patients with SI/B have no prior indication of a mental health problem. (In fact, the Applicant makes this same point when discussing the case of the completed suicide.)

4. The C-SSRS was not designed to be self-report electronic instrument.
   DP response: The C-SSRS is a safety screening tool not an efficacy endpoint. As such, it is perfectly reasonable to administer it as a self-report electronic instrument. (As our guidances for conducting trials during COVID stated.) In fact, there is some data to

indicate that self-assessments may be more accurate than clinician-administered scales/interviews.

5. "Wish to be dead" is not considered SI/B, and we prespecified that "wish to be dead" did not represent a signal for the Neuropsychiatric Adjudication Committee (NAC).
   DP response: DP team certainly considers a "wish to be dead" to be suicidal ideation (SI). It is considered SI in the Columbia Classification Algorithm of Suicide Assessment. It has also been shown to be an important risk factor for completed suicide (see, for example, Hoertel N, Blanco C, Olfson M, et al. A Comprehensive Model of Predictors of Suicide Attempt in Depressed Individuals and Effect of Treatment-Seeking Behavior: Results from a National 3-Year Prospective Study. The Journal of Clinical Psychiatry. 2018 Jul;79(5). DOI: 10.4088/jcp.17m11704.)

6. The SI/B signal was not related to starting the drug or changes in dose. Reports of SI did not continue throughout the trial (most were single, isolated reports). Subjects reporting SI/B had external stressors and there is no demonstrated causality.
   DP response: We do not know the mechanism of drug-related SI/B. It is unlikely to be as straightforward as something like Stevens-Johnson syndrome. It is most likely that the drug sets up a condition where the subject is more vulnerable to SI/B in response to stressors. As such, it is very plausible that the vulnerability starts when the subject starts the drug, but the SI/B is not experienced/identified until the subject encounters stressors. In this scenario, one would observe an elevated risk in the drug group, but the timing would not match the start of the drug or necessarily be related to the time spent on the drug. And one would expect the presence of stressors.

7. There was no statistical difference in SI/B between bimekizumab group and placebo group (confidence intervals cross 0).
   DP response: FDA does not make decisions on safety signals solely based on statistical significance. Most programs are underpowered in reference to rare signals. FDA makes safety decisions depending on whether we see a reasonable likelihood of increased risk. Because SI/B is so rare, this program probably did not have the power to identify a statistically significant difference in risk.

Conclusions and Recommendations from the DP team
The DP review team provided the following comments and conclusions (Consult review by Jennifer Reid, MD and Bernard Fischer, MD dated June 5, 2023):

"Taken alone, the neuropsychiatric AE cases may not be strong evidence of an association between bimekizumab and SI/B, particularly when there is an elevated background rate of SI/B in patients with psoriasis. Completed suicide is a rare event and it is impossible to definitively determine if the suicide is related to the study drug, the underlying illness (psoriasis), or neither of the two. However, having a completed suicide in someone without a past psychiatric history

while on study drug is a potential signal… In the context of the completed suicide, the AE cases, which include three suicide attempts (subjects (b) (6) (PS0015), (b) (6) (PS0015), (b) (6) (PS0014)), and the eC-SSRS differences are consistent with a possible signal for an association between SI/B and bimekizumab. The SI/B rates in the bimekizumab development program are elevated beyond what one would expect from psoriasis alone… DP recommends the potential risk of SI/B should be listed as a boxed warning, a warning and precaution in section 5, and the suicide should be mentioned in section 6 of the label."

"DP does not believe that a risk evaluation and mitigation strategy (REMS) would mitigate the risk beyond what labeling would accomplish." Because of the serious, potentially life-threatening risk of SI/B associated with treatment with bimekizumab, the review team considered whether additional measures beyond product labeling may be necessary to address this potential risk. As such, the division sought advice from the Division of Risk Management. In addition, the division consulted with the REMS Oversight Committee (ROC meetings held on June 2, 2023, and June 13, 2023) and Medical Policy and Program Review Council (MPPRC meeting held July 19, 2023) to gain advice from CDER Senior Leadership on the most effective strategy to address the potential risk of SI/B and ensure safe use of this product.

In addition, the DP team did not recommend a PMR because SI/B is a rare event, and it is not feasible to power an adequate study.

Conclusions and recommendations from the clinical review team

Analyses of data from the original BLA submission and resubmission that included positive eC-SSRS responses, one completed suicide and three suicide attempts raised concern about a potential signal for suicidal ideation and behavior (SI/B) associated with bimekizumab use. However, there are uncertainties surrounding the potential signal of SI/B. The reason for the uncertainties and the recommendations to address the potential safety concern of SI/B in view of these uncertainties are described below:

- SI/B is a serious, but rare event that can occur in the general population.

- The trials in the development program are not powered or designed to reliably assess a difference in the rate of SI/B between bimekizumab and placebo or active controls.

- The rate of SI/B observed in this development program may or may not surpass the background rate of SI/B. Much of the literature supports the conclusion that patients with plaque psoriasis have a higher risk of depression and suicide than the general population. It is not clear whether this elevated risk is related to the burden of chronic disease, cytokine levels or other immune mediated factors, or a combination of factors. The data on the background rates for SI/B in patients with psoriasis are variable and depend on methodology of data collection and whether the data accounted for disease severity. A population-based cohort study of 8 million people in United Kingdom found

excess risk of "suicidality" (diagnosis of ideation, attempts, or suicide) of one case per 2,500 patients.[2] In a nationwide, population-based, retrospective cohort study that analyzed data from the Korean National Health Insurance Service claim data of 348, 439 adults with psoriasis found that the risk of suicidality was greater in the group with psoriasis than age- and sex-matched controls (adjusted hazard ratio of 1.21). [3] In addition, the study population in the bimekizumab development program was narrowed by psychiatric exclusion criteria and, therefore, this might limit the generalizability of the data to inform the risk of SI/B in population with moderate to severe psoriasis.

- The additional analysis of eC-SSRS data from two placebo-controlled trials (Trials P0009 and P0013) estimated a Mantel-Haenszel risk difference for the proportion of subjects who experienced new onset SI/B in these two trials over 16 weeks of 1.19% (-0.34%, 2.72%) and a corresponding Relative Risk of 3 (0.39, 22.74). However, because of the small number of events in this analysis, the confidence intervals are wide and cannot provide a precise estimate of the outcome of interest, SI/B.

- An analysis of eC-SSRS pooled data from three active-controlled and active/placebo-controlled trials (Trial PS0008, Trial PS0009 and Trial PS0013) that compared bimekizumab with adalimumab, ustekinumab or secukinumab, showed a Mantel-Haenszel risk difference for the proportion of subjects who experienced SI/B in these three trials over 16 weeks of -0.29% (-1.41%, 0.84%) and a corresponding Relative Risk of 0.80 (0.34, 1.85). In addition, the Mantel-Haenszel risk difference for the proportion of subjects who experienced SI/B in the two active-controlled trials (Trial PS0009 and Trial PS0015) of 1 year duration (48 to 52 weeks) was 0.07% (-1.74%, 1.88%) and the corresponding Relative Risk was 1.03 (0.51, 2.07). Although the analyses did not show a difference in the risk for SI/B between bimekizumab and active comparators (Relative Risk = 1.03 (0.51, 2.07)), SI/B events are rare, and the available trials were not powered to detect differences in SI/B among active treatments. The data did not include enough observations to evaluate whether there is a difference between SI/B risk with bimekizumab and other treatments.

- There is a difference in the result of the single PHQ-9 item related to suicide/suicidal ideation compared with the results on the eC-SSRS. The Division of Psychiatry instituted a policy of recommending greater prospective monitoring of SI/B for drugs affecting the central nervous system because events were not adequately captured with commonly employed depression ratings (such as the PHQ-9); see the draft guidance for industry,

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[2] Kurd SK, et al. The risk of depression, anxiety, and suicidality in patients with psoriasis: a population-based cohort study. Arch Dermatol. 2010;146(8):891–5.
[3] Kim SM et al. Increased risk of suicidality in patients with psoriasis: A Nationwide cohort study in Korea. J Eur Acad Dermatol Venereol. 2023;37: 75-84.

Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials (August 2012). Although it is unclear why the SI/B item of the PHQ-9 would provide inconsistent (or contradictory) results when compared to the eC-SSRS, it is worth noting that the eC-SSRS is a more comprehensive rating of SI/B. The PHQ-9 item is "double-barreled" in the sense that it assesses two concepts: "thoughts that you would be better off dead", or "thoughts of hurting yourself in some way". Regardless of which scale demonstrated an increase of SI/B in a drug arm (i.e., whether the PHQ-9 item or the eC-SSRS scale showed an increase in SI/B in a bimekizumab group), in the context of a completed suicide and three suicide attempts, the lack of findings on the PHQ-9 item does not negate the positive findings on the eC-SSRS and does not indicate that there is no risk; however, it reinforces the uncertainty of the SI/B signal strength.

- A total of 7 subjects discontinued from clinical trials for plaque psoriasis (PSO) because they met neuropsychiatric potential withdrawal criteria or no longer met the neuropsychiatric enrollment criteria. Of the 7 subjects, 6 subjects were from the bimekizumab treatment group, and 1 subject was from the placebo treatment group; there were no subjects from the active comparator treatment group. Discontinuation rates are provided for Pool S2-3b, the most comprehensive view of bimekizumab in PSO which included all phase 3 safety data and accounts for 5461.4 subject-years of bimekizumab exposure and 673.4 subject-years of exposure to placebo or active comparators. The exposures result in a discontinuation rate related to neuropsychiatric criteria of 0.11/100 PYs for bimekizumab and 0.15/100 PYs for placebo/active comparator. However, because of psychiatric stopping criteria and exclusion criteria, the true risk of SI/B associated with the use of bimekizumab in the population with moderate to severe psoriasis is not known.

- Bimekizumab is approved in 39 countries worldwide with an unrestricted, first-line indication and without labeling restrictions related to SIB or neuropsychiatric events. Per Applicant, the total post-marketing exposure currently exceeds 8850 patient-years and approximately 10000 patients have received at least one dose of bimekizumab. There were no additional reports of completed suicide or suicide attempt from other jurisdictions to date (SDN 87 dated July 10, 2023 and confirmed by direct communication with regulatory agencies). However, it should be noted that due to the inherent limitations of post-marketing data which include under-reporting, difficulty in identifying rare events (1/1,000) and difficulty in quantifying risk, the absence of cases of suicide or suicide attempts in foreign post-marketing data provides limited support for the safety of bimekizumab post approval.

Conclusions

Taken together, the completed suicide, suicide attempts, and positive eC-SSRS responses are consistent with a possible increased risk for SI/B with bimekizumab use. Given the nature of the adverse event of suicide, appropriate and reasonable regulatory steps are justified as follows:

- Product labeling
    - SI/B is a serious adverse event, but also a rare adverse event that can occur in the general population. Considering the uncertainties surrounding the risk of SI/B, the population for whom the risk is justified by the potential benefit are adult patients with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. (b) (4)
    - DP team recommends that the potential risk of SIB associated with bimekizumab use be described in the Warnings and Precautions section of product labeling and the risk highlighted for prescribers with the use of a boxed warning.

      Per guidance for industry *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products — Content and Format,* a boxed warning should be used *when there is a serious adverse reaction that can be prevented or reduced in frequency or severity by appropriate use of the drug (e.g., patient selection, careful monitoring, avoiding certain concomitant therapy, addition of another drug.* However, as noted in the "Conclusions and recommendations" from the clinical review team section above, there is uncertainty with regard to the SI/B signal. In addition, SI/B is a serious adverse event that cannot be prevented or reduced in frequency or severity by appropriate use of the drug. Therefore, the potential risk of SI/B will be described in Warnings and Precautions (W&P) Section of labeling (21CFR 201.57 (c)(6)). SI/B is a serious, clinically significant adverse event that has implications for prescribing decisions and patient management. Although a causal association between treatment with bimekizumab and increased risk of suicidal ideation and behavior has not been definitely established, regulations pertaining to the W&P section state that only "reasonable evidence of a causal association with a drug" is needed.

- In summary, the potential risk of SI/B will be communicated to prescribers and patients through:

1. Labeling:

a. Prescribing Information: The potential risk for SI/B will be described in Warnings and Precautions (§ 201.57(c)(6)), and Sections 6 and 17 of the prescribing information. This section may also include the number for the National Suicide and Crisis Lifeline at 988.

b. Medication Guide: The potential risk for SI/B in association with bimekizumab will be described in the Medication Guide. Patients will be instructed to seek help if they develop any symptoms of depression and/or self-destructive thoughts or behaviors. Patients may be instructed to call their healthcare provider or the National Suicide and Crisis Lifeline at 988 if they develop suicidal thoughts and/or behavior.

2. Applicant's proposed voluntary activities

(b) (4)

Labeling Recommendations:

(b) (4)

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/ TS) immediately following this page

8.2.5.2. Inflammatory Bowel Disease

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. Language related to the risk of IBD is included in Section 5 (Warnings and Precautions) of labeling for ant-IL-17A mAbs secukinumab and ixekizumab, as well as anti-IL-17A Receptor mAb brodalumab. The Applicant also conducted a proof-of-concept trial to evaluate bimekizumab for the treatment of active, moderate to severe ulcerative colitis (UC). However, this trial was terminated early based on an on an imbalance in TEAEs and SAEs between bimekizumab and placebo treatment together with an observed increase in clinical signs of UC.

During review of the initial BLA, the review team evaluated the potential risk of IBD associated with treatment with bimekizumab in conjunction with consultants from the Division of Gastroenterology (DG). Refer to the Consult Review by Dr. Anil Nayyar dated March 22, 2021, and Section 8.2.5.2 of the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022.

During the review of the initial BLA, one subject (1/1789, EAIR 0.05/100 subject-years) treated with bimekizumab 320 mg Q4W developed new-onset UC which was serious, led to discontinuation, and was considered related to treatment by the investigator. Based on this case, language was included in Section 5 (Warnings and Precautions) and Section 6 (Adverse Reactions). The Applicant agreed with inclusion of this language in the labeling.

Since the time of the initial submission, an independent inflammatory bowel disease adjudication committee (IBD-CAC) was established across the bimekizumab clinical development programs. The safety update provided with the resubmission included 7 new cases in subjects treated with bimekizumab which were adjudicated as "definite IBD" by the IBD-CAC. These cases were reviewed in conjunction with a consultant from the Division of Gastroenterology (DG). Refer to the DG consult review by Dr. Tara Altepeter dated May 2, 2023.

The additional cases of IBD included three cases of UC, three cases of Crohn's Disease (CD), and one case of IBD unclassified. Based on the clinical narratives and summaries provided by the Applicant, the DG reviewer concluded that the 7 cases that were adjudicated as "definite IBD" appear reasonably likely to represent IBD. The DG reviewer also commented that "It is likely that some of the additional "probable" or "possible" cases reported also represent new onset IBD. However, given the limited details available to confirm this diagnosis, labeling should be limited to the confirmed/adjudicated cases that were considered definite IBD." A summary table of the cases adjudicated as "definite IBD" was provided by the DG consultant and is presented below.

Table 17: Cases Adjudicated as "Definite IBD" by the IBD-CAC

Patient ID	Age at enrollment, Time from initiation of bimekizumab to onset of event	Adjudicated Diagnosis	Reviewer Comments
PS0008-(b) (6)	39-year-old male, 890 days after initiation of bimekizumab	CD	Narrative includes details of CT findings of terminal ileal thickening, subsequent colonoscopy with biopsy where biopsies were reported as consistent with CD. Assessment appears reasonable.
PS0009-(b) (6)	60-year-old male, 377 days after initiation of bimekizumab	IBD unclassified	Patient initially considered to have "drug induced enteritis" but on subsequent colonoscopy was reported to have UC. Although the narrative states the final diagnosis was UC, there are features in the case history that make this less clear (including prior presence of gastritis and mild abnormalities in the ileum, as well as pharyngeal/laryngeal ulcerations of unclear etiology which are sometimes features of CD). Adjudicated classification of "IBD unclassified" appears reasonable.
PS0009-(b) (6)	32-year-old male, 88 days after initiation of bimekizumab	UC	Narrative contains endoscopic, imaging, and histologic details consistent with UC, classification appears reasonable.

Patient ID	Age at enrollment, Time from initiation of bimekizumab to onset of event	Adjudicated Diagnosis	Reviewer Comments
PS0013-(b) (6)	23-year-old female, 706 days after initiation of bimekizumab	CD	Patient was diagnosed with esophagitis and Crohn's disease reportedly on the basis of colonoscopy, gastroscopy, abdominal ultrasound and abdominal MRI. Narrative specifically notes that the first set of biopsies from the intestine showed "no evidence of CD or other inflammatory disease", which is in contrast to other findings. However, patient reportedly had a second colonoscopy at a later time which confirmed dx of CD (biopsy information was not provided). Based on overall clinical presentation summarized, as well as laboratory values and response to treatment, a dx of IBD seems reasonable. The narrative is lacking details of the evidence that confirmed the type of IBD as CD.
PS0015-(b) (6)	43-year-old male, 69 days after initiation of bimekizumab	UC	Narrative includes symptoms of bloody diarrhea leading to hospitalization. Details of colonoscopy findings are limited but are consistent with UC (erythema and loss of vascular pattern in rectum, details of rest of colon were not provided) Histology was reported to be consistent with UC. Adjudicated diagnosis is reasonable.

Patient ID	Age at enrollment, Time from initiation of bimekizumab to onset of event	Adjudicated Diagnosis	Reviewer Comments
PS0015-(b) (6)	21-year-old male, 499 days after initiation of bimekizumab (prior exposure to secukinumab)	UC	Patient experienced three hospitalizations reportedly due to UC at days 830, 882, and 908 after initiating bimekizumab; the last two events were adjudicated as "definite IBD- UC." There is no report of colonoscopy and biopsy in the narrative. However, the clinical signs/symptoms and laboratory values are consistent with IBD. Treatments administered are consistent with diagnosis of UC. Although narrative lacks some important details, the adjudication to UC appears reasonable (though reviewer may have considered this case to be "probable" rather than definite, the IBD-CAC may have had additional information available leading to the determination).
PS0015-(b) (6)	26-year-old female, 149 days after initiation of bimekizumab (prior exposure to secukinumab)	CD	Inadequate information was contained in the sponsor's summary to corroborate the "definite CD" diagnosis. There were no details provided on the diagnostic workup for this patient. Patient was treated with mesalamine for reported 'mild' CD and the study drug was not discontinued.

Source: Reviewer's Table from DG consult review by Dr. Tara Altepeter dated May 2, 2022

Recommendations for Labeling:

The DG consultant recommended no changes to Section 5 (W&P):

> 5.6 Inflammatory Bowel Disease
>
> Cases of inflammatory bowel disease (IBD) have been reported in patients treated with IL-17 inhibitors, including BIMZELX *[see Adverse Reactions (6.1)].* Avoid use of BIMZELX in patients with active IBD. During BIMZELX treatment, monitor patients for signs and symptoms of IBD and discontinue treatment if new onset or worsening of signs and symptoms occurs.

The DG consultant recommended the following update to Section 6 (Adverse Reactions [AR]):

> Specific Adverse Reactions
>
> *Inflammatory Bowel Disease*
> In clinical trials in subjects with plaque psoriasis, subjects with active inflammatory bowel disease were excluded. In these trials, which included 2480 subjects exposed to BIMZELX accounting for 5830 patient-years, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC), Crohn's disease (CD) and IBD-undetermined) occurred in seven subjects (0.12 per 100 patient-years); the majority of these cases were serious and resulted in discontinuation of therapy. In clinical development programs for other disease conditions, new cases of Crohn's disease (CD) and UC, some serious, and exacerbations of pre-existing CD and UC, were reported with BIMZELX use.

8.2.5.3. Hepatotoxicity/DILI

During the review of the initial BLA, the review team evaluated potential hepatotoxicity in conjunction with consultants from the Drug-Induced Liver Injury (DILI) team from the Division of Hepatology and Nutrition. Refer to the consult review dated August 6, 2021, by Paul Hayashi, MD, MPH and Section 8.2.5.3 of the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022.

During the initial BLA review, the review team discovered potential cases of drug-induced liver injury (DILI) associated with treatment with bimekizumab. In addition, the review team identified an imbalance for transaminases > 3x the upper limit of normal (ULN) during the placebo-controlled period of Trials PS0009 and PS0013. Transaminase elevations >3x ULN occurred in 7/670 (1.0%) of subjects treated with bimekizumab and 1/169 (0.6%) of subjects treated with placebo. Based on the findings during the initial BLA review, labeling recommendations included testing of liver enzymes, alkaline phosphatase, and bilirubin prior to

initiating treatment with bimekizumab in Section 2.1 and related language for Section 5 (W&P) and Section 6 (AR). The Applicant agreed to the proposed language at that time.

In the SUR provided with the BLA resubmission, the review team identified three subjects with possible DILI. These subjects were evaluated by the DILI team who concluded that "None of the three were probable DILI due to bimekizumab (BKZ)." Refer to the Review Memorandum by Paul Hayashi, MD, MPH dated April 18, 2023.

Labeling Recommendations

(b) (4) the following modifications to Section 5.3 Liver Biochemical Abnormalities (added text in bold font, deleted text in ~~strikethrough~~):

> Treatment with BIMZELX was associated with increased incidence of liver enzyme elevations compared to treatment with placebo in randomized clinical trials. Liver serum transaminase elevations > 3 times the upper limit of normal were reported in subjects treated with BIMZELX [*see Adverse Reactions (6.1)*]. Elevated liver serum transaminases resolved after discontinuation of BIMZELX. The time to onset of these adverse reactions varied between 28 and 198 days after starting BIMZELX treatment.
>
> Test liver enzymes, alkaline phosphatase and bilirubin at baseline and periodically during treatment with BIMZELX according to routine patient management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt BIMZELX until a diagnosis of liver injury is excluded. ~~Permanently discontinue BIMZELX in patients with causally associated combined elevations of transaminases and bilirubin.~~ Patients with acute liver disease or cirrhosis may be at increased risk for severe hepatic injury; avoid use of BIMZELX in these patients.

(b) (4)

(b) (4) These cases essentially meet Hy's Law and drug should be stopped if causally related." The review team agreed with the inclusion of the phrase "according to routine patient management" with a slight modification. The Review team's recommendations for labeling are presented below:

Section 2.1- Recommended Evaluations and Immunization Prior to Treatment Initiation (unchanged):

Test liver enzymes, alkaline phosphatase and bilirubin prior to initiating treatment with BIMZELX *[see Warnings and Precautions (5.5)]*.

Section 5.5 Liver Biochemical Abnormalities (new text in bold font)

Treatment with BIMZELX was associated with increased incidence of liver enzyme elevations compared to treatment with placebo in randomized clinical trials. Liver serum transaminase elevations > 3 times the upper limit of normal were reported in subjects treated with BIMZELX [*see Adverse Reactions (6.1)*]. Elevated liver serum transaminases resolved after discontinuation of BIMZELX. The time to onset of these adverse reactions varied between 28 and 198 days after starting BIMZELX treatment.

Test liver enzymes, alkaline phosphatase and bilirubin at baseline, periodically during treatment with BIMZELX and according to routine patient management. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt BIMZELX until a diagnosis of liver injury is excluded. Permanently discontinue BIMZELX in patients with causally associated combined elevations of transaminases and bilirubin. Patients with acute liver disease or cirrhosis may be at increased risk for severe hepatic injury; avoid use of BIMZELX in these patients.

Section 6.1 Clinical Trials Experience (unchanged)

Specific Adverse (b) (4) Reactions

Liver Biochemical Abnormalities

During the placebo-controlled period of Trials Ps-1 and Ps-2, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.0% of subjects treated with BIMZELX versus 0.6% of subjects treated with placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

8.2.5.4. Infections

During the review of the initial BLA, the review team analyzed the frequency of overall infections, serious infections and opportunistic infections that occurred during multiple treatment periods. Refer to Section 8.2.5.1 of the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022, for a discussion of the rates of infection from the data in the initial BLA.

The safety update in the resubmission contains additional safety data to inform the analysis of the risk of infection associated with longer term exposure to bimekizumab. While the proportion of subjects reporting overall, serious, and opportunistic infections is slightly higher with greater exposure, the exposure adjusted incident rates (EAIR) are lower. This data suggests that increased exposure to bimekizumab did not result in an increased risk of infection. The review team did not recommend labeling changes based on the additional data.

Overall Infections

In the initial BLA submission, infections were reported in 63% (EAIR 120.4/100 subject-years) of subjects treated with bimekizumab during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials. In the safety update provided with the BLA resubmission, infections were reported in 75% (EAIR 79.3/100 subject-years) of subjects treated with bimekizumab during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials (including PS0015).

Similar to the initial BLA review, the most commonly reported TEAEs by preferred term (PT) were nasopharyngitis, oral candidiasis, and upper respiratory infection.

Serious infections

In the initial BLA submission, serious infections were reported in 1.5% (EAIR 1.6/100 subject-years) of subjects treated with bimekizumab during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials. In the safety update provided with the BLA resubmission, serious infections were reported in 3.3% (EAIR 1.3/100 subject-years) of subjects treated with bimekizumab during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials (including PS0015). The most frequently reported serious infection by TEAE was corona virus infection (14 subjects). None of these subjects were fully vaccinated at the time of infection and all had relevant risk factors for severe infection including obesity/overweight, diabetes, and/or older age.

Opportunistic infections and TB

In data reviewed during the initial BLA as well as in the safety update provided with the resubmission, opportunistic infections were primarily mucocutaneous fungal infections. During review of the initial BLA, opportunistic infections were reported in 1.7% (EAIR 1.8/100 subject-years) of subjects treated with bimekizumab during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials. In the safety update provided with the BLA resubmission, opportunistic infections were reported in 2.2% (EAIR 0.9/100 subject-years) of subjects treated with bimekizumab during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials (including PS0015).

Although subjects with active TB were excluded from clinical trials, subjects with latent TB could be enrolled provided they began prophylactic treatment prior to the beginning of the trial. No subjects developed new onset TB infection during the clinical trials. Among subjects with latent TB who were enrolled in the phase 3 trials and received prophylactic treatment for TB, none of these subjects developed active TB.

Labeling Recommendations

The review team recommends no changes to the previously agreed-upon labeling for Section 5.3 Infections or Section 6.1 Adverse Reactions/Clinical Trials Experience, Specific Adverse Reactions, *Infections*. However, the review team recommends the following change to Section 5.4 of labeling:

> Section 5.4 Tuberculosis (deletion in ~~strikethrough~~)
>
> Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with BIMZELX. Avoid the use of BIMZELX in patients with active TB infection. Initiate treatment of latent TB prior to administering BIMZELX. (b) (4) –Consider anti-TB therapy prior to initiation of BIMZELX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Closely monitor patients treated with BIMZELX for signs and symptoms of active TB during and after treatment.

8.2.5.5. Malignancies

Subjects with any active malignancy or history of malignancy within 5 years prior to the Screening Visit were excluded from phase 3 trials. The only exceptions to the exclusion criteria were cutaneous squamous or basal cell carcinoma that were treated and considered cured, or in situ cervical cancer. This review will focus on comparison of malignancy rates using pooled data from the phase 2/3 trials provided in the 120- day safety update during review of the initial BLA (Pool S2) and pooled data from the phase 2/3 trials included in the safety update provided with the resubmission (Pool S2-3b).

In Pool S2 (as of the 120-day safety update) 20/1789 subjects (1.1%; EAIR 0.8/100 subject-years) experienced malignancy TEAEs. In Pool S2-3b, there were an additional 31 subjects with malignancy TEAEs for a total of 51/2480 subjects (2.1%; EAIR 0.9/100 subject-years). This was primarily driven by 15 additional subjects with basal cell carcinoma. Other new malignancies reported in the resubmission included three new subjects with malignant melanoma in situ, two new subjects with squamous cell carcinoma (site not specified) and one new subject with squamous cell carcinoma of the skin. New cases of malignancy also included a thyroid

neoplasm and a fatal brain neoplasm. A narrative for the subject with the fatal brain neoplasm is provided in Section 8.2.4 of this review.

Although the overall frequency of TEAEs of malignancy was greater in Pool S2-3b, EAIRs between the data pools are similar despite almost double the total exposure to bimekizumab in Pool S2-3b. This demonstrates that based on the available data, the risk of malignancy does not appear to increase with increased duration of exposure to bimekizumab.

However, because of the long latency period associated with malignancy, this will be an outcome of interest in the prospective long-term safety study which will be a PMR. In addition, the risk of lymphoma will be evaluated via Active Risk and Identification Analysis (ARIA) system.

8.2.5.6. Major Adverse Cardiovascular Events

In view of the epidemiologic associations between psoriasis and cardiovascular (CV) comorbidities, and the potential association between anti-cytokine therapies used in the treatment of moderate-to-severe psoriasis and CV events, the Applicant conducted analyses on all events related to the CV system. The Applicant also established a Cardiovascular Clinical Event Adjudication Committee (CV-CAC) for adjudication of CV TEAEs. Major Adverse Cardiovascular Events (MACE) was defined as cardiovascular death, nonfatal myocardial infarction (MI), and stroke.

The Applicant also evaluated extended MACE, which was defined as all MACE, plus adjudicated event types of hospitalization for unstable angina with urgent revascularization, hospitalization for heart failure, coronary revascularization procedures (percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG]) or urgent revascularization procedures (i.e., due to symptoms of brain ischemia or pending infarction).

Subjects with stable CV disease were not excluded from the clinical trials unless they had a history of MI or stroke within 6 months prior to Screening. Risk factors for CV disease were common in the updated phase 2/3 population (Pool S2-3b). The majority of subjects were obese or overweight. A total of 7.4% had a BMI $\geq$40kg/m^2, 35.6% had a BMI $\geq$30 to <40kg/m^2, and 32.5% had a BMI $\geq$25 to <30kg/m^2. Additional information regarding CV risk factors was not provided in the safety update. In the phase 2/3 population evaluated during review of the initial BLA, approximately half of the population were current or past smokers, more than 30% had a medical history of hypertension, and approximately 20% had a history of dyslipidemia.

As of the 120- day safety update submitted during review of the initial BLA, adjudicated MACE were reported in 14/1798 subjects (0.8%; EAIR 0.6/100 subject-years). In the safety update provided with the resubmission, adjudicated MACE were reported in 30/2480 subjects (1.2%; EAIR 0.5/100 subject-years).

As of the 120- day safety update submitted during review of the initial BLA, extended MACE were reported in 17/1798 subjects (1.0%; EAIR 0.7/100 subject-years). In the safety update provided with the resubmission, extended MACE were reported in 39/2480 subjects (1.6%; EAIR 0.7/100 subject-years).

According to the exposure adjusted rates, the risk of MACE, including extended MACE was not increased with increased duration of exposure to bimekizumab.

During review of the initial BLA, a total of three deaths were reported which were attributable to MACE. All MACE were evaluated in collaboration with consultants from the Division of Cardiology and Nephrology (DCN Review dated April 12, 2023.) The previous CV safety analysis from DCN (dated March 3, 2021) included data from the safety pool, S1, comprised of adult subjects exposed to bimekizumab 320 mg Q4W (n=670) or placebo (n=169) in the initial treatment period (ITP; 16-week placebo-controlled) of the phase 3 trials PS0009 and PS0013. According to the consultant, Selena DeConti, PharmD, MPH, "The review did not reveal a clinical concern from the cardiovascular perspective and no labeling language was recommended."

The safety update provided with the BLA resubmission included eight additional deaths related to adjudicated MACE events. Seven deaths were reported in Trial PS0014 and one death in Trial PS0015. Brief narratives are provided below:

Trial PS0014

- A 63 y/o WM (Subject PS0014-(b) (6)) treated with bimekizumab (BKZ) 320 mg Q4W experienced a fatal AE of cardiac arrest. The event occurred 772 days after his first dose of BKZ and 16 days after his most recent dose. The subject's cardiovascular (CV) risk factors included hyperlipidemia, hypertension, type 2 diabetes mellitus and tobacco use.
- A 64 y/o WF (Subject PS0014-(b) (6)) treated with BKZ 320 mg Q4W experienced a fatal AE of cardiac arrest. The event occurred 814 days after her first dose of BKZ and 27 days after her most recent dose. The subject's CV risk factors included hypertension, myocardial ischemia, and current tobacco use.
- A 56 y/o WM (Subject PS0014-(b) (6)) treated with BKZ 320 mg Q8W experienced sudden death related to cardiac arrest and exacerbation of chronic obstructive pulmonary disease (COPD). The event occurred 778 days after his first dose of BKZ and 51 days after his most recent dose. The subject's CV risk factors included hypertension, hypercholesterolemia, and COPD in addition to obesity with sleep apnea syndrome.
- A 42 y/o WM (Subject PS0014-(b) (6)) treated with BKZ 320 mg Q8W died with cause of death undetermined. The death occurred 846 days after his first dose of BKZ

and 83 days after his most recent dose. Although the cause of death was undetermined, this was an adjudicated MACE. The subject's CV risk factors included hypertension and morbid obesity.

- A 63 y/o WM (Subject PS0014-(b) (6)) treated with BKZ 320 mg Q8W experienced a fatal AE of Coronavirus infection. The event occurred 849 days after his first dose of BKZ and 10 days after his most recent dose. The event was reported as a suspected COVID-19 death by the family. However, the infection was not confirmed. The Applicant considered the chronology of events suggestive for sudden death due to MACE. The subject's CV risk factors included congestive heart failure, coronary artery disease, diabetes mellitus, morbid obesity, supraventricular tachycardia, intraventricular conduction defect, and history of tobacco use.

- A 69 y/o WM (Subject PS0014-(b) (6)) treated with BKZ 320 mg Q8W had fatal AES of aortic aneurysm rupture and hemorrhagic anemia. The events occurred 1094 days after his first dose of BKZ and 30 days after his most recent dose. The acute post-hemorrhagic anemia as a result of rupture of an abdominal aortic aneurysm. The subject's risk factors included symptomatic arteriosclerosis (angina pectoris) and a prior ischemic stroke with known vascular encephalopathy. Additional CV risk factors included obesity, type 2 diabetes mellitus, hypertension, and current tobacco use.
- A 63 y/o WM (Subject PS0014-(b) (6)) treated with BKZ 320 mg Q8W had a fatal AE of Circulatory collapse. The event occurred 619 days after his first dose of BKZ and 3 days after his most recent dose. The subject's CV risk factors included hypertension, type 2 diabetes mellitus, and overweight.

<u>Trial PS0015</u>

- A 64 y/o WM (Subject PS0015-(b) (6) treated with BKZ 320 mg Q8W had a fatal AE of Cardiac arrest. The event occurred during the open-label extension period, 867 days after his first dose of BKZ and 27 days after his most recent dose. The subject's CV risk factors included hypertension, obesity, hyperlipidemia, diabetes mellitus type 2, tobacco use, sleep apnea syndrome, and family history of heart attack and hypertension.

The DCN review provided an updated CV safety analysis that includes data from PS0015 (Review dated April 12, 2023). CV events were reviewed for the Safety Set, which includes the double-blind treatment periods (48 weeks, consisting of an Initial Treatment Period through Week 16 and a Maintenance Treatment Period from Week 16 through Week 48; final dose at Week 44) for bimekizumab 320 mg (n=373) or secukinumab 300 mg (n=370). The reviewer

concluded that "Overall, the analysis of the updated safety data did not raise clinical CV concerns and no labeling language is necessary." The DCN reviewer noted that "Hypertension was the most reported CV adverse event and had a higher incidence in those treated with bimekizumab (6%) than secukinumab (3%). This may be due to the imbalance of previous or ongoing hypertension and elevated blood pressure (BP) reported at baseline for the treatment arms … Overall mean and median changes from baseline of clinic monitored SBP and DBP were similar and not clinically meaningful for any treatment group."

The DCN review team also reviewed the adjudicated MACE deaths. Dr. DeConti stated that "All cases had significant and multiple CV risk factors (obesity, hypertension, hyperlipidemia, atherosclerosis, and long-time current or previous smoker), and it's known that patients with psoriasis have an increased risk of vascular inflammation and MACE beyond that attributable to known CV risk factors. Further, the cases included a mean time to onset of around 2 years (713.3 days; min, 437; max, 1049) with confounders such as suspected COVID-19 infection, ruptured aortic aneurysm, underlying intraventricular conduction defect, or lacked information to determine cause of death. Thus, it's doubtful that the drug has any contribution. "(Email communication dated May 16, 2023)

8.2.5.7. Neutropenia

Reduction in neutrophil counts is a potential pharmacodynamic effect of blockade of IL-17A. During review of the initial BLA, neutropenia was included in Section 6 (Adverse Reactions) of labeling as an adverse reaction that occurred in < 1% but > 0.1% of subjects treated with bimekizumab during the placebo-controlled period. In this Safety Update, results were comparable to those in the original BLA submission and 120-Day safety update. Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022. In the 120-day safety update during the initial BLA review, 24/1789 subjects (1.3%) treated with bimekizumab developed any neutropenia TEAE. A total of 15/1789 (0.8%; EAIR 0.6/100 subject-years) developed Neutropenia and 9/1789 (0.5%; EAIR 0.5/100 subject years) developed Neutrophil count decreased. In addition, the results for the individual trials PS0014 and PS0015 were similar to Pool S2-3b. In Pool S2-3b, 37/2480 (1.5%; EAIR 0.6/100 subject-years) of subjects developed any neutropenia TEAE. A total of 25/2480 (1%; EAIR 0.4/100 subject-years) of subjects developed Neutropenia, and 12/2480 (0.5%; EAIR 0.2/100 subject years) of subjects developed Neutrophil count decreased. None of the TEAEs were serious. No serious infections were associated with neutropenia. Based on the EAIRs, the data did not demonstrate an increased treatment-related risk of neutropenia with longer duration of treatment with bimekizumab.

8.2.5.8. Hypersensitivity and Injection Site Reactions

Hypersensitivity was considered an AESI in the development program for bimekizumab (BKZ). In order to investigate the potential occurrence of hypersensitivity reactions with bimekizumab, the Applicant conducted the following searches of their safety database:

- Acute anaphylactic events based on the MedDRA anaphylaxis algorithm
- Other hypersensitivity reactions using the Hypersensitivity (narrow) SMQ
- Injection site reactions reviewing the HLTs "Administration site reactions NEC" and "Injection site reactions"

In the initial submission, a total of 13/1789 subjects (0.7%, EAIR 0.8/100 subject-years) had TEAEs of urticaria in Pool 2. However, none of the TEAEs led to discontinuation and were unlikely to represent hypersensitivity to bimekizumab. In the safety update provided with the resubmission, 29/1789 subjects (1.6 %; EAIR 0.8/100 subject-years) had TEAEs of urticaria in Pool 2-updated. According to the exposure adjusted incidence rates (EAIR), the risk of urticaria was not increased with increased duration of exposure to bimekizumab.

The Applicant stated that there were no reports of anaphylaxis related to bimekizumab in the development program. In the combined Initial, Maintenance, and OLE Treatment Period of Trial PS0015, 7 subjects developed urticaria (1.0%; EAIR: 0.4/100 subject-years), 2 subjects developed hypersensitivity (0.3% EAIR 0.1/100 subject years), and 2 subjects developed drug hypersensitivity (0.3% EAIR 0.1/100 subject years). Narratives for the 4 cases of hypersensitivity reactions had clear alternative explanations and were considered not related. One subject developed eosinophilia and systemic symptoms (DRESS) which was temporally related to nitrofurantoin administration (PS0015-(b) (6). All events related to hypersensitivity were mild to moderate in severity, none were SAEs, and none led to discontinuation.

During Trial PS0014, there was one TEAE of acute anaphylactic reaction which was temporally related to an insect bite in the BKZ 320 mg Q4W group. All adverse events related to hypersensitivity were mild to moderate in severity, and none led to discontinuation. Because these events were assessed as non-serious, limited details were documented. Six subjects had hypersensitivity TEAEs considered related by the investigator. However, all six subjects continued treatment with BKZ. Therefore, a role for BKZ in the hypersensitivity reaction is unlikely.

A total of 7 subjects (0.5%, EAIR 0.3) treated with bimekizumab (both regimens) developed TEAEs with PTs drug hypersensitivity and hypersensitivity. Of these, one subject developed a hypersensitivity reaction that was considered by the investigator to be related to BKZ as described below:

- 61 y/o White male (Subject PS0014-(b) (6) with noncontributory medical history developed a nonserious AE of hypersensitivity reaction (verbatim terms suspected allergic reaction of unknown reason [swelling of the lip and tongue]), 182 days after the

first dose and 14 days after the most recent dose of BKZ. The subject was treated with prednisolone and rupatadine for the AE. Action taken with BKZ was drug interrupted. The investigator considered the event of hypersensitivity reaction moderate in intensity and related to treatment with BKZ.

However, based on the timing of the reaction (swelling of lips and tongue began 14 days after the most recent dose), and that the subject was able to resume treatment with BKZ without recurrence of the AE, the Applicant considered the event of hypersensitivity reaction to be not related to treatment with BKZ. I concur with the Applicant that successful resumption of treatment makes a contributory role of BKZ to the hypersensitivity reaction unlikely.

Selected additional narratives (Information Request (IR) response SD 81 dated April 26, 2023)

- PS0014-(b) (6): 41 y/o WF with noncontributory PMHx completed Trial PS0013 and was enrolled in Trial PS0014 and assigned to BKZ 320 mg Q4W (first dose (b) (6)). On (b) (6), she experienced a nonserious AE of Drug hypersensitivity (verbatim term: allergic reaction to penicillin). The AE occurred 517 days after her first and 13 days after her most recent dose of BKZ. The investigator considered the event moderate in severity and not related to treatment with bimekizumab. She was treated with methylprednisolone aceponate, cetirizine, and prednisolone and the AE resolved after 5 days. She continued treatment with BKZ in the trial and was switched to BKZ 320 mg Q8W on (b) (6). Because the subject was able to resume treatment with BKZ without recurrence of the AE, I concur with the investigator's assessment that the AE was not related to treatment with BKZ.
- PS0014-(b) (6): 64 y/o WF with noncontributory PMHx completed Trial PS0013 and was enrolled in Trial PS0014 and assigned to BKZ 320 mg Q4W. She received her first dose of BKZ in Trial PS0014 on (b) (6) She began treatment with Suvardio (rosuvastatin) on (b) (6) On the same day after beginning treatment with rosuvastatin, she experienced a nonserious AE of Drug hypersensitivity (verbatim term: allergic drug reaction after Suvardio). The symptoms associated with the AE were not provided in the narrative. The AE occurred 568 days after her first and 8 days after the most recent dose of BKZ. Rosuvastatin was discontinued and she was treated with rupatadine. The event resolved after 4 days. The investigator considered the event mild in severity and not related to treatment with bimekizumab. She continued treatment with BKZ in the trial. Because of the timing of the AE relative to initiating rosuvastatin therapy, and that the subject was able to resume treatment with BKZ, I concur with the investigator's assessment that the AE was not related to treatment with BKZ.
- PS0014-(b) (6): 50 y/o WM with noncontributory PMHx completed Trial PS0013 and was enrolled in Trial PS0014 and assigned to BKZ 320 mg Q8W. He received his first dose of BKZ in Trial PS0014 on (b) (6) He experienced a nonserious AE of UTI on (b) (6) and was treated with Furaginum (not listed as an approved drug product in the US; per online search is a nitrofuran marketed for the treatment of UTI). On (b) (6) he experienced a nonserious AE of Drug hypersensitivity (verbatim

term: allergic skin reaction to Furaginum). The AE occurred 135 days after the first and 51 days after the most recent dose of BKZ. Treatment with BKZ had been interrupted because of nonserious AEs of Diarrhea and Abdominal pain. He was treated with clobetasol and cetirizine for the skin rash. The AE resolved after 18 days. The investigator considered the AE moderate in intensity and not related to treatment with BKZ. He resumed treatment with BKZ on (b) (6) and continued in the trial. Because the AE occurred during administration of Furaginum, and he was able to resume treatment with BKZ without recurrence of the AE, I concur with the investigator's assessment that the AE was not related to treatment with BKZ.

There is no additional information in the resubmission or IR response to support a safety concern for serious hypersensitivity reactions.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

The safety update provided with the BLA resubmission did not include any patient-reported outcome assessments. For information regarding COA analyses evaluated during review of the initial BLA, refer to the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) and as the DCOA consult review by Dr. Mira Patel dated April 18, 2021.

8.2.7. Safety Analyses by Demographic Subgroups

During the review of the initial BLA, the review team conducted additional analyses to evaluate the safety of bimekizumab in demographic subgroups. We conducted these analyses on adverse reactions (ARs) identified during the placebo-controlled periods of Trials PS0009 and PS0013 (Pool S1). Although imbalances in certain ARs between demographic subgroups were noted, because of the small subgroup sample sizes, the review team did not conclude that these differences are clinically meaningful. Refer to Section 8.2.7 of the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for tabular summaries of ARs by demographic subgroup during the placebo-controlled period (Pool S1).

8.2.8. Specific Safety Studies/Clinical Trials

The safety update provided with the resubmission was comprised of data from ongoing Trials PS0014 and PS0015. Refer to Section 8.2.8 of the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for summaries of additional clinical trials conducted during the development program for psoriasis.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Because they are large proteins, monoclonal antibodies are not expected to gain access to the nucleus and directly interact with DNA to promote carcinogenesis. Bimekizumab will be catabolized to peptides and constituent amino acids via normal metabolic pathways. However, for any product that produces immunosuppression, and which is indicated for chronic administration, there is a theoretical risk of increased malignancy. In patients with psoriasis, this risk may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of bimekizumab. Refer to Section 5.5.3 of the BLA 761151 Multi-disciplinary Review and Evaluation (dated May 11, 2022) for a discussion of the carcinogenicity risk from a Pharmacology /Toxicology perspective.

AEs of malignancy reported in the safety update were discussed in Section 8.2.5.5 of this review. The data available, to date, do not support the conclusion that chronic administration of bimekizumab is associated with an increased risk of carcinogenesis. However, the limited duration of observation during the drug development program is unlikely to allow detection of rare events with a long latency period such as malignancy. Therefore, postmarketing data are needed to evaluate the long-term risk of malignancy in patients with psoriasis receiving bimekizumab. Refer to Section 11 of this review for a summary of the required post-marketing studies.

Human Reproduction and Pregnancy

Female subjects of childbearing potential were required to have a negative pregnancy test at Screening and to use a highly effective method of birth control. Pregnancy testing was performed at appropriate intervals, and study drug was discontinued as per pre-specified withdrawal criteria if they became pregnant. Wherever possible, subjects who were pregnant were followed until delivery. The Applicant considered the following pregnancy outcomes to be SAEs:

- Miscarriage
- Elective abortion when medically indicated (e.g., when pregnancy is endangering life or health of woman or when fetus will be born with severe abnormalities)
- Unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used)
- Ectopic pregnancy
- Fetal demise
- Any congenital anomaly/birth defect of the baby.

In the BLA resubmission, a total of 20 pregnancy exposure cases were reported to the UCB Global Safety Database as of the Safety Update clinical cutoff date of May 12, 2022: 15 under the indication of psoriasis (PSO), 4 under the indication of psoriatic arthritis (PsA), and 1 under the indication of axial spondyloarthritis (axSpA). These cases include 11 pregnancies evaluated during review of the initial BLA. The reported outcomes of the pregnancies included:

- 8 normal livebirths (all healthy, although 1 was born preterm at 33 wks 1 day)
- 1 neonatal death (pregnancy complicated by sequalae following placement of a urinary stent due to nephrolithiasis, which resulted in septic shock, placental abruption, Hemolysis, Elevated Liver enzymes and Low Platelets (HELLP) syndrome and preterm birth by emergency C-section at 25wks 5d)
- 2 spontaneous abortions (both 1st trimester)
- 2 induced abortions (both 1st trimester; reason not provided)
- 3 ongoing
- 4 lost to follow-up

No congenital anomalies were reported, and no major maternal complications associated with bimekizumab-bkzx. The Applicant concluded, "no safety signals emerged from the very limited number of pregnancies reported throughout the clinical development program."

The review team evaluated pregnancy outcomes in conjunction with consultants from the Division of Pediatric and Maternal Health (DPMH)/ Maternal Health Team. Per DPMH review, "Available data from the 20 reported cases of inadvertent pregnancy exposure during the clinical development program (of which only 13 pregnancy outcomes are known and in which Bimzelx was immediately discontinued) are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes." Refer to reviews by Kristie Baisden, D.O dated February 3, 2021 (initial BLA submission) and April 26, 2023 (BLA resubmission).

The review also noted that "there are no available pregnancy pharmacokinetic (PK) data for bimekizumab-bkzx to inform evidence-based dosing recommendations during pregnancy…(and) there also no available human data regarding the amount of bimekizumab-bkzx placental transfer, bimekizumab-bkzx levels at birth in infants exposed in utero, or the duration of persistence of bimekizumab-bkzx in infant serum after delivery."

DPMH recommended Postmarketing Requirements (PMRs) for pregnancy registry studies, a lactation study, and a pregnancy PK and placental transfer study (to include PK assessments of infants exposed to bimekizumab in utero). Refer to Section 13 (Postmarketing Requirements and Commitments) of this review for more details regarding the PMRs and proposed timelines.

DDD agreed with the proposed PMRs for the pregnancy registry studies and the lactation study. After multiple discussions, the team determined that a placental transfer study would not be meaningful without an understanding of the effects of that exposure to bimekizumab in the

neonate and developing infant. In a consult memo dated July 3, 2023, Dr. Ndidi Nwokorie of the DPMH Pediatrics team concurred with DDD's decision. Dr. Nwokorie further recommended that prior to conducting such a study, "there should be consensus on the appropriate pharmacodynamic measures to be included…that that would best assess the impact of persistently detectable bimekizumab concentrations in the newborn on the child's developing immune system through the first year of life."

The DPMH review conveyed the following recommendations for labeling of Pregnancy and Lactation sections of labeling (new text in underline, deleted text in ~~strikethrough~~):

> DPMH Proposed Bimzelx (bimekizumab-bkzx) Pregnancy and Lactation Labeling FULL PRESCRIBING INFORMATION
> 8.1 Pregnancy
> Pregnancy Exposure Registry
> There ~~will be~~ is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to Bimzelx during pregnancy. (b) (4) -For more information, healthcare providers or patients can contact the Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases Study at 1-877-311-8972 or visit http://mothertobaby.org/pregnancy-studies/.
>
> Risk Summary
> Available data from case reports on Bimzelx use in pregnant women are insufficient to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Transport of human IgG antibody (b) (4) across the placenta increases as pregnancy progresses and peaks during the third trimester; therefore, Bimzelx may be transmitted from the mother to the developing fetus *(see Clinical Considerations).* In an enhanced pre- and postnatal development study, no adverse developmental effects were observed in infants born to pregnant monkeys after subcutaneous administration of bimekizumab-bkzx during the period of organogenesis through parturition at doses up to 38 times the maximum recommended human dose (MRHD) *(see Data).*
>
> All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The (b) (4) background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively.
>
> Clinical Considerations
> *Fetal/Neonatal Adverse Reactions*

Because bimekizumab-bkzx may interfere with immune response to infections, risks and benefits should be considered prior to administering live vaccines to infants exposed to Bimzelx in utero. There are no data regarding infant serum levels of bimekizumab-bkzx at birth and the duration of persistence of bimekizumab-bkzx in infant serum after birth. Although a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown, a minimum of 4 months after birth may be considered because of the half-life of the product.

Data

Animal Data

An enhanced pre- and postnatal developmental toxicity study was conducted in cynomolgus monkeys. Pregnant cynomolgus monkeys were administered subcutaneous doses of bimekizumab-bkzx of 20 or 50 mg/kg/week from gestation day 20 to parturition and the cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No maternal toxicity was noted in this study. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. The no observed adverse effect level (NOAEL) for both maternal and developmental toxicity was identified as 50 mg/kg/week (38 times the MRHD, based on mg/kg comparison of 1.33 mg/kg/week administered as a 320 mg dose to a 60 kg individual once every 4 weeks).

8.2 Lactation

Risk Summary

There are no data on the presence of bimekizumab-bkzx in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Endogenous IgG and monoclonal antibodies are transferred in human milk (b) (4) . The effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to bimekizumab-bkzx are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for Bimzelx and any potential adverse effects on the breastfed infant from Bimzelx or from the underlying maternal condition.

17 Patient Counseling Information

Pregnancy

Advise patients that there is a (b) (4) pregnancy registry that monitors pregnancy outcomes in women exposed to Bimzelx during pregnancy (b) (4)

[see Use in Specific Populations (8.1)].

Pediatrics and Assessment of Effects on Growth

The Applicant did not include new pediatric information in the resubmission. Refer to Section 8.2.9 of the Multi-disciplinary Review and Evaluation of BLA 761151 (dated May 11, 2022) for a discussion of the Agreed initial Pediatric Study Plan (iPSP) and the Pediatric Assessments presented to the Pediatric Review Committee (PeRC) during review of the initial BLA. Refer to Section 11 (Postmarketing Requirements and Commitments) of this review for the pediatric study requirements under PREA.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The safety update provided with the resubmission included no new information regarding overdose, drug abuse potential, withdrawal, or rebound. Refer to Section 8.2.9 of the Multi-disciplinary Review and Evaluation of BLA 761151 (dated May 11, 2022) for a discussion of the evaluation of overdose, drug abuse potential, withdrawal, and rebound conducted by the review team during review of the initial BLA.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

According to the Applicant, bimekizumab is currently marketed in 38 countries for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy. The Applicant stated that the estimated cumulative postmarketing exposure across these jurisdictions exceeds 7200 patients, 4840 patient-years as of February 19, 2023. As such, patients in the postmarketing safety database are still relatively early in their treatment courses, with the longest-treated subjects having less than 2 years of exposure. In addition, the overall reported exposure in the postmarketing safety database is less than the 5830 subject-years of exposure during the development program for psoriasis.

In the safety update provided with the BLA resubmission, the Applicant stated that in their post-marketing safety database, “No efficacy and/or safety related findings have been identified and the benefit-risk balance of bimekizumab for the moderate to severe plaque PSO indication remains favorable.” In addition, in the most recent development safety update report covering the period from October 24, 2021, to August 19, 2022 (IND 128707, SDN 427, October 18, 2022), the Applicant stated, “During the reporting period of this DSUR, no key safety findings from marketing experience became available for bimekizumab.” Specifically in reference to reports of psychiatric adverse events, the Applicant stated that there were no reports of completed suicides or suicide attempts in their post-marketing safety database (Response to information request submitted April 25, 2023). However, because bimekizumab has been marketed for a limited time in any jurisdiction (first marketing approval in August 2021) and many subjects are early in their treatment courses, it may be premature to expect identification or confirmation of a safety signal.

Expectations on Safety in the Postmarket Setting

In the post market setting, the prescribers are expected to be dermatologists. Although, there is increasing awareness of the elevated risk of depression and suicidal ideation in patients with psoriasis, screening for mental health issues is not the standard of care. Dermatologists lack the training to conduct effective psychiatric screening/evaluation and interpret the results.
In a survey of dermatology residents (Streight, 2020), 64% of responders stated that they received no education on depression screening. There is an important knowledge and practice gap around screening for and discussing depression and SI/B with patients. In a survey of dermatologists to assess the performance of SI/B screening in patients with psoriasis (Liang, 2019), nearly 57% of physicians agreed or strongly agreed that patients with psoriasis require regular monitoring for depression and SI/B. However, only 27% stated that they asked about mood in most of their encounters and only 7% reported using a depression screening tool.

Postmarketing data has inherent limitations which include under-reporting, challenges in identifying rare events (1/1,000) and difficulties in quantifying risk. In general, death by suicide and suicide attempt are underreported. Psychological distress experienced by patients with psoriasis often goes unrecognized by dermatologists in a busy practice environment. Conclusions based on incomplete postmarketing data may be misleading. Because dermatologists recognize that their patients with psoriasis are at greater risk of depression and suicidality, it is unlikely that they will attribute SI/B to drug exposure in a postmarket setting, particularly for patients with a known psychiatric history.

The safety profile of the proposed product in some special populations (pregnant and lactating females and the pediatric population age ≥ 6 years) is not well characterized. Additional data is also needed to explore potential adverse events associated with chronic immunosuppression that have long latency periods such as malignancy. Refer to Section 11 of this review for the postmarketing requirements.

8.2.11. Integrated Assessment of Safety

The safety profile of bimekizumab was further characterized by the safety data provided in the Safety Update included with the BLA resubmission. The overall safety database consisted of 2480 subjects enrolled in the phase 2 and phase 3 trials (Pool S2-3b). The Safety Update included data from 691 new subjects from Trial PS0015, for whom safety data was not available during review of the initial BLA. A total of 558 subjects completed 144 weeks of treatment in Trial PS0015. The Safety Update also provided additional safety data for 1353 subjects in Trial PS0014. Of these subjects, a total of 1108 had completed ≥96 weeks, 473 had completed ≥112 weeks, and 122 had completed ≥128 weeks of treatment in Trial PS0014. The review team conducted safety analyses for Trials PS0015 and PS0014 separately due to the differences in the study designs. The review team evaluated rare TEAEs using Pool S2-3b.

Our review of the safety data provided in the resubmission identified a potential new safety signal for suicidal ideation and behavior (SI/B). New safety data included a completed suicide in a subject with no prior psychiatric history and three cases of suicide attempt associated with the use of bimekizumab. There were five and nine cases of serious neuropsychiatric adverse events (AEs) in subjects exposed to bimekizumab in Trials PS0015 and PS0014, respectively. These new data prompted a re-evaluation of all relevant data by the Division of Psychiatry. A re-review of eC-SSRS data from the controlled period of Trials PS0008, PS0009, and PS0013, found nearly threefold more positive responses in the pooled bimekizumab group compared to a pooled placebo group (most of the positive responses were passive wish to be dead, 1.7% versus 0.6%, respectively). Of the 17 positive responses in bimekizumab-treated subjects, only 4 were in subjects with a previous psychiatric history.

Of note, the study population was not representative of the real-world population (target population) of expected users of this product as subjects with certain risk factors for SI/B were excluded from trials. These risk factors included active suicidal ideation or suicidal ideation within the month prior to Screening, history of suicide attempt within the past 5 years prior to screening, and moderately severe major depression or severe major depression indicated by a score of ≥15 using the screening Patient Health Questionnaire-9 (PHQ-9). Furthermore, during the conduct of clinical trials, subjects who developed an elevated risk of SI/B based on Patient Health Questionnaire-9 (PHQ-9) ≥ 15 or positive scores on the eC-SSRS were discontinued from treatment with bimekizumab. This safety monitoring likely reduced the number of attempted or completed suicides in the clinical trials.

Taken together, the completed suicide, suicide attempts, and positive eC-SSRS responses are consistent with a possible increased risk for SI/B with bimekizumab use. The risk of SI/B should be adequately described in product labeling (Warning and Precautions, Section 6, Section 17 and the Medication Guide) to convey the importance of these potentially fatal adverse events to healthcare providers and patients.

The Applicant reported a total of 17 additional deaths in the Safety Update provided with the BLA resubmission. A total of 8 fatalities were adjudicated MACE. Narratives for these subjects are provided in Section 8.2.5.6 of this review. These were reviewed in conjunction with consultants from the Division of Cardiology and Nephrology (DCN), who concluded that any relationship of these events to treatment with bimekizumab was doubtful. A total of 4 fatalities were SARS-CoV-2 infections. The deaths resulting from SARS-CoV-2 infection occurred in subjects with risk factors for severe coronavirus infection and who were unvaccinated or inadequately vaccinated. However, treatment with biologic immunomodulators, including bimekizumab, are known to increase the risk of infection due to immunosuppression. As such, a contributory role of bimekizumab in these events cannot be excluded. Additional fatal events included hypovolemic shock from GI bleeding, brain neoplasm, road traffic accident (pedestrian hit by car), hepatic pain (thought to be secondary to metastatic pancreatic cancer), and suicide.

During the Initial Treatment Period (Weeks 0-16) of Trial PS0015, serious TEAEs (SAEs) were reported in 10/373 (2.7%) of subjects treated with bimekizumab 320 mg Q4W and 6/370 (1.6%) of subjects treated with secukinumab. During the Maintenance Treatment Period (Weeks 16-48) of Trial PS0015, SAEs were reported in 6/147 (4.1%) of subjects treated with bimekizumab 320 mg Q4W, 10/215 (4.7%) of subjects treated with bimekizumab 320 mg Q8W, and 19/254 (5.4%) of subjects treated with secukinumab. During the OLE Period (Weeks 48-144) of Trial PS0015, 10% (64/654) of subjects treated with either dosage of bimekizumab developed SAEs.

In OLE Trial PS0014, 11% of subjects who received bimekizumab developed an SAE. SAEs are discussed in more detail in Section 8.2.4 of this review.

The most common adverse reactions (ARs) identified during review of data from the placebo-controlled periods of Trials PS0009 and PS0013 during review of the initial BLA were upper respiratory infections (15%), oral candidiasis (9%), headache (3%), injection site reactions (3%), Tinea infections (3%), gastroenteritis (2%), Herpes simplex infections (1%), acne (1%), folliculitis (1%), other Candida infections (1%), and fatigue (1%). These ARs are recommended for inclusion in Section 6 (Adverse Reactions) of labeling for bimekizumab and are discussed in more detail in Section 8.2.4 of the initial Unireview dated May 11, 2022. Overall, based on the EAIRs reported in the initial BLA compared to the resubmission, the frequency of ARs did not increase with increased duration of treatment with bimekizumab.

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. Subjects with a history of IBD could be enrolled in the clinical trials as long as they had no active symptomatic disease at Screening or Baseline. The safety update provided with the resubmission included 7 new cases in subjects treated with bimekizumab which were adjudicated as "definite IBD" by the independent inflammatory bowel disease adjudication committee (IBD-CAC). These cases were reviewed in conjunction with a consultant from the Division of Gastroenterology (DG). The additional cases of IBD included three cases of UC, three cases of Crohn's Disease (CD), and one case of IBD unclassified. Based on the clinical narratives and summaries provided by the Applicant, the DG reviewer concluded that the 7 cases that were adjudicated as "definite IBD" appear reasonably likely to represent IBD. The review team recommends inclusion of IBD in Sections 5 and 6 of product labeling.

During review of the initial BLA, the review team identified potential cases of drug-induced liver injury (DILI) associated with treatment with bimekizumab. In the Safety Update provided with the resubmission, the review team identified three new subjects with possible DILI. These cases were reviewed by consultants from the Drug-Induced Liver Injury (DILI) team from the Division of Hepatology and Nutrition. The consultants concluded that none of the new cases were probable DILI due to bimekizumab. Based on the findings during the initial BLA review, labeling recommendations will include testing of liver enzymes, alkaline phosphatase, and bilirubin prior to initiating treatment with bimekizumab in Section 2.1 and related language for Section 5 (W&P) and Section 6 (AR).

Based on the EAIRs in the initial BLA compared to the Safety Update provided in the resubmission, the risk for infections (including serious and opportunistic infections), and malignancies did not increase with increased duration of treatment with bimekizumab. Infections and malignancies are discussed in more detail in Sections 8.2.5.4 and 8.2.5.5 of this review, respectively. The review team continues to recommend inclusion of infections in Sections 5 and 6 of product labeling.

In the resubmission, the Applicant reported a total of 20 pregnancy exposures. The pregnancy outcomes, as well as the effect of bimekizumab on human reproduction and pregnancy is discussed in further detail in Section 8.2.9 of this review. Because the available data are insufficient to evaluate the risk of major birth defects, miscarriage, or adverse fetal or maternal outcomes associated with treatment with bimekizumab, we will require post-approval prospective and retrospective studies assessing maternal, fetal, and neonatal outcomes of women exposed to bimekizumab during pregnancy compared to an unexposed control population. Refer to Section 11 (Postmarketing Requirements and Commitments) for further details.

The safety data provided in the resubmission included evidence of potential increased risk of SI/B with the use of bimekizumab. As described above, strategies to mitigate this risk will include product labeling including a medication guide and other patient/ provider educational measures. Additional postmarketing risk management activities will include assessment of the risk of lymphoma using the ARIA system. A long-term observational study will evaluate the long-term risk of other potential adverse events associated with bimekizumab such as malignancy, inflammatory bowel disease, and elevated liver enzymes/DILI. Data will be obtained in the pediatric population and pregnant and lactating women. The maternal, fetal, and infant outcomes of women exposed to bimekizumab during pregnancy will be evaluated by a registry based observational exposure cohort study and a study with another design.

8.3. Statistical Issues

The resubmission included no new statistical data. Therefore, this section is not applicable.

8.4. Conclusions and Recommendations

During the initial review cycle for BLA 761151, the Applicant provided substantial evidence of the effectiveness of bimekizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. To support the efficacy of their product in the target population, the Applicant submitted data from two adequate and well-controlled trials (PS0009 and PS0013).

Most of the safety data confirmed the safety profile determined by review of the safety data in the initial submission. However, the resubmission included a case of completed suicide and three new cases of suicide attempt associated with the use of bimekizumab. The new data

prompted a re-evaluation of all relevant data by the review team which included psychiatry consultants. Following a thorough re-analysis of previously submitted suicidal ideation and behavior (SI/B) data and new SI/B data, the review team considers that this new safety information would require adequate labeling to communicate this potential risk to patients and providers to ensure the safe use of the product.

Based on our review, the review team concludes that the benefit-risk of bimekizumab is favorable in the proposed population with appropriate labeling and recommend approval of this application.

9 Pediatrics

The Applicant planned to evaluate the efficacy, safety, and PK of bimekizumab in the pediatric population ages 6 to < 18 years with deferred studies under Pediatric Research Equity Act (PREA). A discussion of the pediatric development program and required pediatric assessments is included in the Multi-disciplinary Review and Evaluation of BLA 761151 (dated May 11, 2022) under the following sections:

- Section 8.2.9 *Pediatrics and Assessment of Effects on Growth* for a discussion regarding the Pediatric Study Plan.
- Section 13 *Postmarketing Requirements and Commitments* of this review for the deferred pediatric studies, which are required under PREA (21 CFR 314.55(b) and 601.27(b)).

10 Labeling Recommendations

10.1. Prescription Drug Labeling

With the resubmission, the Applicant provided proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling. The Division of Medication Error Prevention and Analysis (DMEPA) team reviewed the proposed BIMZELX PI, MG, IFU, container labels, and carton labeling for areas of vulnerability that may lead to medication errors (Review by Corwin D. Howard, PharmD, RPh dated March 28, 2023). The review provided recommendations regarding potential improvements in the PI and carton and container that may promote safe use from a medication error perspective. Office of Prescription Drug Promotion (OPDP) reviewed the PI, MG/IFU, container labels, and carton labeling. OPDP had no comments regarding the proposed container labels, and carton labeling but provided comments on the PI (Review by David Foss dated September 25, 2023.) Labeling negotiations are currently ongoing.

The following table provides the location of the labeling discussion for each section. Because the resubmission included only safety data and quality information, many sections of labeling were not discussed during this review cycle.

Table 18: Location of the Labeling Discussion

Summary of Significant High Level Labeling Changes	
Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	N/A
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	Section 8.2
6 ADVERSE REACTIONS	Section 8.2
7 DRUG INTERACTIONS	N/A
8 USE IN SPECIFIC POPULATIONS	Section 8.2
12 CLINICAL PHARMACOLOGY	N/A
13 NONCLINICAL TOXICOLOGY	N/A
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling

Source: Reviewer's Table

Refer to the Multi-disciplinary Review and Evaluation for BLA 761151 (dated May 11, 2022) for information regarding labeling discussions that occurred during the review of the original submission.

10.2 Patient labeling

The Applicant submitted a proposed Medication Guide (MG) and Instructions for Use (IFU) for BIMZELX (bimekizumab). The Division of Medical Policy Programs (DMPP) and OPDP teams reviewed the MG and IFU and provided comments. The final labeling will reflect their recommendations. (Review by Susan Redwood, MPH, BSN, RN and David Foss, PharmD dated September 29, 2023).

11 Postmarketing Requirements and Commitment

During the initial review cycle, the Agency and Applicant agreed on the clinical postmarketing requirements (PMRs) and milestone dates that would be issued with the product approval. With the resubmission, the Applicant proposed modified milestone dates for the agreed upon PRMs. The final PMR language and revised milestone dates are as follows:

<u>Postmarketing Requirements under 505(o)</u>

Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to bimekizumab during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol submission: 12/2023
Final Protocol Submission: 08/2024
Interim Report: 01/2030
Study Completion: 06/2034
Final Report Submission: 06/2035

Conduct an additional pregnancy study that uses a different design from the pregnancy registry. For example, a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, small for gestational age, and preterm birth in women exposed to bimekizumab during pregnancy compared to an unexposed control population.

Draft Protocol submission: 12/2023
Final Protocol Submission: 12/2024
Interim Report: 12/2028
Study Completion: 12/2034
Final Report Submission: 12/2035

Perform a lactation study (milk only) in lactating women who have received therapeutic doses of bimekizumab to assess concentrations of bimekizumab in breastmilk using a validated assay and to assess the effects on the breastfed infant. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

Draft Protocol submission: 11/2023
Final Protocol Submission: 11/2024
Study Completion: 05/2027
Final Report Submission: 11/2028

Conduct a prospective observational study to assess the long-term safety of bimekizumab treatment in U.S. adult patients with moderate to severe plaque psoriasis. Fully ascertain and centrally verify malignancy (including lymphoma), opportunistic infections, reactivation of Hepatitis B, tuberculosis, and serious infections. Other outcomes include hypersensitivity, gastrointestinal events (including inflammatory bowel disease, elevated liver enzymes/drug-

induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), and hematologic events.

For each adverse-event outcome separately, compare incidence in bimekizumab-treated patients against reference rates internally derived from analyses conducted in patients treated with other chronic systemic treatments for moderate-to-severe plaque psoriasis. Regardless of treatment discontinuation or switch to a different treatment for plaque psoriasis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events in representative U.S. patients who start treatment with bimekizumab for plaque psoriasis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with bimekizumab. Enroll patients over a 4-year period and plan to follow for a minimum of 8 years from time of enrollment.

Draft Protocol submission: 12/2023
Final Protocol Submission: 11/2024
Study Completion: 03/2037
Final Report Submission: 03/2038

REQUIRED PEDIATRIC ASSESSMENTS: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

Bimekizumab triggers the Pediatric Research Equity Act (PREA) as a new active ingredient. The following studies in the pediatric population age 6 years to less than 18 years of age were included in the Agreed iPSP and will be deferred:

Conduct a multicenter, open-label trial to assess the pharmacokinetics and safety of bimekizumab in adolescents 12 to <18 years of age with moderate to severe plaque psoriasis.[5]

Final Protocol Submission: 12/2021-ongoing
Study Completion: 05/2025
Final Report Submission: 12/2025

Conduct a multicenter, randomized, parallel-group, blinded active-controlled trial to assess the safety, and pharmacokinetics of bimekizumab in pediatric subjects 6 to <18 years old with moderate to severe plaque psoriasis.[4]

Draft Protocol submission: 06/2023
Final Protocol Submission: 06/2024

[4] No efficacy assessment was included because the efficacy in the pediatric population may be extrapolated from the efficacy in the adult population.

Study Completion:	01/2031
Final Report Submission:	08/2031

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. We are deferring submission of pediatric studies for ages 6 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. Refer to Section 8.2.9 of this review for a more detailed discussion of the waiver and deferral of pediatric studies.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the identification of the potential safety signal of SI/B and the need for an adequate risk mitigation strategy, the review team sought the advice of the REMS Oversight Committee (ROC). The review team, which included representatives from the Division of Risk Management (DRM), met with the ROC on June 2, 2023, and June 13, 2023.

Because there is no identifiable risk factor to predict depression or SI/B, this adverse event is not preventable. However, SI/B is treatable if identified. Therefore, the team determined that the focus of risk mitigation efforts will be on patient/provider education. In addition, in view of the uncertainties surrounding the potential signal of SI/B, the review team concluded that the risk of SI/B will be adequately communicated though labeling.

13 Associate Director for Therapeutic Review Comments

I concur with the review team's recommendation to approve BLA 761151 for bimekizumab for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

This resubmission is a complete response to the deficiencies outlined in the Complete Response Letter (dated May 12, 2022) during the initial review cycle because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility by the Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing. Based on data submitted, the Office of Pharmaceutical Quality concluded that the data are adequate to support the conclusion that the manufacture of bimekizumab is well-controlled and leads to a product that is pure and potent and recommended that this product be approved for human use under conditions specified in the package insert.

However, in this resubmission, the Applicant provided new safety data from Trial PS0014 (an open- label extension trial) and Trial PS0015 (a double-blind, active comparator-controlled trial). All trials for bimekizumab in psoriasis development program included the same study population define by inclusion (e.g., disease severity) and exclusion criteria.

New safety data included a report of completed suicide in a subject with no prior psychiatric history and three cases of suicide attempt (two of these subjects had a history of prior suicide attempts) associated with the use of bimekizumab. There were five and nine cases of serious neuropsychiatric adverse events (AEs) in subjects exposed to bimekizumab in trials PS0015 and PS0014, respectively. The new data prompted a re-evaluation of all relevant data.

Suicidal ideation and behavior were prospectively monitored using the Columbia Suicide Severity Rating Scale (C-SSRS) in clinical trials of psoriasis. A re-review of a pool of subjects from the initial treatment period of the placebo/active-controlled phase 3 trials, PS0008, PS0009, and PS0013, indicated 18 positive responses on the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) (most reporting a passive wish to be dead without active suicidal ideation). Of these, 17 positive responses were in bimekizumab group (1.7%) while only 1 was in placebo group (0.6%). Of the 17 positive responses in subjects treated with bimekizumab, only 4 were in subjects with a previous psychiatric history. Pooled analysis of eC-SSRS data from two 16-week, placebo-controlled trials indicated that 12/670 (1.8%) subjects treated with bimekizumab and 1/169 (0.6%) subject on placebo reported passive suicidal ideation with an estimated relative risk of 3.0 (95% confidence interval: 0.39, 22.74). Subjects without prior history of SI/B treated with bimekizumab also reported a higher rate of new-onset suicidal ideation on the eC-SSRS than subjects treated with placebo (1.3% vs. 0.6%). In a pool of subjects from the open-label maintenance period of the phase 3 trials, PS0008, PS0009, and PS0013, there were 16 positive responses on the eC-SSRS (most reporting a passive wish to be dead without active suicidal ideation). Of the 16 positive responses in bimekizumab-treated subjects, only 2 were in subjects with a previous psychiatric history.

Re-analysis of previously submitted SI/B data and new SI/B data, in the context of the completed suicide, three suicide attempts and the eC-SSRS differences, are consistent with a signal for an association between bimekizumab use and SI/B.

This new safety information should be adequately described in product labeling to convey the importance of this potentially fatal AE to the healthcare provider and patient. The potential risk for SI/B should be described in Section Warnings and Precautions [§ 201.57(c)(6)], and 6 and 17 of the prescribing information and MedGuide. I agree with recommendations for labeling from the clinical review team (Rerefer to Section 8.2.5.1.)

During the initial review cycle for BLA 761151, the Applicant provided substantial evidence of the effectiveness of bimekizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and met the

evidentiary standard required by 21 CFR 314.126(a)(b) to support approval. Refer to Multi-disciplinary Review and Evaluation for BLA 761151 dated May 11, 2022. Except for new safety signal of SI/B, the safety data in the resubmission supported the conclusions regarding safety from the initial submission.

Approval of bimekizumab will include postmarketing requirements for assessment of a long-term safety of bimekizumab treatment for adult patients with moderate to severe plaque psoriasis by conduct a prospective observational study. Additional postmarketing study requirements will focus on the collection of safety data in populations that have not yet been studied (e.g., pregnant and lactating females, and pediatric subjects age ≥ 12 years).

14 Office Director (or designated signatory authority) Comments

I concur with the review team's assessment and recommendation to approve BLA 761151 for bimekizumab-bkzx injection for the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy.

The original BLA submission received a Complete Response action on May 12, 2022, due to manufacturing inspection deficiencies. The current re-submission is a complete response to the deficiencies outlined in the Complete Response Letter. Based on data submitted, the Office of Pharmaceutical Quality concluded that the data are adequate to support the conclusion that the manufacture of bimekizumab is well-controlled and leads to a product that is pure and potent and recommended that this product be approved for human use under conditions specified in the package insert.

However, during the review of the re-submission, which included new safety information from Trial PS0014 (an open- label extension trial) and Trial PS0015 (a double-blind, active comparator-controlled trial), the review team has identified a potential signal for suicidal ideation and behavior (SI/B) associated with bimekizumab use based on positive eC-SSRS responses, one completed suicide and three suicide attempts, as detailed in the team's review above. The team has also acknowledged that there are uncertainties surrounding this potential signal. Accordingly, the team has concluded, and I agree, that the potential risk can be adequately communicated to prescribers and patients through labeling to include a Warning and Precaution on Suicidal Ideation and Behavior, description of the relevant data and information in Sections 6, Specific Adverse Reactions, Section 17 Patient Counseling, and through a Medication Guide. The newly identified potential safety signal required additional time for review and consideration which resulted in missing the PDUFA goal date of May 21, 2023.

During the initial review cycle for BLA 761151, the team has also concluded, and I agree, that the Applicant has provided substantial evidence of the effectiveness of bimekizumab for the

treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

The overall benefit-risk of bimekizumab is favorable for the proposed indication and the regulatory action for BLA 761151 is Approval with agreed upon labeling.

Postmarketing requirements (PMRs) will include:

- A prospective observational study to assess the long-term safety of bimekizumab treatment in U.S. adult patients with moderate to severe plaque psoriasis,
- Pregnancy registry, an additional pregnancy study that uses a different design and lactation studies,
- PREA-required pediatric assessment studies.

15 Appendices

15.1. References

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15.2. Financial Disclosure

The Applicant provided substantial evidence of efficacy which was demonstrated during the phase 3 trials submitted and reviewed under the original BLA. For a discussion of financial disclosures from clinical investigators and sub-investigators who participated in covered clinical studies during the review of the initial BLA submission, refer to the BLA 761151 Multi-disciplinary Review and Evaluation dated May 11, 2022.

The data from Trials PS0014 and PS0015 provided in the safety update in the BLA resubmission do not meet the definition of "covered clinical studies" as defined in 21 CFR 54.2(e). As such, this section is not applicable.

15.3. Additional Clinical Analyses

Overall Exposure in Trial PS0014

The overall exposure of subjects to bimekizumab in subjects enrolled in Trial PS0014 is presented in the tables below. Separate tables are provided for exposure during Trial PS0014 alone and cumulative exposure from the phase 3 feeder trials PS0008, PS0009, and PS0013 plus PS0014.

Table 19: Exposure to Bimekizumab in Subjects Enrolled in PS0014 Beginning at Week 0 of PS0014

	Number of subjects Exposed to Bimekizumab in Trial PS0014 beginning at Week 0 of PS0014 through end of Treatment in Trial PS0014
Trial Medication Duration (Weeks)	
n	1287
Mean (SD)	102.26 (26.637)
Median	104.14

Min, Max	0.1, 143.6
Duration of exposure beginning at Week 0 of Trial PS0014, n (%)	
>0 weeks	1287 (100)
≥16 weeks	1247 (96.9)
≥32 weeks	1227 (95.3)
≥48 weeks	1197 (93.0)
≥64 weeks	1178 (91.5)
≥80 weeks	1160 (90.1)
≥96 weeks	1108 (86.1)
≥112 weeks	473 (36.8)
≥128 weeks	122 (9.5)
≥144 weeks	0
≥160 weeks	0
≥176 weeks	0

BKZ=bimekizumab; Max=maximum; Min=minimum; SD=standard deviation. Note: The clinical cutoff date is 23 Oct 2021 (PS0014).
Source: Applicant's Response to Information request submitted April 25, 2023.

Table 20: Cumulative Exposure to Bimekizumab during Phase 3 Feeder Trials and PS0014

	Number of subjects Exposed to Bimekizumab in Trial PS0014 from Week 0 of Trials PS0008, PS0009, and PS0013 through end of Treatment in Trial PS0014
Trial Medication Duration (Weeks)	
n	1287
Mean (SD)	145.42 (30.166)
Median	156.14
Min, Max	12.4, 189.4
Duration of exposure, n (%)	
>0 weeks	1287 (100)
≥16 weeks	1286 (>99.9)
≥32 weeks	1281 (99.5)
≥48 weeks	1266 (98.4)
≥64 weeks	1246 (96.8)
≥80 weeks	1219 (94.7)

≥96 weeks	1194 (92.8)
≥112 weeks	1118 (86.9)
≥128 weeks	1010 (78.5)
≥144 weeks	850 (66.0)
≥160 weeks	561 (43.6)
≥176 weeks	67 (5.2)
≥200 weeks	0

BKZ=bimekizumab; Max=maximum; Min=minimum; SD=standard deviation. Note: The clinical cutoff date is 23 Oct 2021 (PS0014).
Source: Applicant's Response to Information request submitted April 25, 2023.

Summary of Serious TEAEs Trial PS0014

Table 21: Summary of Serious TEAEs-Trial PS0014

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Blood and lymphatic system disorders	**2 (0.2)**	**1 (0.1)**	**3 (0.2)**
Hemorrhagic anemia	0 (0.0)	1 (0.1)	1 (0.1)
Hemorrhagic diathesis	1 (0.1)	0 (0.0)	1 (0.1)
Microcytic anemia	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac disorders	**10 (1.0)**	**11 (0.9)**	**20 (1.5)**
Acute coronary syndrome	0 (0.0)	2 (0.2)	2 (0.1)
Acute myocardial infarction	1 (0.1)	1 (0.1)	2 (0.1)
Angina pectoris	3 (0.3)	2 (0.2)	4 (0.3)
Atrial fibrillation	1 (0.1)	1 (0.1)	2 (0.1)
Cardiac arrest	2 (0.2)	1 (0.1)	3 (0.2)
Cardiac failure congestive	1 (0.1)	0 (0.0)	1 (0.1)
Cardiopulmonary failure	1 (0.1)	0 (0.0)	1 (0.1)
Hypertensive cardiomyopathy	0 (0.0)	1 (0.1)	1 (0.1)
Myocardial infarction	1 (0.1)	1 (0.1)	2 (0.1)
Myocardial ischemia	0 (0.0)	1 (0.1)	1 (0.1)
Systolic dysfunction	1 (0.1)	0 (0.0)	1 (0.1)
Ventricular tachycardia	1 (0.1)	0 (0.0)	1 (0.1)
Wolff-Parkinson-white syndrome	0 (0.0)	1 (0.1)	1 (0.1)
Endocrine disorders	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**
Hyperparathyroidism primary	0 (0.0)	1 (0.1)	1 (0.1)
Eye disorders	**1 (0.1)**	**3 (0.2)**	**4 (0.3)**
Cataract	1 (0.1)	2 (0.2)	3 (0.2)
Retinal detachment	0 (0.0)	1 (0.1)	1 (0.1)
Gastrointestinal disorders	**5 (0.5)**	**10 (0.8)**	**15 (1.1)**
Anal prolapse	0 (0.0)	1 (0.1)	1 (0.1)
Crohn's disease	1 (0.1)	1 (0.1)	2 (0.1)
Diarrhoea	1 (0.1)	0 (0.0)	1 (0.1)
Diverticular perforation	0 (0.0)	2 (0.2)	2 (0.1)

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Diverticulum intestinal	0 (0.0)	1 (0.1)	1 (0.1)
Diverticulum intestinal hemorrhagic	1 (0.1)	1 (0.1)	2 (0.1)
Duodenal ulcer	0 (0.0)	1 (0.1)	1 (0.1)
Enteritis	1 (0.1)	0 (0.0)	1 (0.1)
Gastroesophageal reflux disease	0 (0.0)	1 (0.1)	1 (0.1)
Hemorrhoids	0 (0.0)	1 (0.1)	1 (0.1)
Inguinal hernia	0 (0.0)	1 (0.1)	1 (0.1)
Large intestine polyp	0 (0.0)	1 (0.1)	1 (0.1)
Nausea	1 (0.1)	0 (0.0)	1 (0.1)
Esophagitis	1 (0.1)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	**3 (0.3)**	**4 (0.3)**	**6 (0.4)**
Chest pain	0 (0.0)	1 (0.1)	1 (0.1)
Death	1 (0.1)	1 (0.1)	1 (0.1)
Non-cardiac chest pain	0 (0.0)	1 (0.1)	1 (0.1)
Oedema peripheral	1 (0.1)	0 (0.0)	1 (0.1)
Pain	1 (0.1)	0 (0.0)	1 (0.1)
Stent-graft endoleak	0 (0.0)	1 (0.1)	1 (0.1)
Hepatobiliary disorders	**3 (0.3)**	**3 (0.2)**	**5 (0.4)**
Autoimmune hepatitis	0 (0.0)	1 (0.1)	1 (0.1)
Cholecystitis	1 (0.1)	0 (0.0)	1 (0.1)
Cholecystocholangitis	1 (0.1)	0 (0.0)	1 (0.1)
Cholelithiasis	0 (0.0)	1 (0.1)	1 (0.1)
Drug-induced liver injury	1 (0.1)	1 (0.1)	1 (0.1)
Immune system disorders	**1 (0.1)**	**0 (0.0)**	**1 (0.1)**
Anaphylactic shock	1 (0.1)	0 (0.0)	1 (0.1)
Infections and infestations	**12 (1.2)**	**19 (1.5)**	**30 (2.2)**
Abdominal wall abscess	0 (0.0)	1 (0.1)	1 (0.1)
Abscess limb	2 (0.2)	0 (0.0)	2 (0.1)
Appendicitis	1 (0.1)	0 (0.0)	1 (0.1)
Bursitis infective	0 (0.0)	1 (0.1)	1 (0.1)
Cellulitis	2 (0.2)	0 (0.0)	2 (0.1)
Colonic abscess	0 (0.0)	1 (0.1)	1 (0.1)
Corona virus infection	0 (0.0)	9 (0.7)	9 (0.7)
Diverticulitis	1 (0.1)	2 (0.2)	2 (0.1)
Erysipelas	1 (0.1)	1 (0.1)	2 (0.1)
Groin infection	0 (0.0)	1 (0.1)	1 (0.1)
Ophthalmic herpes zoster	1 (0.1)	0 (0.0)	1 (0.1)
Pneumonia	1 (0.1)	1 (0.1)	2 (0.1)
Pneumonia bacterial	1 (0.1)	0 (0.0)	1 (0.1)
Sinusitis	1 (0.1)	0 (0.0)	1 (0.1)
Staphylococcal skin infection	1 (0.1)	0 (0.0)	1 (0.1)
Streptococcal abscess	1 (0.1)	0 (0.0)	1 (0.1)
Subcutaneous abscess	0 (0.0)	1 (0.1)	1 (0.1)
Urinary tract infection	0 (0.0)	2 (0.2)	2 (0.1)
Injury, poisoning and procedural complications	**7 (0.7)**	**13 (1.0)**	**19 (1.4)**
Ankle fracture	1 (0.1)	0 (0.0)	1 (0.1)
Femoral neck fracture	1 (0.1)	0 (0.0)	1 (0.1)
Hand fracture	0 (0.0)	1 (0.1)	1 (0.1)
Head injury	1 (0.1)	1 (0.1)	2 (0.1)
Joint injury	0 (0.0)	1 (0.1)	1 (0.1)

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Limb injury	1 (0.1)	0 (0.0)	1 (0.1)
Lower limb fracture	0 (0.0)	2 (0.2)	2 (0.1)
Lumbar vertebral fracture	0 (0.0)	2 (0.2)	2 (0.1)
Meniscus injury	0 (0.0)	1 (0.1)	1 (0.1)
Patella fracture	1 (0.1)	0 (0.0)	1 (0.1)
Pneumothorax traumatic	0 (0.0)	1 (0.1)	1 (0.1)
Post lumbar puncture syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Procedural pain	0 (0.0)	1 (0.1)	1 (0.1)
Radius fracture	1 (0.1)	0 (0.0)	1 (0.1)
Spinal column injury	1 (0.1)	0 (0.0)	1 (0.1)
Spinal fracture	0 (0.0)	1 (0.1)	1 (0.1)
Tendon rupture	0 (0.0)	2 (0.2)	2 (0.1)
Tibia fracture	1 (0.1)	1 (0.1)	2 (0.1)
Metabolism and nutrition disorders	**2 (0.2)**	**5 (0.4)**	**7 (0.5)**
Diabetic ketoacidosis	0 (0.0)	1 (0.1)	1 (0.1)
Hyponatremia	0 (0.0)	1 (0.1)	1 (0.1)
Ketoacidosis	1 (0.1)	0 (0.0)	1 (0.1)
Obesity	0 (0.0)	1 (0.1)	1 (0.1)
Type 2 diabetes mellitus	1 (0.1)	2 (0.2)	3 (0.2)
Musculoskeletal and connective tissue disorders	**8 (0.8)**	**4 (0.3)**	**12 (0.9)**
Arthropathy	1 (0.1)	0 (0.0)	1 (0.1)
Fibromyalgia	1 (0.1)	0 (0.0)	1 (0.1)
Inclusion body myositis	1 (0.1)	0 (0.0)	1 (0.1)
Intervertebral disc protrusion	1 (0.1)	0 (0.0)	1 (0.1)
Kyphosis	0 (0.0)	1 (0.1)	1 (0.1)
Muscular weakness	1 (0.1)	0 (0.0)	1 (0.1)
Osteitis	1 (0.1)	0 (0.0)	1 (0.1)
Osteoarthritis	2 (0.2)	2 (0.2)	4 (0.3)
Rhabdomyolysis	0 (0.0)	1 (0.1)	1 (0.1)
Spinal column stenosis	1 (0.1)	1 (0.1)	2 (0.1)
Spinal osteoarthritis	1 (0.1)	0 (0.0)	1 (0.1)
Tendonitis	1 (0.1)	0 (0.0)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (0.4)**	**15 (1.2)**	**19 (1.4)**
Adenocarcinoma of colon	0 (0.0)	1 (0.1)	1 (0.1)
Basal cell carcinoma	1 (0.1)	0 (0.0)	1 (0.1)
Bladder transitional cell carcinoma	1 (0.1)	0 (0.0)	1 (0.1)
Breast cancer	0 (0.0)	1 (0.1)	1 (0.1)
Colon cancer	1 (0.1)	1 (0.1)	2 (0.1)
Colon cancer metastatic	0 (0.0)	1 (0.1)	1 (0.1)
Colorectal cancer metastatic	0 (0.0)	1 (0.1)	1 (0.1)
Gastrointestinal tract adenoma	0 (0.0)	1 (0.1)	1 (0.1)
Invasive breast carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Lip and/or oral cavity cancer	0 (0.0)	1 (0.1)	1 (0.1)
Malignant melanoma	0 (0.0)	1 (0.1)	1 (0.1)
Metastatic bronchial carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	1 (0.1)	1 (0.1)
Prostate cancer	0 (0.0)	1 (0.1)	1 (0.1)
Prostatic adenoma	0 (0.0)	1 (0.1)	1 (0.1)
Squamous cell carcinoma of lung	1 (0.1)	0 (0.0)	1 (0.1)

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Thyroid cancer	0 (0.0)	1 (0.1)	1 (0.1)
Thyroid neoplasm	0 (0.0)	1 (0.1)	1 (0.1)
Nervous system disorders	**8 (0.8)**	**4 (0.3)**	**12 (0.9)**
Cerebral infarction	1 (0.1)	0 (0.0)	1 (0.1)
Cerebral ischemia	1 (0.1)	0 (0.0)	1 (0.1)
Cerebrovascular accident	1 (0.1)	0 (0.0)	1 (0.1)
Cerebrovascular disorder	1 (0.1)	0 (0.0)	1 (0.1)
Hemiplegic migraine	1 (0.1)	0 (0.0)	1 (0.1)
Intracranial pressure increased	1 (0.1)	0 (0.0)	1 (0.1)
Loss of consciousness	0 (0.0)	1 (0.1)	1 (0.1)
Migraine	1 (0.1)	0 (0.0)	1 (0.1)
Relapsing-remitting multiple sclerosis	0 (0.0)	1 (0.1)	1 (0.1)
Seizure	1 (0.1)	1 (0.1)	2 (0.1)
Spondylitis myelopathy	1 (0.1)	0 (0.0)	1 (0.1)
Toxic encephalopathy	0 (0.0)	1 (0.1)	1 (0.1)
Transient ischemic attack	1 (0.1)	1 (0.1)	2 (0.1)
Pregnancy, puerperium and perinatal conditions	**2 (0.2)**	**0 (0.0)**	**2 (0.1)**
Abortion spontaneous	1 (0.1)	0 (0.0)	1 (0.1)
Pregnancy on oral contraceptive	1 (0.1)	0 (0.0)	1 (0.1)
Psychiatric disorders	**4 (0.4)**	**1 (0.1)**	**5 (0.4)**
Alcohol withdrawal syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Bipolar i disorder	1 (0.1)	0 (0.0)	1 (0.1)
Completed suicide	1 (0.1)	0 (0.0)	1 (0.1)
Drug dependence	1 (0.1)	0 (0.0)	1 (0.1)
Suicidal ideation	0 (0.0)	1 (0.1)	1 (0.1)
Renal and urinary disorders	**2 (0.2)**	**1 (0.1)**	**3 (0.2)**
Acute kidney injury	2 (0.2)	0 (0.0)	2 (0.1)
Renal cyst	0 (0.0)	1 (0.1)	1 (0.1)
Renal failure	1 (0.1)	0 (0.0)	1 (0.1)
Reproductive system and breast disorders	**2 (0.2)**	**3 (0.2)**	**4 (0.3)**
Cervical dysplasia	0 (0.0)	1 (0.1)	1 (0.1)
Genital hemorrhage	0 (0.0)	1 (0.1)	1 (0.1)
Ovarian cyst	0 (0.0)	1 (0.1)	1 (0.1)
Uterine polyp	1 (0.1)	0 (0.0)	1 (0.1)
Uterine prolapse	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**5 (0.5)**	**8 (0.6)**	**12 (0.9)**
Acute respiratory failure	1 (0.1)	1 (0.1)	2 (0.1)
Asthma	0 (0.0)	1 (0.1)	1 (0.1)
Chronic obstructive pulmonary disease	1 (0.1)	4 (0.3)	4 (0.3)
Dyspnea exertional	0 (0.0)	1 (0.1)	1 (0.1)
Hypoxia	0 (0.0)	1 (0.1)	1 (0.1)
Laryngeal ulceration	1 (0.1)	0 (0.0)	1 (0.1)
Lung disorder	0 (0.0)	1 (0.1)	1 (0.1)
Pharyngeal ulceration	1 (0.1)	0 (0.0)	1 (0.1)
Pleurisy	1 (0.1)	0 (0.0)	1 (0.1)
Pulmonary embolism	2 (0.2)	0 (0.0)	2 (0.1)
Skin and subcutaneous tissue disorders	**3 (0.3)**	**1 (0.1)**	**4 (0.3)**
Dermatitis	1 (0.1)	0 (0.0)	1 (0.1)
Dermatitis atopic	1 (0.1)	0 (0.0)	1 (0.1)
Diabetic foot	1 (0.1)	1 (0.1)	2 (0.1)

Summary of Serious TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Psoriasis	1 (0.1)	0 (0.0)	1 (0.1)
Vascular disorders	**5 (0.5)**	**4 (0.3)**	**9 (0.7)**
Aortic aneurysm	1 (0.1)	1 (0.1)	2 (0.1)
Aortic aneurysm rupture	0 (0.0)	1 (0.1)	1 (0.1)
Circulatory collapse	0 (0.0)	1 (0.1)	1 (0.1)
Deep vein thrombosis	1 (0.1)	1 (0.1)	2 (0.1)
Femoral artery embolism	1 (0.1)	0 (0.0)	1 (0.1)
Hypertension	1 (0.1)	0 (0.0)	1 (0.1)
Hypovolemic shock	1 (0.1)	0 (0.0)	1 (0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTIAN = 5 to 5 (BKZ Q4W); TRTIAN = 6 to 6 (BKZ Q8W); TRTIAN = 7 to 7 (BKZ Total); TRTEMFL = "Y" and ASER = "Y" (Adverse Events).

Dropouts and/or Discontinuations Due to Adverse Effects

Table 22: Summary of TEAEs Leading to Discontinuation PS0014

Summary of TEAEs Leading to Discontinuation

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Blood and lymphatic system disorders	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**
Hemorrhagic anemia	0 (0.0)	1 (0.1)	1 (0.1)
Cardiac disorders	**3 (0.3)**	**2 (0.2)**	**5 (0.4)**
Cardiac arrest	2 (0.2)	1 (0.1)	3 (0.2)
Cardiopulmonary failure	1 (0.1)	0 (0.0)	1 (0.1)
Myocardial infarction	0 (0.0)	1 (0.1)	1 (0.1)
Ear and labyrinth disorders	**1 (0.1)**	**0 (0.0)**	**1 (0.1)**
External ear inflammation	1 (0.1)	0 (0.0)	1 (0.1)
Eye disorders	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**
Blepharitis	0 (0.0)	1 (0.1)	1 (0.1)
Gastrointestinal disorders	**4 (0.4)**	**4 (0.3)**	**8 (0.6)**
Abdominal pain upper	0 (0.0)	1 (0.1)	1 (0.1)
Crohn's disease	1 (0.1)	2 (0.2)	3 (0.2)
Diarrhoea	1 (0.1)	0 (0.0)	1 (0.1)
Diverticular perforation	0 (0.0)	1 (0.1)	1 (0.1)
Enteritis	1 (0.1)	0 (0.0)	1 (0.1)
Glossitis	1 (0.1)	0 (0.0)	1 (0.1)
General disorders and administration site conditions	**1 (0.1)**	**2 (0.2)**	**2 (0.1)**
Death	1 (0.1)	1 (0.1)	1 (0.1)
Drug ineffective	0 (0.0)	1 (0.1)	1 (0.1)
Hepatobiliary disorders	**1 (0.1)**	**2 (0.2)**	**2 (0.1)**
Drug-induced liver injury	1 (0.1)	2 (0.2)	2 (0.1)
Infections and infestations	**4 (0.4)**	**9 (0.7)**	**13 (1.0)**
Abdominal wall abscess	0 (0.0)	1 (0.1)	1 (0.1)
Cellulitis	1 (0.1)	0 (0.0)	1 (0.1)
Colonic abscess	0 (0.0)	1 (0.1)	1 (0.1)
Corona virus infection	0 (0.0)	3 (0.2)	3 (0.2)

Summary of TEAEs Leading to Discontinuation

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Diverticulitis	0 (0.0)	1 (0.1)	1 (0.1)
Ear infection	1 (0.1)	0 (0.0)	1 (0.1)
Oral candidiasis	0 (0.0)	2 (0.2)	2 (0.1)
Oral fungal infection	1 (0.1)	0 (0.0)	1 (0.1)
Pneumonia	0 (0.0)	1 (0.1)	1 (0.1)
Staphylococcal skin infection	0 (0.0)	1 (0.1)	1 (0.1)
Streptococcal infection	1 (0.1)	0 (0.0)	1 (0.1)
Investigations	**2 (0.2)**	**3 (0.2)**	**5 (0.4)**
Alanine aminotransferase increased	0 (0.0)	1 (0.1)	1 (0.1)
Aspartate aminotransferase increased	0 (0.0)	1 (0.1)	1 (0.1)
Hepatic enzyme increased	0 (0.0)	1 (0.1)	1 (0.1)
Liver function test increased	0 (0.0)	1 (0.1)	1 (0.1)
Psychiatric evaluation abnormal	2 (0.2)	0 (0.0)	2 (0.1)
Musculoskeletal and connective tissue disorders	**2 (0.2)**	**1 (0.1)**	**3 (0.2)**
Muscular weakness	1 (0.1)	0 (0.0)	1 (0.1)
Osteitis	1 (0.1)	0 (0.0)	1 (0.1)
Rheumatoid arthritis	0 (0.0)	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2 (0.2)**	**9 (0.7)**	**11 (0.8)**
Colon cancer	1 (0.1)	1 (0.1)	2 (0.1)
Colon cancer metastatic	0 (0.0)	1 (0.1)	1 (0.1)
Colorectal cancer metastatic	0 (0.0)	1 (0.1)	1 (0.1)
Invasive breast carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Lip and/or oral cavity cancer	0 (0.0)	1 (0.1)	1 (0.1)
Metastatic bronchial carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	1 (0.1)	1 (0.1)
Prostate cancer	0 (0.0)	1 (0.1)	1 (0.1)
Squamous cell carcinoma of lung	1 (0.1)	0 (0.0)	1 (0.1)
Thyroid cancer	0 (0.0)	1 (0.1)	1 (0.1)
Nervous system disorders	**1 (0.1)**	**1 (0.1)**	**2 (0.1)**
Headache	0 (0.0)	1 (0.1)	1 (0.1)
Hemiplegic migraine	1 (0.1)	0 (0.0)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	**1 (0.1)**	**0 (0.0)**	**1 (0.1)**
Pregnancy on oral contraceptive	1 (0.1)	0 (0.0)	1 (0.1)
Psychiatric disorders	**1 (0.1)**	**3 (0.2)**	**4 (0.3)**
Adjustment disorder with depressed mood	0 (0.0)	1 (0.1)	1 (0.1)
Alcohol abuse	0 (0.0)	1 (0.1)	1 (0.1)
Completed suicide	1 (0.1)	0 (0.0)	1 (0.1)
Depression	0 (0.0)	1 (0.1)	1 (0.1)
Suicidal ideation	0 (0.0)	1 (0.1)	1 (0.1)
Renal and urinary disorders	**1 (0.1)**	**0 (0.0)**	**1 (0.1)**
Renal failure	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory, thoracic and mediastinal disorders	**2 (0.2)**	**2 (0.2)**	**4 (0.3)**
Chronic obstructive pulmonary disease	0 (0.0)	1 (0.1)	1 (0.1)
Interstitial lung disease	1 (0.1)	0 (0.0)	1 (0.1)
Pneumonitis	0 (0.0)	1 (0.1)	1 (0.1)
Pulmonary cavitation	1 (0.1)	0 (0.0)	1 (0.1)
Skin and subcutaneous tissue disorders	**5 (0.5)**	**2 (0.2)**	**7 (0.5)**
Dermatitis allergic	1 (0.1)	0 (0.0)	1 (0.1)
Dermatitis atopic	1 (0.1)	0 (0.0)	1 (0.1)
Diabetic foot	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs Leading to Discontinuation

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Eczema	1 (0.1)	0 (0.0)	1 (0.1)
Psoriasis	2 (0.2)	1 (0.1)	3 (0.2)
Vascular disorders	**1 (0.1)**	**2 (0.2)**	**3 (0.2)**
Aortic aneurysm rupture	0 (0.0)	1 (0.1)	1 (0.1)
Circulatory collapse	0 (0.0)	1 (0.1)	1 (0.1)
Hypovolemic shock	1 (0.1)	0 (0.0)	1 (0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTIAN = 5 to 5 (BKZ Q4W); TRTIAN = 6 to 6 (BKZ Q8W); TRTIAN = 7 to 7 (BKZ Total); TRTEMFL = "Y" and AEDROP = "Y" (Adverse Events).

Treatment Emergent Adverse Events and Adverse Reactions

Table 23: Treatment Emergent Adverse Events -PS0015 OLE

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Blood and lymphatic system disorders	**3 (1.0)**	**16 (2.6)**	**18 (2.8)**
Anemia	0 (0.0)	2 (0.3)	2 (0.3)
Hemorrhagic anemia	0 (0.0)	2 (0.3)	2 (0.3)
Iron deficiency anemia	0 (0.0)	1 (0.2)	1 (0.2)
Leukocytosis	1 (0.3)	1 (0.2)	1 (0.2)
Leukopenia	0 (0.0)	1 (0.2)	1 (0.2)
Lymphadenopathy	1 (0.3)	3 (0.5)	4 (0.6)
Lymphopenia	1 (0.3)	2 (0.3)	3 (0.5)
Neutropenia	0 (0.0)	6 (1.0)	6 (0.9)
Cardiac disorders	**5 (1.7)**	**15 (2.4)**	**19 (2.9)**
Acute coronary syndrome	1 (0.3)	0 (0.0)	1 (0.2)
Arrhythmia	0 (0.0)	2 (0.3)	2 (0.3)
Arteriosclerosis coronary artery	0 (0.0)	1 (0.2)	1 (0.2)
Atrial fibrillation	3 (1.0)	3 (0.5)	5 (0.8)
Atrial flutter	0 (0.0)	2 (0.3)	2 (0.3)
Atrial tachycardia	0 (0.0)	1 (0.2)	1 (0.2)
Bradycardia	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac arrest	0 (0.0)	1 (0.2)	1 (0.2)
Cardiac failure congestive	0 (0.0)	2 (0.3)	2 (0.3)
Coronary artery disease	1 (0.3)	0 (0.0)	1 (0.2)
Extrasystoles	1 (0.3)	0 (0.0)	1 (0.2)
Left ventricular hypertrophy	0 (0.0)	1 (0.2)	1 (0.2)
Myocardial infarction	0 (0.0)	1 (0.2)	1 (0.2)
Pericardial effusion	0 (0.0)	2 (0.3)	2 (0.3)
Supraventricular extrasystoles	0 (0.0)	1 (0.2)	1 (0.2)
Tachycardia	0 (0.0)	1 (0.2)	1 (0.2)
Tachycardia induced cardiomyopathy	0 (0.0)	1 (0.2)	1 (0.2)
Ear and labyrinth disorders	**5 (1.7)**	**10 (1.6)**	**15 (2.3)**
Cerumen impaction	2 (0.7)	0 (0.0)	2 (0.3)
Ear discomfort	1 (0.3)	2 (0.3)	3 (0.5)
Ear pain	0 (0.0)	2 (0.3)	2 (0.3)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Excessive cerumen production	0 (0.0)	1 (0.2)	1 (0.2)
External ear inflammation	0 (0.0)	2 (0.3)	2 (0.3)
Otosclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Tinnitus	1 (0.3)	2 (0.3)	3 (0.5)
Vertigo	1 (0.3)	3 (0.5)	4 (0.6)
Endocrine disorders	**1 (0.3)**	**4 (0.6)**	**5 (0.8)**
Endocrine disorder	0 (0.0)	1 (0.2)	1 (0.2)
Hyperthyroidism	0 (0.0)	2 (0.3)	2 (0.3)
Hypothyroidism	1 (0.3)	2 (0.3)	3 (0.5)
Eye disorders	**5 (1.7)**	**35 (5.6)**	**39 (6.0)**
Angle closure glaucoma	0 (0.0)	1 (0.2)	1 (0.2)
Blepharitis	3 (1.0)	12 (1.9)	15 (2.3)
Blepharitis allergic	0 (0.0)	1 (0.2)	1 (0.2)
Cataract	0 (0.0)	4 (0.6)	4 (0.6)
Chalazion	0 (0.0)	1 (0.2)	1 (0.2)
Conjunctivitis allergic	1 (0.3)	2 (0.3)	3 (0.5)
Cyclitis	1 (0.3)	1 (0.2)	1 (0.2)
Karyostenotic acquired	0 (0.0)	1 (0.2)	1 (0.2)
Dry eye	0 (0.0)	2 (0.3)	2 (0.3)
Eczema eyelids	0 (0.0)	2 (0.3)	2 (0.3)
Endocrine ophthalmopathy	0 (0.0)	1 (0.2)	1 (0.2)
Episcleritis	0 (0.0)	1 (0.2)	1 (0.2)
Exophthalmos	0 (0.0)	1 (0.2)	1 (0.2)
Eye irritation	0 (0.0)	1 (0.2)	1 (0.2)
Eye pruritus	1 (0.3)	0 (0.0)	1 (0.2)
Eye swelling	0 (0.0)	1 (0.2)	1 (0.2)
Eyelid exfoliation	0 (0.0)	1 (0.2)	1 (0.2)
Eyelid margin crusting	0 (0.0)	1 (0.2)	1 (0.2)
Glaucoma	0 (0.0)	1 (0.2)	1 (0.2)
Vision blurred	0 (0.0)	2 (0.3)	2 (0.3)
Visual acuity reduced	1 (0.3)	0 (0.0)	1 (0.2)
Xerophthalmia	0 (0.0)	1 (0.2)	1 (0.2)
Gastrointestinal disorders	**25 (8.5)**	**63 (10.1)**	**84 (12.8)**
Abdominal distension	0 (0.0)	1 (0.2)	1 (0.2)
Abdominal hernia	0 (0.0)	1 (0.2)	1 (0.2)
Abdominal pain	1 (0.3)	7 (1.1)	8 (1.2)
Abdominal pain upper	0 (0.0)	6 (1.0)	6 (0.9)
Anal fistula	1 (0.3)	0 (0.0)	1 (0.2)
Aphthous ulcer	0 (0.0)	4 (0.6)	4 (0.6)
Cheilosis	0 (0.0)	2 (0.3)	2 (0.3)
Colitis ulcerative	0 (0.0)	1 (0.2)	1 (0.2)
Constipation	2 (0.7)	0 (0.0)	2 (0.3)
Crohn's disease	1 (0.3)	0 (0.0)	1 (0.2)
Dental caries	1 (0.3)	4 (0.6)	5 (0.8)
Diarrhoea	4 (1.4)	8 (1.3)	11 (1.7)
Diverticulum	1 (0.3)	0 (0.0)	1 (0.2)
Dry mouth	0 (0.0)	1 (0.2)	1 (0.2)
Dyspepsia	1 (0.3)	1 (0.2)	2 (0.3)
Enteritis	0 (0.0)	1 (0.2)	1 (0.2)
Food poisoning	1 (0.3)	1 (0.2)	2 (0.3)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Gastritis	0 (0.0)	3 (0.5)	3 (0.5)
Gastritis erosive	0 (0.0)	1 (0.2)	1 (0.2)
Gastrointestinal inflammation	1 (0.3)	0 (0.0)	1 (0.2)
Gastrointestinal necrosis	0 (0.0)	1 (0.2)	1 (0.2)
Gastroesophageal reflux disease	4 (1.4)	4 (0.6)	8 (1.2)
Gingival pain	0 (0.0)	1 (0.2)	1 (0.2)
Gingival swelling	1 (0.3)	0 (0.0)	1 (0.2)
Glossitis	0 (0.0)	1 (0.2)	1 (0.2)
Hematochezia	0 (0.0)	1 (0.2)	1 (0.2)
Hemorrhoidal hemorrhage	0 (0.0)	1 (0.2)	1 (0.2)
Hemorrhoids	2 (0.7)	1 (0.2)	3 (0.5)
Hiatus hernia	1 (0.3)	0 (0.0)	1 (0.2)
Ileus	0 (0.0)	1 (0.2)	1 (0.2)
Inguinal hernia	0 (0.0)	5 (0.8)	5 (0.8)
Intestinal obstruction	1 (0.3)	0 (0.0)	1 (0.2)
Irritable bowel syndrome	0 (0.0)	2 (0.3)	2 (0.3)
Leukoplakia oral	0 (0.0)	1 (0.2)	1 (0.2)
Mouth ulceration	0 (0.0)	1 (0.2)	1 (0.2)
Nausea	1 (0.3)	3 (0.5)	4 (0.6)
Pancreatic disorder	0 (0.0)	1 (0.2)	1 (0.2)
Peritoneal adhesions	0 (0.0)	1 (0.2)	1 (0.2)
Plicated tongue	1 (0.3)	0 (0.0)	1 (0.2)
Rectal discharge	0 (0.0)	1 (0.2)	1 (0.2)
Sensitivity of teeth	0 (0.0)	1 (0.2)	1 (0.2)
Stomatitis	0 (0.0)	1 (0.2)	1 (0.2)
Tongue coated	0 (0.0)	1 (0.2)	1 (0.2)
Toothache	2 (0.7)	4 (0.6)	6 (0.9)
Umbilical hernia	0 (0.0)	1 (0.2)	1 (0.2)
General disorders and administration site conditions	**14 (4.8)**	**37 (5.9)**	**49 (7.5)**
Asthenia	1 (0.3)	2 (0.3)	3 (0.5)
Cyst	1 (0.3)	1 (0.2)	2 (0.3)
Fatigue	2 (0.7)	5 (0.8)	7 (1.1)
Impaired healing	0 (0.0)	1 (0.2)	1 (0.2)
Influenza like illness	1 (0.3)	4 (0.6)	5 (0.8)
Injection site bruising	0 (0.0)	2 (0.3)	2 (0.3)
Injection site erythema	3 (1.0)	1 (0.2)	4 (0.6)
Injection site hematoma	0 (0.0)	1 (0.2)	1 (0.2)
Injection site hemorrhage	0 (0.0)	1 (0.2)	1 (0.2)
Injection site inflammation	0 (0.0)	1 (0.2)	1 (0.2)
Injection site pain	0 (0.0)	5 (0.8)	5 (0.8)
Injection site rash	0 (0.0)	1 (0.2)	1 (0.2)
Injection site reaction	4 (1.4)	0 (0.0)	4 (0.6)
Local swelling	0 (0.0)	1 (0.2)	1 (0.2)
Mass	1 (0.3)	0 (0.0)	1 (0.2)
Non-cardiac chest pain	0 (0.0)	2 (0.3)	2 (0.3)
Oedema	0 (0.0)	3 (0.5)	3 (0.5)
Oedema peripheral	0 (0.0)	2 (0.3)	2 (0.3)
Pain	0 (0.0)	1 (0.2)	1 (0.2)
Peripheral swelling	0 (0.0)	4 (0.6)	4 (0.6)
Pyrexia	1 (0.3)	3 (0.5)	4 (0.6)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Vaccination site erythema	0 (0.0)	1 (0.2)	1 (0.2)
Xerosis	0 (0.0)	1 (0.2)	1 (0.2)
Hepatobiliary disorders	**2 (0.7)**	**15 (2.4)**	**17 (2.6)**
Bile duct stone	0 (0.0)	1 (0.2)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)	1 (0.2)
Cholecystitis acute	0 (0.0)	1 (0.2)	1 (0.2)
Cholelithiasis	0 (0.0)	2 (0.3)	2 (0.3)
Hepatic cyst	0 (0.0)	1 (0.2)	1 (0.2)
Hepatic lesion	0 (0.0)	1 (0.2)	1 (0.2)
Hepatic pain	1 (0.3)	0 (0.0)	1 (0.2)
Hepatic steatosis	0 (0.0)	3 (0.5)	3 (0.5)
Hepatomegaly	0 (0.0)	1 (0.2)	1 (0.2)
Hyperbilirubinemia	0 (0.0)	2 (0.3)	2 (0.3)
Non-alcoholic fatty liver	1 (0.3)	1 (0.2)	2 (0.3)
Steatohepatitis	0 (0.0)	1 (0.2)	1 (0.2)
Immune system disorders	**3 (1.0)**	**3 (0.5)**	**6 (0.9)**
Allergy to animal	1 (0.3)	0 (0.0)	1 (0.2)
Drug hypersensitivity	0 (0.0)	1 (0.2)	1 (0.2)
House dust allergy	1 (0.3)	1 (0.2)	2 (0.3)
Seasonal allergy	2 (0.7)	2 (0.3)	4 (0.6)
Infections and infestations	**148 (50.3)**	**311 (49.7)**	**390 (59.6)**
Abdominal wall abscess	0 (0.0)	1 (0.2)	1 (0.2)
Abscess limb	0 (0.0)	1 (0.2)	1 (0.2)
Acrodermatitis	1 (0.3)	1 (0.2)	2 (0.3)
Acute sinusitis	1 (0.3)	4 (0.6)	5 (0.8)
Alternaria infection	0 (0.0)	1 (0.2)	1 (0.2)
Anal abscess	1 (0.3)	1 (0.2)	2 (0.3)
Anal fungal infection	0 (0.0)	1 (0.2)	1 (0.2)
Angular cheilitis	2 (0.7)	1 (0.2)	3 (0.5)
Appendicitis	0 (0.0)	1 (0.2)	1 (0.2)
Arthritis bacterial	0 (0.0)	1 (0.2)	1 (0.2)
Asymptomatic bacteriuria	0 (0.0)	2 (0.3)	2 (0.3)
Bacterial rhinitis	1 (0.3)	1 (0.2)	2 (0.3)
Bacterial vaginosis	1 (0.3)	0 (0.0)	1 (0.2)
Balanitis candida	1 (0.3)	0 (0.0)	1 (0.2)
Body tinea	3 (1.0)	4 (0.6)	7 (1.1)
Bone abscess	0 (0.0)	1 (0.2)	1 (0.2)
Bronchitis	1 (0.3)	6 (1.0)	7 (1.1)
Bronchitis viral	0 (0.0)	1 (0.2)	1 (0.2)
Bursitis infective	0 (0.0)	1 (0.2)	1 (0.2)
Campylobacter gastroenteritis	0 (0.0)	1 (0.2)	1 (0.2)
Candida infection	0 (0.0)	1 (0.2)	1 (0.2)
Candida sepsis	1 (0.3)	0 (0.0)	1 (0.2)
Candiduria	0 (0.0)	1 (0.2)	1 (0.2)
Capillariasis	0 (0.0)	1 (0.2)	1 (0.2)
Cellulitis	2 (0.7)	1 (0.2)	3 (0.5)
Chronic sinusitis	0 (0.0)	1 (0.2)	1 (0.2)
Conjunctivitis	4 (1.4)	11 (1.8)	14 (2.1)
Conjunctivitis bacterial	2 (0.7)	0 (0.0)	2 (0.3)
Corona virus infection	10 (3.4)	53 (8.5)	61 (9.3)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Cystitis	0 (0.0)	1 (0.2)	1 (0.2)
Cystitis bacterial	0 (0.0)	1 (0.2)	1 (0.2)
Dermatitis infected	0 (0.0)	1 (0.2)	1 (0.2)
Diverticulitis	0 (0.0)	1 (0.2)	1 (0.2)
Ear infection	2 (0.7)	8 (1.3)	10 (1.5)
Ear infection bacterial	2 (0.7)	0 (0.0)	2 (0.3)
Ear infection fungal	1 (0.3)	0 (0.0)	1 (0.2)
Eczema infected	2 (0.7)	1 (0.2)	3 (0.5)
Erysipelas	2 (0.7)	3 (0.5)	5 (0.8)
Erythema migrans	0 (0.0)	1 (0.2)	1 (0.2)
Erythrasma	0 (0.0)	1 (0.2)	1 (0.2)
Eyelid infection	1 (0.3)	3 (0.5)	4 (0.6)
Folliculitis	5 (1.7)	12 (1.9)	16 (2.4)
Fungal infection	0 (0.0)	1 (0.2)	1 (0.2)
Fungal skin infection	3 (1.0)	11 (1.8)	13 (2.0)
Furuncle	4 (1.4)	3 (0.5)	6 (0.9)
Gastritis viral	1 (0.3)	0 (0.0)	1 (0.2)
Gastroenteritis	4 (1.4)	3 (0.5)	7 (1.1)
Gastroenteritis bacterial	0 (0.0)	1 (0.2)	1 (0.2)
Gastroenteritis viral	1 (0.3)	0 (0.0)	1 (0.2)
Gastrointestinal candidiasis	3 (1.0)	5 (0.8)	6 (0.9)
Gastrointestinal infection	0 (0.0)	2 (0.3)	2 (0.3)
Genital candidiasis	0 (0.0)	1 (0.2)	1 (0.2)
Genital infection bacterial	0 (0.0)	1 (0.2)	1 (0.2)
Genital infection fungal	1 (0.3)	1 (0.2)	2 (0.3)
Gingivitis	2 (0.7)	1 (0.2)	3 (0.5)
Groin abscess	0 (0.0)	1 (0.2)	1 (0.2)
Helicobacter infection	2 (0.7)	1 (0.2)	3 (0.5)
Herpes simplex	0 (0.0)	2 (0.3)	2 (0.3)
Herpes virus infection	0 (0.0)	1 (0.2)	1 (0.2)
Herpes zoster	2 (0.7)	3 (0.5)	5 (0.8)
Hordeolum	2 (0.7)	5 (0.8)	7 (1.1)
Impetigo	1 (0.3)	8 (1.3)	9 (1.4)
Infected bite	0 (0.0)	1 (0.2)	1 (0.2)
Infected dermal cyst	0 (0.0)	1 (0.2)	1 (0.2)
Infectious disease carrier	0 (0.0)	1 (0.2)	1 (0.2)
Influenza	2 (0.7)	7 (1.1)	9 (1.4)
Labyrinthitis	0 (0.0)	2 (0.3)	2 (0.3)
Laryngitis	1 (0.3)	2 (0.3)	3 (0.5)
Latent tuberculosis	0 (0.0)	1 (0.2)	1 (0.2)
Lower respiratory tract infection	0 (0.0)	1 (0.2)	1 (0.2)
Lyme disease	1 (0.3)	0 (0.0)	1 (0.2)
Malassezia infection	0 (0.0)	1 (0.2)	1 (0.2)
Myringitis	1 (0.3)	0 (0.0)	1 (0.2)
Nasal vestibulitis	0 (0.0)	1 (0.2)	1 (0.2)
Nasopharyngitis	34 (11.6)	62 (9.9)	94 (14.4)
Onychomycosis	1 (0.3)	2 (0.3)	3 (0.5)
Ophthalmic herpes zoster	0 (0.0)	1 (0.2)	1 (0.2)
Oral candidiasis	39 (13.3)	53 (8.5)	81 (12.4)
Oral fungal infection	6 (2.0)	10 (1.6)	15 (2.3)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Oral hairy leukoplakia	0 (0.0)	1 (0.2)	1 (0.2)
Oral herpes	2 (0.7)	4 (0.6)	6 (0.9)
Oral infection	0 (0.0)	1 (0.2)	1 (0.2)
Orchitis	0 (0.0)	1 (0.2)	1 (0.2)
Oropharyngeal candidiasis	1 (0.3)	1 (0.2)	1 (0.2)
Otitis externa	3 (1.0)	4 (0.6)	7 (1.1)
Otitis media	3 (1.0)	4 (0.6)	6 (0.9)
Otitis media acute	0 (0.0)	2 (0.3)	2 (0.3)
Paronychia	2 (0.7)	5 (0.8)	7 (1.1)
Periodontitis	0 (0.0)	1 (0.2)	1 (0.2)
Periorbital cellulitis	1 (0.3)	0 (0.0)	1 (0.2)
Peritonsillar abscess	0 (0.0)	2 (0.3)	2 (0.3)
Pharyngitis	3 (1.0)	5 (0.8)	8 (1.2)
Pharyngitis bacterial	0 (0.0)	1 (0.2)	1 (0.2)
Pharyngitis streptococcal	0 (0.0)	3 (0.5)	3 (0.5)
Pneumonia	1 (0.3)	2 (0.3)	3 (0.5)
Pneumonia bacterial	1 (0.3)	1 (0.2)	2 (0.3)
Post procedural infection	1 (0.3)	0 (0.0)	1 (0.2)
Postoperative abscess	0 (0.0)	1 (0.2)	1 (0.2)
Pulpitis dental	1 (0.3)	3 (0.5)	4 (0.6)
Pyelonephritis	1 (0.3)	0 (0.0)	1 (0.2)
Pyelonephritis acute	1 (0.3)	1 (0.2)	2 (0.3)
Rash pustular	1 (0.3)	2 (0.3)	3 (0.5)
Rectal abscess	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory tract infection	0 (0.0)	2 (0.3)	2 (0.3)
Rhinitis	1 (0.3)	2 (0.3)	3 (0.5)
Rhinovirus infection	0 (0.0)	1 (0.2)	1 (0.2)
Sinusitis	7 (2.4)	15 (2.4)	22 (3.4)
Skin bacterial infection	2 (0.7)	0 (0.0)	2 (0.3)
Skin candida	4 (1.4)	8 (1.3)	12 (1.8)
Skin infection	0 (0.0)	1 (0.2)	1 (0.2)
Soft tissue infection	1 (0.3)	0 (0.0)	1 (0.2)
Staphylococcal bacteraemia	0 (0.0)	1 (0.2)	1 (0.2)
Staphylococcal impetigo	1 (0.3)	1 (0.2)	2 (0.3)
Staphylococcal infection	0 (0.0)	1 (0.2)	1 (0.2)
Staphylococcal skin infection	0 (0.0)	1 (0.2)	1 (0.2)
Subcutaneous abscess	1 (0.3)	3 (0.5)	4 (0.6)
Tinea cruris	1 (0.3)	1 (0.2)	2 (0.3)
Tinea faciei	0 (0.0)	1 (0.2)	1 (0.2)
Tinea infection	1 (0.3)	1 (0.2)	2 (0.3)
Tinea manuum	1 (0.3)	1 (0.2)	2 (0.3)
Tinea pedis	4 (1.4)	3 (0.5)	7 (1.1)
Tinea versicolour	1 (0.3)	3 (0.5)	4 (0.6)
Tongue fungal infection	2 (0.7)	4 (0.6)	5 (0.8)
Tonsillitis	1 (0.3)	6 (1.0)	6 (0.9)
Tooth abscess	3 (1.0)	3 (0.5)	6 (0.9)
Tooth infection	1 (0.3)	4 (0.6)	5 (0.8)
Tracheitis	0 (0.0)	1 (0.2)	1 (0.2)
Upper respiratory tract infection	13 (4.4)	35 (5.6)	45 (6.9)
Urinary tract infection	19 (6.5)	31 (5.0)	46 (7.0)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Urogenital infection fungal	0 (0.0)	1 (0.2)	1 (0.2)
Viral infection	0 (0.0)	1 (0.2)	1 (0.2)
Viral pharyngitis	0 (0.0)	1 (0.2)	1 (0.2)
Viral upper respiratory tract infection	1 (0.3)	1 (0.2)	2 (0.3)
Vulvovaginal candidiasis	6 (2.0)	8 (1.3)	14 (2.1)
Vulvovaginal mycotic infection	2 (0.7)	7 (1.1)	9 (1.4)
Injury, poisoning and procedural complications	**26 (8.8)**	**45 (7.2)**	**65 (9.9)**
Animal bite	0 (0.0)	1 (0.2)	1 (0.2)
Ankle fracture	2 (0.7)	1 (0.2)	3 (0.5)
Arthropod bite	0 (0.0)	1 (0.2)	1 (0.2)
Arthropod sting	0 (0.0)	1 (0.2)	1 (0.2)
Burns second degree	0 (0.0)	1 (0.2)	1 (0.2)
Chillblains	1 (0.3)	0 (0.0)	1 (0.2)
Concussion	0 (0.0)	1 (0.2)	1 (0.2)
Contusion	1 (0.3)	5 (0.8)	6 (0.9)
Epicondylitis	1 (0.3)	0 (0.0)	1 (0.2)
Excoriation	0 (0.0)	1 (0.2)	1 (0.2)
Eye contusion	0 (0.0)	1 (0.2)	1 (0.2)
Face injury	1 (0.3)	0 (0.0)	1 (0.2)
Fall	0 (0.0)	4 (0.6)	4 (0.6)
Foot fracture	0 (0.0)	1 (0.2)	1 (0.2)
Foreign body	0 (0.0)	1 (0.2)	1 (0.2)
Foreign body in eye	1 (0.3)	0 (0.0)	1 (0.2)
Hand fracture	1 (0.3)	1 (0.2)	2 (0.3)
Head injury	0 (0.0)	2 (0.3)	2 (0.3)
Inflammation of wound	0 (0.0)	1 (0.2)	1 (0.2)
Injection related reaction	0 (0.0)	1 (0.2)	1 (0.2)
Injury	1 (0.3)	0 (0.0)	1 (0.2)
Joint dislocation	0 (0.0)	2 (0.3)	2 (0.3)
Joint injury	2 (0.7)	2 (0.3)	4 (0.6)
Laceration	3 (1.0)	0 (0.0)	3 (0.5)
Ligament sprain	2 (0.7)	1 (0.2)	3 (0.5)
Limb injury	3 (1.0)	7 (1.1)	10 (1.5)
Lower limb fracture	0 (0.0)	1 (0.2)	1 (0.2)
Meniscus injury	0 (0.0)	2 (0.3)	2 (0.3)
Multiple fractures	0 (0.0)	1 (0.2)	1 (0.2)
Muscle rupture	1 (0.3)	0 (0.0)	1 (0.2)
Muscle strain	2 (0.7)	6 (1.0)	7 (1.1)
Pneumothorax traumatic	0 (0.0)	1 (0.2)	1 (0.2)
Rib fracture	1 (0.3)	2 (0.3)	2 (0.3)
Road traffic accident	0 (0.0)	2 (0.3)	2 (0.3)
Scratch	1 (0.3)	0 (0.0)	1 (0.2)
Skin abrasion	1 (0.3)	1 (0.2)	2 (0.3)
Spinal fracture	0 (0.0)	1 (0.2)	1 (0.2)
Sunburn	1 (0.3)	1 (0.2)	2 (0.3)
Tendon rupture	0 (0.0)	1 (0.2)	1 (0.2)
Thermal burn	0 (0.0)	1 (0.2)	1 (0.2)
Tooth fracture	2 (0.7)	0 (0.0)	2 (0.3)
Upper limb fracture	0 (0.0)	1 (0.2)	1 (0.2)
Urinary retention postoperative	0 (0.0)	1 (0.2)	1 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Investigations	**23 (7.8)**	**73 (11.7)**	**92 (14.1)**
Alanine aminotransferase increased	3 (1.0)	7 (1.1)	10 (1.5)
Aspartate aminotransferase increased	4 (1.4)	9 (1.4)	13 (2.0)
Blood alkaline phosphatase increased	0 (0.0)	1 (0.2)	1 (0.2)
Blood bilirubin increased	0 (0.0)	3 (0.5)	3 (0.5)
Blood calcium increased	0 (0.0)	1 (0.2)	1 (0.2)
Blood cholesterol increased	0 (0.0)	4 (0.6)	4 (0.6)
Blood creatine increased	0 (0.0)	1 (0.2)	1 (0.2)
Blood creatine phosphokinase increased	0 (0.0)	1 (0.2)	1 (0.2)
Blood glucose increased	0 (0.0)	1 (0.2)	1 (0.2)
Blood iron decreased	0 (0.0)	1 (0.2)	1 (0.2)
Blood parathyroid hormone increased	0 (0.0)	1 (0.2)	1 (0.2)
Blood potassium increased	2 (0.7)	2 (0.3)	3 (0.5)
Blood pressure increased	2 (0.7)	11 (1.8)	13 (2.0)
Blood testosterone decreased	0 (0.0)	1 (0.2)	1 (0.2)
Blood triglycerides increased	2 (0.7)	4 (0.6)	6 (0.9)
Blood uric acid	0 (0.0)	1 (0.2)	1 (0.2)
Blood urine present	1 (0.3)	0 (0.0)	1 (0.2)
Body temperature increased	1 (0.3)	0 (0.0)	1 (0.2)
Cardiac murmur	0 (0.0)	1 (0.2)	1 (0.2)
Columbia suicide severity rating scale abnormal	0 (0.0)	1 (0.2)	1 (0.2)
Coronavirus test positive	1 (0.3)	5 (0.8)	5 (0.8)
Electrocardiogram abnormal	0 (0.0)	1 (0.2)	1 (0.2)
Electrocardiogram t wave amplitude decreased	1 (0.3)	0 (0.0)	1 (0.2)
Electrocardiogram t wave biphasic	0 (0.0)	1 (0.2)	1 (0.2)
Electrocardiogram t wave inversion	0 (0.0)	1 (0.2)	1 (0.2)
False positive tuberculosis test	2 (0.7)	7 (1.1)	9 (1.4)
Gamma-glutamyl transferase increased	3 (1.0)	12 (1.9)	15 (2.3)
Heart rate increased	0 (0.0)	1 (0.2)	1 (0.2)
Hepatic enzyme increased	3 (1.0)	4 (0.6)	5 (0.8)
Liver function test increased	0 (0.0)	1 (0.2)	1 (0.2)
Low density lipoprotein increased	0 (0.0)	1 (0.2)	1 (0.2)
Neutrophil count decreased	1 (0.3)	0 (0.0)	1 (0.2)
Occult blood positive	0 (0.0)	1 (0.2)	1 (0.2)
Prostatic specific antigen increased	1 (0.3)	0 (0.0)	1 (0.2)
Psychiatric evaluation abnormal	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory rate increased	0 (0.0)	1 (0.2)	1 (0.2)
Transaminases increased	1 (0.3)	3 (0.5)	4 (0.6)
Vitamin d decreased	1 (0.3)	0 (0.0)	1 (0.2)
Weight decreased	0 (0.0)	3 (0.5)	3 (0.5)
Weight increased	0 (0.0)	6 (1.0)	6 (0.9)
Metabolism and nutrition disorders	**18 (6.1)**	**43 (6.9)**	**56 (8.6)**
Dehydration	0 (0.0)	2 (0.3)	2 (0.3)
Diabetes mellitus	3 (1.0)	5 (0.8)	7 (1.1)
Diabetic ketoacidosis	0 (0.0)	2 (0.3)	2 (0.3)
Dyslipidemia	0 (0.0)	1 (0.2)	1 (0.2)
Folate deficiency	0 (0.0)	1 (0.2)	1 (0.2)
Glucose tolerance impaired	0 (0.0)	1 (0.2)	1 (0.2)
Gout	3 (1.0)	3 (0.5)	6 (0.9)
Hypercalcemia	1 (0.3)	1 (0.2)	2 (0.3)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Hypercholesterolemia	0 (0.0)	4 (0.6)	4 (0.6)
Hyperglycemia	0 (0.0)	2 (0.3)	2 (0.3)
Hyperlipidemia	3 (1.0)	3 (0.5)	5 (0.8)
Hypertriglyceridemia	3 (1.0)	5 (0.8)	7 (1.1)
Hyperuricemia	0 (0.0)	2 (0.3)	2 (0.3)
Hypocalcemia	0 (0.0)	1 (0.2)	1 (0.2)
Magnesium deficiency	1 (0.3)	0 (0.0)	1 (0.2)
Polydipsia	1 (0.3)	0 (0.0)	1 (0.2)
Type 2 diabetes mellitus	3 (1.0)	10 (1.6)	11 (1.7)
Vitamin b12 deficiency	0 (0.0)	1 (0.2)	1 (0.2)
Vitamin d deficiency	1 (0.3)	4 (0.6)	5 (0.8)
Musculoskeletal and connective tissue disorders	**24 (8.2)**	**96 (15.3)**	**117 (17.9)**
Arthralgia	6 (2.0)	26 (4.2)	31 (4.7)
Arthritis	1 (0.3)	2 (0.3)	3 (0.5)
Arthrofibrosis	1 (0.3)	1 (0.2)	2 (0.3)
Back pain	5 (1.7)	12 (1.9)	17 (2.6)
Bursitis	1 (0.3)	4 (0.6)	5 (0.8)
Chondropathy	0 (0.0)	1 (0.2)	1 (0.2)
Dactylitis	0 (0.0)	1 (0.2)	1 (0.2)
Foot deformity	1 (0.3)	0 (0.0)	1 (0.2)
Intervertebral disc degeneration	0 (0.0)	1 (0.2)	1 (0.2)
Intervertebral disc disorder	0 (0.0)	2 (0.3)	2 (0.3)
Intervertebral disc protrusion	1 (0.3)	4 (0.6)	5 (0.8)
Jaw cyst	0 (0.0)	1 (0.2)	1 (0.2)
Joint stiffness	0 (0.0)	1 (0.2)	1 (0.2)
Joint swelling	2 (0.7)	2 (0.3)	4 (0.6)
Lumbar spinal stenosis	0 (0.0)	1 (0.2)	1 (0.2)
Muscle spasms	0 (0.0)	2 (0.3)	2 (0.3)
Musculoskeletal chest pain	0 (0.0)	1 (0.2)	1 (0.2)
Musculoskeletal pain	1 (0.3)	5 (0.8)	6 (0.9)
Musculoskeletal stiffness	0 (0.0)	2 (0.3)	2 (0.3)
Myalgia	2 (0.7)	1 (0.2)	3 (0.5)
Neck pain	0 (0.0)	1 (0.2)	1 (0.2)
Osteoarthritis	1 (0.3)	8 (1.3)	9 (1.4)
Osteonecrosis of jaw	0 (0.0)	1 (0.2)	1 (0.2)
Osteopenia	0 (0.0)	1 (0.2)	1 (0.2)
Pain in extremity	2 (0.7)	6 (1.0)	8 (1.2)
Periarthritis	0 (0.0)	1 (0.2)	1 (0.2)
Psoriatic arthropathy	4 (1.4)	6 (1.0)	10 (1.5)
Rotator cuff syndrome	0 (0.0)	5 (0.8)	5 (0.8)
Sjogren's syndrome	1 (0.3)	0 (0.0)	1 (0.2)
Spinal osteoarthritis	1 (0.3)	0 (0.0)	1 (0.2)
Spinal pain	0 (0.0)	3 (0.5)	3 (0.5)
Synovial cyst	0 (0.0)	1 (0.2)	1 (0.2)
Synovitis	0 (0.0)	1 (0.2)	1 (0.2)
Tendonitis	0 (0.0)	2 (0.3)	2 (0.3)
Trigger finger	0 (0.0)	1 (0.2)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**4 (1.4)**	**27 (4.3)**	**29 (4.4)**
Angiofibroma	0 (0.0)	1 (0.2)	1 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Basal cell carcinoma	1 (0.3)	5 (0.8)	6 (0.9)
Bladder cancer stage iii	0 (0.0)	1 (0.2)	1 (0.2)
Colon adenoma	0 (0.0)	1 (0.2)	1 (0.2)
Fibrous histiocytoma	1 (0.3)	0 (0.0)	1 (0.2)
Gastrointestinal tract adenoma	0 (0.0)	1 (0.2)	1 (0.2)
Hemangioma of liver	0 (0.0)	2 (0.3)	2 (0.3)
Hodgkin's disease nodular sclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Lentigo maligna	0 (0.0)	1 (0.2)	1 (0.2)
Lipoma	0 (0.0)	2 (0.3)	2 (0.3)
Malignant melanoma in situ	1 (0.3)	0 (0.0)	1 (0.2)
Rectal adenoma	0 (0.0)	1 (0.2)	1 (0.2)
Renal cell carcinoma	0 (0.0)	1 (0.2)	1 (0.2)
Seborrheic keratosis	1 (0.3)	1 (0.2)	2 (0.3)
Skin papilloma	0 (0.0)	7 (1.1)	7 (1.1)
Uterine leiomyoma	0 (0.0)	3 (0.5)	3 (0.5)
Nervous system disorders	**10 (3.4)**	**42 (6.7)**	**50 (7.6)**
Ageusia	1 (0.3)	0 (0.0)	1 (0.2)
Carpal tunnel syndrome	0 (0.0)	1 (0.2)	1 (0.2)
Cerebral infarction	0 (0.0)	2 (0.3)	2 (0.3)
Cerebrovascular accident	0 (0.0)	1 (0.2)	1 (0.2)
Cervical radiculopathy	0 (0.0)	1 (0.2)	1 (0.2)
Dementia	0 (0.0)	1 (0.2)	1 (0.2)
Dizziness	0 (0.0)	2 (0.3)	2 (0.3)
Dysesthesia	0 (0.0)	1 (0.2)	1 (0.2)
Dysgeusia	1 (0.3)	0 (0.0)	1 (0.2)
Facial paralysis	0 (0.0)	1 (0.2)	1 (0.2)
Headache	3 (1.0)	21 (3.4)	23 (3.5)
Hemianesthesia	0 (0.0)	1 (0.2)	1 (0.2)
Hypoesthesia	1 (0.3)	1 (0.2)	2 (0.3)
Migraine	0 (0.0)	1 (0.2)	1 (0.2)
Nerve compression	1 (0.3)	0 (0.0)	1 (0.2)
Paranesthesia	1 (0.3)	0 (0.0)	1 (0.2)
Paralysis	0 (0.0)	1 (0.2)	1 (0.2)
Paresis	0 (0.0)	1 (0.2)	1 (0.2)
Polyneuropathy	0 (0.0)	1 (0.2)	1 (0.2)
Post herpetic neuralgia	0 (0.0)	1 (0.2)	1 (0.2)
Presyncope	0 (0.0)	2 (0.3)	2 (0.3)
Relapsing-remitting multiple sclerosis	0 (0.0)	1 (0.2)	1 (0.2)
Sciatica	2 (0.7)	2 (0.3)	4 (0.6)
Sensory loss	1 (0.3)	0 (0.0)	1 (0.2)
Syncope	0 (0.0)	1 (0.2)	1 (0.2)
Transient ischemic attack	0 (0.0)	1 (0.2)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	**0 (0.0)**	**1 (0.2)**	**1 (0.2)**
Pregnancy on contraceptive	0 (0.0)	1 (0.2)	1 (0.2)
Psychiatric disorders	**5 (1.7)**	**25 (4.0)**	**30 (4.6)**
Adjustment disorder with depressed mood	0 (0.0)	1 (0.2)	1 (0.2)
Alcohol abuse	0 (0.0)	2 (0.3)	2 (0.3)
Anxiety	1 (0.3)	6 (1.0)	7 (1.1)
Anxiety disorder	0 (0.0)	1 (0.2)	1 (0.2)
Attention deficit/hyperactivity disorder	0 (0.0)	1 (0.2)	1 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Depression	3 (1.0)	10 (1.6)	13 (2.0)
Insomnia	2 (0.7)	4 (0.6)	6 (0.9)
Neurosis	0 (0.0)	1 (0.2)	1 (0.2)
Persistent depressive disorder	0 (0.0)	1 (0.2)	1 (0.2)
Psychotic disorder	0 (0.0)	1 (0.2)	1 (0.2)
Stress	0 (0.0)	1 (0.2)	1 (0.2)
Suicide attempt	0 (0.0)	1 (0.2)	1 (0.2)
Renal and urinary disorders	**17 (5.8)**	**21 (3.4)**	**38 (5.8)**
Acute kidney injury	2 (0.7)	0 (0.0)	2 (0.3)
Bladder pain	0 (0.0)	1 (0.2)	1 (0.2)
Chronic kidney disease	1 (0.3)	0 (0.0)	1 (0.2)
Glycosuria	1 (0.3)	3 (0.5)	4 (0.6)
Hematuria	2 (0.7)	5 (0.8)	7 (1.1)
Iga nephropathy	0 (0.0)	1 (0.2)	1 (0.2)
Leukocyturia	1 (0.3)	0 (0.0)	1 (0.2)
Nephrocalcinosis	1 (0.3)	0 (0.0)	1 (0.2)
Nephrolithiasis	3 (1.0)	5 (0.8)	8 (1.2)
Obstructive nephropathy	1 (0.3)	0 (0.0)	1 (0.2)
Pollakiuria	1 (0.3)	2 (0.3)	3 (0.5)
Proteinuria	1 (0.3)	5 (0.8)	6 (0.9)
Renal colic	1 (0.3)	1 (0.2)	2 (0.3)
Renal cyst	1 (0.3)	2 (0.3)	3 (0.5)
Renal disorder	0 (0.0)	1 (0.2)	1 (0.2)
Renal pain	1 (0.3)	0 (0.0)	1 (0.2)
Urethral disorder	1 (0.3)	0 (0.0)	1 (0.2)
Urinary incontinence	0 (0.0)	1 (0.2)	1 (0.2)
Urinary tract inflammation	1 (0.3)	0 (0.0)	1 (0.2)
Reproductive system and breast disorders	**0 (0.0)**	**12 (1.9)**	**12 (1.8)**
Benign prostatic hyperplasia	0 (0.0)	1 (0.2)	1 (0.2)
Breast cyst	0 (0.0)	1 (0.2)	1 (0.2)
Breast disorder	0 (0.0)	1 (0.2)	1 (0.2)
Endometriosis	0 (0.0)	1 (0.2)	1 (0.2)
Fallopian tube cyst	0 (0.0)	1 (0.2)	1 (0.2)
Genital rash	0 (0.0)	1 (0.2)	1 (0.2)
Hemorrhagic ovarian cyst	0 (0.0)	1 (0.2)	1 (0.2)
Metrorrhagia	0 (0.0)	1 (0.2)	1 (0.2)
Orchitis noninfective	0 (0.0)	1 (0.2)	1 (0.2)
Ovarian cyst	0 (0.0)	1 (0.2)	1 (0.2)
Prostatomegaly	0 (0.0)	1 (0.2)	1 (0.2)
Retrograde ejaculation	0 (0.0)	1 (0.2)	1 (0.2)
Uterine cervical erosion	0 (0.0)	1 (0.2)	1 (0.2)
Uterine polyp	0 (0.0)	1 (0.2)	1 (0.2)
Varicose veins pelvic	0 (0.0)	1 (0.2)	1 (0.2)
Vulvovaginal pruritus	0 (0.0)	1 (0.2)	1 (0.2)
Respiratory, thoracic and mediastinal disorders	**19 (6.5)**	**34 (5.4)**	**51 (7.8)**
Allergic respiratory disease	0 (0.0)	1 (0.2)	1 (0.2)
Asthma	1 (0.3)	0 (0.0)	1 (0.2)
Atelectasis	0 (0.0)	1 (0.2)	1 (0.2)
Chronic obstructive pulmonary disease	0 (0.0)	2 (0.3)	2 (0.3)
Cough	9 (3.1)	6 (1.0)	14 (2.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Dysphonia	0 (0.0)	1 (0.2)	1 (0.2)
dyspnea	0 (0.0)	3 (0.5)	3 (0.5)
dyspneal exertional	2 (0.7)	1 (0.2)	3 (0.5)
Epistaxis	0 (0.0)	1 (0.2)	1 (0.2)
Hiccups	0 (0.0)	1 (0.2)	1 (0.2)
Interstitial lung disease	0 (0.0)	1 (0.2)	1 (0.2)
Nasal inflammation	1 (0.3)	1 (0.2)	2 (0.3)
Nasal mucosal erosion	0 (0.0)	1 (0.2)	1 (0.2)
Nasal obstruction	0 (0.0)	1 (0.2)	1 (0.2)
Nasal polyps	0 (0.0)	1 (0.2)	1 (0.2)
Oropharyngeal pain	2 (0.7)	7 (1.1)	9 (1.4)
Pleural effusion	0 (0.0)	1 (0.2)	1 (0.2)
Pneumothorax	0 (0.0)	1 (0.2)	1 (0.2)
Pulmonary calcification	1 (0.3)	0 (0.0)	1 (0.2)
Pulmonary embolism	0 (0.0)	1 (0.2)	1 (0.2)
Pulmonary mass	1 (0.3)	0 (0.0)	1 (0.2)
Respiratory failure	0 (0.0)	1 (0.2)	1 (0.2)
Rhinitis allergic	2 (0.7)	1 (0.2)	3 (0.5)
Rhinorrhea	0 (0.0)	1 (0.2)	1 (0.2)
Sinus congestion	1 (0.3)	0 (0.0)	1 (0.2)
Sleep apnea syndrome	1 (0.3)	3 (0.5)	4 (0.6)
Tonsillar hypertrophy	0 (0.0)	1 (0.2)	1 (0.2)
Wheezing	1 (0.3)	0 (0.0)	1 (0.2)
Skin and subcutaneous tissue disorders	**43 (14.6)**	**115 (18.4)**	**146 (22.3)**
Acne	1 (0.3)	3 (0.5)	4 (0.6)
Actinic keratosis	0 (0.0)	1 (0.2)	1 (0.2)
Alopecia	0 (0.0)	7 (1.1)	7 (1.1)
Alopecia areata	0 (0.0)	1 (0.2)	1 (0.2)
Angioedema	1 (0.3)	0 (0.0)	1 (0.2)
Chronic spontaneous urticaria	1 (0.3)	0 (0.0)	1 (0.2)
Dandruff	0 (0.0)	1 (0.2)	1 (0.2)
Dermatitis	2 (0.7)	5 (0.8)	7 (1.1)
Dermatitis allergic	0 (0.0)	4 (0.6)	4 (0.6)
Dermatitis atopic	1 (0.3)	5 (0.8)	6 (0.9)
Dermatitis contact	8 (2.7)	12 (1.9)	19 (2.9)
Dermatitis exfoliative	0 (0.0)	3 (0.5)	3 (0.5)
Drug reaction with eosinophilia and systemic symptoms	1 (0.3)	0 (0.0)	1 (0.2)
Dry skin	0 (0.0)	2 (0.3)	2 (0.3)
Dyshidrotic eczema	1 (0.3)	1 (0.2)	2 (0.3)
Ecchymosis	1 (0.3)	0 (0.0)	1 (0.2)
Eczema	7 (2.4)	11 (1.8)	17 (2.6)
Erythema	0 (0.0)	3 (0.5)	3 (0.5)
Erythrodermic psoriasis	0 (0.0)	1 (0.2)	1 (0.2)
Guttate psoriasis	1 (0.3)	1 (0.2)	1 (0.2)
Hidradenitis	0 (0.0)	1 (0.2)	1 (0.2)
Hyperhidrosis	1 (0.3)	3 (0.5)	4 (0.6)
Ingrowing nail	0 (0.0)	2 (0.3)	2 (0.3)
Intertrigo	1 (0.3)	8 (1.3)	9 (1.4)
Keratosis pilaris	0 (0.0)	1 (0.2)	1 (0.2)
Nail dystrophy	1 (0.3)	0 (0.0)	1 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=294) n (%)	BKZ Q8W (N=626) n (%)	BKZ Total (N=654) n (%)
Neurodermatitis	0 (0.0)	1 (0.2)	1 (0.2)
Papule	0 (0.0)	1 (0.2)	1 (0.2)
Photosensitivity reaction	3 (1.0)	0 (0.0)	3 (0.5)
Pityriasis	0 (0.0)	1 (0.2)	1 (0.2)
Prurigo	0 (0.0)	1 (0.2)	1 (0.2)
Pruritus	1 (0.3)	10 (1.6)	11 (1.7)
Pruritus generalized	1 (0.3)	1 (0.2)	2 (0.3)
Psoriasis	5 (1.7)	38 (6.1)	41 (6.3)
Rash	1 (0.3)	2 (0.3)	3 (0.5)
Rosacea	0 (0.0)	1 (0.2)	1 (0.2)
Seborrheic dermatitis	2 (0.7)	4 (0.6)	6 (0.9)
Skin exfoliation	0 (0.0)	1 (0.2)	1 (0.2)
Skin fissures	0 (0.0)	2 (0.3)	2 (0.3)
Skin hyperpigmentation	0 (0.0)	1 (0.2)	1 (0.2)
Skin lesion	1 (0.3)	0 (0.0)	1 (0.2)
Skin mass	1 (0.3)	0 (0.0)	1 (0.2)
Skin necrosis	0 (0.0)	1 (0.2)	1 (0.2)
Skin ulcer	0 (0.0)	2 (0.3)	2 (0.3)
Solar lentigo	1 (0.3)	1 (0.2)	2 (0.3)
Stasis dermatitis	1 (0.3)	0 (0.0)	1 (0.2)
Toxic skin eruption	0 (0.0)	1 (0.2)	1 (0.2)
Urticaria	2 (0.7)	2 (0.3)	4 (0.6)
Vitiligo	1 (0.3)	1 (0.2)	2 (0.3)
Surgical and medical procedures	**0 (0.0)**	**2 (0.3)**	**2 (0.3)**
Abortion induced	0 (0.0)	1 (0.2)	1 (0.2)
Cardioversion	0 (0.0)	1 (0.2)	1 (0.2)
Vascular disorders	**9 (3.1)**	**22 (3.5)**	**31 (4.7)**
Aortic aneurysm	0 (0.0)	2 (0.3)	2 (0.3)
Hematoma	0 (0.0)	1 (0.2)	1 (0.2)
Hypertension	8 (2.7)	13 (2.1)	21 (3.2)
Hypotension	0 (0.0)	2 (0.3)	2 (0.3)
Lymphoedema	0 (0.0)	1 (0.2)	1 (0.2)
Orthostatic hypotension	0 (0.0)	1 (0.2)	1 (0.2)
Thrombophlebitis	0 (0.0)	1 (0.2)	1 (0.2)
Thrombosis	0 (0.0)	1 (0.2)	1 (0.2)
Varicose vein	0 (0.0)	1 (0.2)	1 (0.2)
Venous thrombosis limb	1 (0.3)	0 (0.0)	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTIAN = 5 to 5 (BKZ Q4W); TRTIAN = 6 to 6 (BKZ Q8W); TRTIAN = 7 to 7 (BKZ Total); TRTEMFL = "Y" (Adverse Events).

Treatment Emergent Adverse Events -PS0014

Table 24: Treatment Emergent Adverse Events -PS0014

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Blood and lymphatic system disorders	**24 (2.5)**	**21 (1.7)**	**45 (3.3)**
Anemia	2 (0.2)	1 (0.1)	3 (0.2)
Anemia megaloblastic	1 (0.1)	0 (0.0)	1 (0.1)
Anemia vitamin b12 deficiency	0 (0.0)	1 (0.1)	1 (0.1)
Anisocytosis	0 (0.0)	1 (0.1)	1 (0.1)
Hemolytic anemia	0 (0.0)	1 (0.1)	1 (0.1)
Hemorrhagic anemia	0 (0.0)	2 (0.2)	2 (0.1)
Hemorrhagic diathesis	1 (0.1)	0 (0.0)	1 (0.1)
Hyperchromic anemia	0 (0.0)	1 (0.1)	1 (0.1)
Iron deficiency anemia	2 (0.2)	2 (0.2)	4 (0.3)
Leukocytosis	2 (0.2)	1 (0.1)	3 (0.2)
Leukopenia	2 (0.2)	4 (0.3)	6 (0.4)
Lymphadenitis	1 (0.1)	0 (0.0)	1 (0.1)
Lymphadenopathy	3 (0.3)	3 (0.2)	6 (0.4)
Lymphopenia	3 (0.3)	1 (0.1)	4 (0.3)
Microcytic anemia	1 (0.1)	0 (0.0)	1 (0.1)
Monoclonal b-cell lymphocytosis	0 (0.0)	1 (0.1)	1 (0.1)
Mon cytosis	0 (0.0)	1 (0.1)	1 (0.1)
Nephrogenic anemia	1 (0.1)	0 (0.0)	1 (0.1)
Neutropenia	4 (0.4)	2 (0.2)	6 (0.4)
Pancytopenia	1 (0.1)	0 (0.0)	1 (0.1)
Polycythemia	0 (0.0)	1 (0.1)	1 (0.1)
Thrombocytopenia	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac disorders	**26 (2.7)**	**36 (2.8)**	**58 (4.3)**
Acute coronary syndrome	0 (0.0)	2 (0.2)	2 (0.1)
Acute myocardial infarction	1 (0.1)	1 (0.1)	2 (0.1)
Angina pectoris	3 (0.3)	2 (0.2)	4 (0.3)
Aortic valve incompetence	1 (0.1)	0 (0.0)	1 (0.1)
Arrhythmia	1 (0.1)	1 (0.1)	2 (0.1)
Arrhythmia supraventricular	1 (0.1)	1 (0.1)	2 (0.1)
Arteriosclerosis coronary artery	1 (0.1)	0 (0.0)	1 (0.1)
Atrial fibrillation	2 (0.2)	3 (0.2)	5 (0.4)
Atrioventricular block first degree	2 (0.2)	4 (0.3)	5 (0.4)
Bradycardia	0 (0.0)	1 (0.1)	1 (0.1)
Bundle branch block left	0 (0.0)	1 (0.1)	1 (0.1)
Bundle branch block right	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac arrest	2 (0.2)	1 (0.1)	3 (0.2)
Cardiac failure chronic	0 (0.0)	1 (0.1)	1 (0.1)
Cardiac failure congestive	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac hypertrophy	1 (0.1)	0 (0.0)	1 (0.1)
Cardiomegaly	0 (0.0)	1 (0.1)	1 (0.1)
Cardiomyopathy	1 (0.1)	1 (0.1)	2 (0.1)
Cardiopulmonary failure	1 (0.1)	0 (0.0)	1 (0.1)
Cardiovascular disorder	0 (0.0)	1 (0.1)	1 (0.1)
Congestive cardiomyopathy	1 (0.1)	0 (0.0)	1 (0.1)
Coronary artery disease	1 (0.1)	0 (0.0)	1 (0.1)
Coronary artery stenosis	1 (0.1)	0 (0.0)	1 (0.1)
Extrasystoles	0 (0.0)	1 (0.1)	1 (0.1)
Hypertensive cardiomyopathy	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Left ventricular dysfunction	1 (0.1)	0 (0.0)	1 (0.1)
Left ventricular hypertrophy	0 (0.0)	1 (0.1)	1 (0.1)
Myocardial infarction	3 (0.3)	1 (0.1)	4 (0.3)
Myocardial ischemia	1 (0.1)	1 (0.1)	2 (0.1)
Palpitations	0 (0.0)	5 (0.4)	5 (0.4)
Sinus bradycardia	1 (0.1)	1 (0.1)	2 (0.1)
Sinus tachycardia	1 (0.1)	0 (0.0)	1 (0.1)
Supraventricular extrasystoles	1 (0.1)	1 (0.1)	1 (0.1)
Supraventricular tachycardia	0 (0.0)	1 (0.1)	1 (0.1)
Systolic dysfunction	1 (0.1)	0 (0.0)	1 (0.1)
Tachyarrhythmia	1 (0.1)	0 (0.0)	1 (0.1)
Tachycardia	3 (0.3)	2 (0.2)	5 (0.4)
Tricuspid valve incompetence	2 (0.2)	0 (0.0)	2 (0.1)
Ventricular extrasystoles	0 (0.0)	3 (0.2)	3 (0.2)
Ventricular tachycardia	1 (0.1)	0 (0.0)	1 (0.1)
Wolff-parkinson-white syndrome	0 (0.0)	1 (0.1)	1 (0.1)
Congenital, familial and genetic disorders	**2 (0.2)**	**2 (0.2)**	**4 (0.3)**
Bicuspid aortic valve	0 (0.0)	1 (0.1)	1 (0.1)
Dermoid cyst	0 (0.0)	1 (0.1)	1 (0.1)
Type v hyperlipidemia	1 (0.1)	0 (0.0)	1 (0.1)
Venous angioma of brain	1 (0.1)	0 (0.0)	1 (0.1)
Ear and labyrinth disorders	**22 (2.3)**	**18 (1.4)**	**40 (3.0)**
Cerumen impaction	0 (0.0)	1 (0.1)	1 (0.1)
Deafness bilateral	1 (0.1)	0 (0.0)	1 (0.1)
Ear discomfort	1 (0.1)	3 (0.2)	4 (0.3)
Ear pain	2 (0.2)	4 (0.3)	6 (0.4)
Ear pruritus	0 (0.0)	1 (0.1)	1 (0.1)
Ear swelling	0 (0.0)	1 (0.1)	1 (0.1)
Excessive cerumen production	1 (0.1)	0 (0.0)	1 (0.1)
External ear inflammation	1 (0.1)	0 (0.0)	1 (0.1)
Hypoacusis	1 (0.1)	1 (0.1)	2 (0.1)
Inner ear disorder	0 (0.0)	1 (0.1)	1 (0.1)
Otorrhea	1 (0.1)	0 (0.0)	1 (0.1)
Sudden hearing loss	1 (0.1)	0 (0.0)	1 (0.1)
Tinnitus	3 (0.3)	1 (0.1)	4 (0.3)
Tympanic membrane perforation	2 (0.2)	0 (0.0)	2 (0.1)
Vertigo	9 (0.9)	4 (0.3)	13 (1.0)
Vertigo positional	1 (0.1)	1 (0.1)	2 (0.1)
Endocrine disorders	**6 (0.6)**	**8 (0.6)**	**14 (1.0)**
Adrenal insufficiency	1 (0.1)	0 (0.0)	1 (0.1)
Autoimmune thyroiditis	1 (0.1)	0 (0.0)	1 (0.1)
Goiter	1 (0.1)	1 (0.1)	2 (0.1)
Hyperparathyroidism primary	0 (0.0)	1 (0.1)	1 (0.1)
Hyperthyroidism	1 (0.1)	0 (0.0)	1 (0.1)
Hypothyroidism	1 (0.1)	7 (0.6)	8 (0.6)
Thyroid mass	1 (0.1)	0 (0.0)	1 (0.1)
Eye disorders	**52 (5.4)**	**55 (4.3)**	**101 (7.5)**
Blepharitis	18 (1.9)	14 (1.1)	31 (2.3)
Blepharitis allergic	0 (0.0)	3 (0.2)	3 (0.2)
Cataract	6 (0.6)	9 (0.7)	15 (1.1)
Chalazion	3 (0.3)	3 (0.2)	6 (0.4)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Conjunctival hemorrhage	1 (0.1)	0 (0.0)	1 (0.1)
Conjunctivitis allergic	7 (0.7)	7 (0.6)	13 (1.0)
Dry eye	5 (0.5)	4 (0.3)	9 (0.7)
Eczema eyelids	2 (0.2)	2 (0.2)	4 (0.3)
Episcleritis	1 (0.1)	2 (0.2)	3 (0.2)
Erythema of eyelid	1 (0.1)	2 (0.2)	3 (0.2)
Eye discharge	0 (0.0)	1 (0.1)	1 (0.1)
Eye inflammation	1 (0.1)	0 (0.0)	1 (0.1)
Eye pain	0 (0.0)	1 (0.1)	1 (0.1)
Eye pruritus	1 (0.1)	1 (0.1)	2 (0.1)
Eyelid cyst	2 (0.2)	1 (0.1)	3 (0.2)
Eyelid oedema	0 (0.0)	1 (0.1)	1 (0.1)
Eyelid ptosis	0 (0.0)	1 (0.1)	1 (0.1)
Eyelid skin dryness	0 (0.0)	1 (0.1)	1 (0.1)
Glaucoma	0 (0.0)	1 (0.1)	1 (0.1)
Keratitis	2 (0.2)	0 (0.0)	2 (0.1)
Lacrimation increased	1 (0.1)	0 (0.0)	1 (0.1)
Macular degeneration	1 (0.1)	0 (0.0)	1 (0.1)
Meibomian gland dysfunction	0 (0.0)	2 (0.2)	2 (0.1)
Neovascular age-related macular degeneration	1 (0.1)	0 (0.0)	1 (0.1)
Ocular hyperemia	0 (0.0)	1 (0.1)	1 (0.1)
Ocular rosacea	0 (0.0)	1 (0.1)	1 (0.1)
Photoelectric conjunctivitis	1 (0.1)	0 (0.0)	1 (0.1)
Presbyopia	1 (0.1)	0 (0.0)	1 (0.1)
Pterygium	0 (0.0)	1 (0.1)	1 (0.1)
Retinal detachment	0 (0.0)	2 (0.2)	2 (0.1)
Retinal tear	0 (0.0)	1 (0.1)	1 (0.1)
Scleritis	2 (0.2)	1 (0.1)	3 (0.2)
Visual impairment	0 (0.0)	2 (0.2)	2 (0.1)
Gastrointestinal disorders	**158 (16.3)**	**142 (11.2)**	**274 (20.3)**
Abdominal discomfort	4 (0.4)	3 (0.2)	7 (0.5)
Abdominal distension	3 (0.3)	4 (0.3)	7 (0.5)
Abdominal pain	6 (0.6)	7 (0.6)	13 (1.0)
Abdominal pain lower	3 (0.3)	0 (0.0)	3 (0.2)
Abdominal pain upper	6 (0.6)	6 (0.5)	11 (0.8)
Abdominal tenderness	0 (0.0)	1 (0.1)	1 (0.1)
Anal fissure	1 (0.1)	2 (0.2)	3 (0.2)
Anal prolapse	0 (0.0)	1 (0.1)	1 (0.1)
Anal pruritus	0 (0.0)	1 (0.1)	1 (0.1)
Aphthous ulcer	7 (0.7)	3 (0.2)	10 (0.7)
Cheilitis	4 (0.4)	2 (0.2)	6 (0.4)
Cheilosis	1 (0.1)	1 (0.1)	2 (0.1)
Chronic gastritis	7 (0.7)	0 (0.0)	7 (0.5)
Coating in mouth	2 (0.2)	0 (0.0)	2 (0.1)
Colitis	1 (0.1)	0 (0.0)	1 (0.1)
Constipation	4 (0.4)	7 (0.6)	11 (0.8)
Crohn's disease	1 (0.1)	2 (0.2)	3 (0.2)
Cyclic vomiting syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Dental caries	10 (1.0)	17 (1.3)	25 (1.8)
Dental cyst	1 (0.1)	1 (0.1)	2 (0.1)
Diarrhoea	23 (2.4)	20 (1.6)	42 (3.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Diarrhoea hemorrhagic	0 (0.0)	1 (0.1)	1 (0.1)
Diverticular perforation	0 (0.0)	2 (0.2)	2 (0.1)
Diverticulum	2 (0.2)	1 (0.1)	3 (0.2)
Diverticulum intestinal	0 (0.0)	1 (0.1)	1 (0.1)
Diverticulum intestinal hemorrhagic	1 (0.1)	1 (0.1)	2 (0.1)
Dry mouth	2 (0.2)	0 (0.0)	2 (0.1)
Duodenal ulcer	1 (0.1)	1 (0.1)	2 (0.1)
Dyspepsia	6 (0.6)	5 (0.4)	11 (0.8)
Dysphagia	0 (0.0)	2 (0.2)	2 (0.1)
Enteritis	3 (0.3)	0 (0.0)	3 (0.2)
Enterocolitis	0 (0.0)	1 (0.1)	1 (0.1)
Eructation	0 (0.0)	1 (0.1)	1 (0.1)
Feces soft	0 (0.0)	1 (0.1)	1 (0.1)
Food poisoning	4 (0.4)	5 (0.4)	9 (0.7)
Gastric mucosa erythema	1 (0.1)	0 (0.0)	1 (0.1)
Gastritis	5 (0.5)	4 (0.3)	9 (0.7)
Gastrointestinal disorder	2 (0.2)	1 (0.1)	3 (0.2)
Gastrointestinal inflammation	1 (0.1)	1 (0.1)	2 (0.1)
Gastroesophageal reflux disease	17 (1.8)	13 (1.0)	30 (2.2)
Gingival pain	1 (0.1)	0 (0.0)	1 (0.1)
Gingival swelling	1 (0.1)	0 (0.0)	1 (0.1)
Glossitis	5 (0.5)	3 (0.2)	7 (0.5)
Hematochezia	0 (0.0)	1 (0.1)	1 (0.1)
Hemorrhoidal hemorrhage	1 (0.1)	0 (0.0)	1 (0.1)
Hemorrhoids	6 (0.6)	2 (0.2)	8 (0.6)
Hiatus hernia	1 (0.1)	1 (0.1)	2 (0.1)
Inguinal hernia	0 (0.0)	1 (0.1)	1 (0.1)
Intestinal polyp	0 (0.0)	1 (0.1)	1 (0.1)
Irritable bowel syndrome	3 (0.3)	0 (0.0)	3 (0.2)
Large intestine polyp	5 (0.5)	4 (0.3)	9 (0.7)
Leukoplakia oral	0 (0.0)	3 (0.2)	3 (0.2)
Lip dry	1 (0.1)	0 (0.0)	1 (0.1)
Lip oedema	0 (0.0)	1 (0.1)	1 (0.1)
Lip swelling	0 (0.0)	1 (0.1)	1 (0.1)
Lumbar hernia	1 (0.1)	0 (0.0)	1 (0.1)
Melaena	1 (0.1)	0 (0.0)	1 (0.1)
Mouth ulceration	2 (0.2)	2 (0.2)	4 (0.3)
Nausea	6 (0.6)	8 (0.6)	13 (1.0)
Noninfective gingivitis	0 (0.0)	1 (0.1)	1 (0.1)
Esophageal food impaction	0 (0.0)	1 (0.1)	1 (0.1)
Esophageal pain	0 (0.0)	1 (0.1)	1 (0.1)
Esophageal ulcer	0 (0.0)	1 (0.1)	1 (0.1)
Esophagitis	2 (0.2)	1 (0.1)	3 (0.2)
Oral disorder	0 (0.0)	1 (0.1)	1 (0.1)
Oral mucosal erythema	0 (0.0)	1 (0.1)	1 (0.1)
Oral pain	1 (0.1)	0 (0.0)	1 (0.1)
Oroantral fistula	0 (0.0)	1 (0.1)	1 (0.1)
Pancreatic insufficiency	0 (0.0)	1 (0.1)	1 (0.1)
Periodontal disease	1 (0.1)	3 (0.2)	4 (0.3)
Periodontal inflammation	0 (0.0)	1 (0.1)	1 (0.1)
Rectal haemorrhage	2 (0.2)	0 (0.0)	2 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Rectal polyp	0 (0.0)	1 (0.1)	1 (0.1)
Reflux gastritis	0 (0.0)	1 (0.1)	1 (0.1)
Salivary gland mucocoele	1 (0.1)	0 (0.0)	1 (0.1)
Stomatitis	7 (0.7)	5 (0.4)	11 (0.8)
Stress ulcer	1 (0.1)	0 (0.0)	1 (0.1)
Tongue discolouration	0 (0.0)	1 (0.1)	1 (0.1)
Tongue dysplasia	0 (0.0)	1 (0.1)	1 (0.1)
Tongue geographic	2 (0.2)	0 (0.0)	2 (0.1)
Tongue ulceration	2 (0.2)	2 (0.2)	4 (0.3)
Tooth disorder	1 (0.1)	1 (0.1)	2 (0.1)
Toothache	11 (1.1)	16 (1.3)	24 (1.8)
Umbilical hernia	1 (0.1)	0 (0.0)	1 (0.1)
Vomiting	3 (0.3)	2 (0.2)	5 (0.4)
General disorders and administration site conditions	**61 (6.3)**	**81 (6.4)**	**137 (10.1)**
Administration site erythema	0 (0.0)	1 (0.1)	1 (0.1)
Asthenia	1 (0.1)	3 (0.2)	4 (0.3)
Chest discomfort	0 (0.0)	1 (0.1)	1 (0.1)
Chest pain	0 (0.0)	1 (0.1)	1 (0.1)
Chills	0 (0.0)	2 (0.2)	2 (0.1)
Death	1 (0.1)	1 (0.1)	1 (0.1)
Drug ineffective	0 (0.0)	1 (0.1)	1 (0.1)
Face oedema	0 (0.0)	1 (0.1)	1 (0.1)
Fatigue	7 (0.7)	8 (0.6)	15 (1.1)
Influenza like illness	8 (0.8)	4 (0.3)	12 (0.9)
Injection site bruising	3 (0.3)	1 (0.1)	4 (0.3)
Injection site eczema	1 (0.1)	0 (0.0)	1 (0.1)
Injection site erythema	3 (0.3)	1 (0.1)	3 (0.2)
Injection site haematoma	0 (0.0)	3 (0.2)	3 (0.2)
Injection site haemorrhage	3 (0.3)	1 (0.1)	4 (0.3)
Injection site induration	0 (0.0)	1 (0.1)	1 (0.1)
Injection site inflammation	1 (0.1)	0 (0.0)	1 (0.1)
Injection site pain	5 (0.5)	12 (0.9)	16 (1.2)
Injection site pruritus	1 (0.1)	0 (0.0)	1 (0.1)
Injection site reaction	3 (0.3)	2 (0.2)	5 (0.4)
Injection site swelling	1 (0.1)	1 (0.1)	2 (0.1)
Malaise	4 (0.4)	1 (0.1)	5 (0.4)
Mass	0 (0.0)	1 (0.1)	1 (0.1)
Non-cardiac chest pain	3 (0.3)	3 (0.2)	6 (0.4)
Oedema	1 (0.1)	1 (0.1)	2 (0.1)
Oedema peripheral	2 (0.2)	6 (0.5)	8 (0.6)
Pain	4 (0.4)	2 (0.2)	6 (0.4)
Peripheral swelling	2 (0.2)	6 (0.5)	8 (0.6)
Polyp	0 (0.0)	1 (0.1)	1 (0.1)
Pyrexia	11 (1.1)	22 (1.7)	32 (2.4)
Sensation of foreign body	0 (0.0)	1 (0.1)	1 (0.1)
Stent-graft endoleak	0 (0.0)	1 (0.1)	1 (0.1)
Swelling	1 (0.1)	0 (0.0)	1 (0.1)
Vaccination site pain	0 (0.0)	5 (0.4)	5 (0.4)
Vaccination site reaction	0 (0.0)	1 (0.1)	1 (0.1)
Xerosis	1 (0.1)	0 (0.0)	1 (0.1)
Hepatobiliary disorders	**18 (1.9)**	**16 (1.3)**	**33 (2.4)**

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Autoimmune hepatitis	0 (0.0)	1 (0.1)	1 (0.1)
Biliary dyskinesia	1 (0.1)	0 (0.0)	1 (0.1)
Cholecystitis	2 (0.2)	0 (0.0)	2 (0.1)
Cholecystocholangitis	1 (0.1)	0 (0.0)	1 (0.1)
Cholelithiasis	2 (0.2)	4 (0.3)	6 (0.4)
Drug-induced liver injury	1 (0.1)	2 (0.2)	2 (0.1)
Fatty liver alcoholic	1 (0.1)	1 (0.1)	2 (0.1)
Gallbladder cholesterolosis	1 (0.1)	0 (0.0)	1 (0.1)
Gallbladder disorder	0 (0.0)	1 (0.1)	1 (0.1)
Hepatic fibrosis	1 (0.1)	0 (0.0)	1 (0.1)
Hepatic function abnormal	1 (0.1)	0 (0.0)	1 (0.1)
Hepatic steatosis	4 (0.4)	4 (0.3)	8 (0.6)
Hepatomegaly	1 (0.1)	0 (0.0)	1 (0.1)
Hyperbilirubinaemia	2 (0.2)	0 (0.0)	2 (0.1)
Liver disorder	1 (0.1)	0 (0.0)	1 (0.1)
Liver injury	0 (0.0)	1 (0.1)	1 (0.1)
Non-alcoholic fatty liver	0 (0.0)	2 (0.2)	2 (0.1)
Non-alcoholic steatohepatitis	2 (0.2)	0 (0.0)	2 (0.1)
Steatohepatitis	1 (0.1)	1 (0.1)	2 (0.1)
Immune system disorders	**16 (1.7)**	**11 (0.9)**	**26 (1.9)**
Allergy to animal	1 (0.1)	0 (0.0)	1 (0.1)
Allergy to arthropod bite	2 (0.2)	1 (0.1)	3 (0.2)
Allergy to arthropod sting	1 (0.1)	0 (0.0)	1 (0.1)
Anaphylactic reaction	0 (0.0)	1 (0.1)	1 (0.1)
Anaphylactic shock	1 (0.1)	0 (0.0)	1 (0.1)
Drug hypersensitivity	3 (0.3)	4 (0.3)	7 (0.5)
Food allergy	0 (0.0)	1 (0.1)	1 (0.1)
Hypersensitivity	0 (0.0)	2 (0.2)	2 (0.1)
Seasonal allergy	8 (0.8)	2 (0.2)	9 (0.7)
Infections and infestations	**582 (60.1)**	**570 (45.0)**	**890 (65.8)**
Abdominal wall abscess	0 (0.0)	1 (0.1)	1 (0.1)
Abscess jaw	1 (0.1)	0 (0.0)	1 (0.1)
Abscess limb	3 (0.3)	0 (0.0)	3 (0.2)
Abscess neck	0 (0.0)	1 (0.1)	1 (0.1)
Acute sinusitis	0 (0.0)	3 (0.2)	3 (0.2)
Anal candidiasis	1 (0.1)	0 (0.0)	1 (0.1)
Angular cheilitis	14 (1.4)	14 (1.1)	27 (2.0)
Appendicitis	1 (0.1)	1 (0.1)	2 (0.1)
Asymptomatic bacteriuria	3 (0.3)	3 (0.2)	6 (0.4)
Bacterial rhinitis	3 (0.3)	0 (0.0)	3 (0.2)
Bacterial vaginosis	1 (0.1)	0 (0.0)	1 (0.1)
Bacteriuria	3 (0.3)	3 (0.2)	6 (0.4)
Balanitis candida	0 (0.0)	1 (0.1)	1 (0.1)
Balanoposthitis infective	1 (0.1)	0 (0.0)	1 (0.1)
Bartholin's abscess	1 (0.1)	0 (0.0)	1 (0.1)
Blastomycosis	0 (0.0)	1 (0.1)	1 (0.1)
Body tinea	2 (0.2)	8 (0.6)	9 (0.7)
Bronchitis	18 (1.9)	11 (0.9)	28 (2.1)
Bronchitis bacterial	1 (0.1)	0 (0.0)	1 (0.1)
Bursitis infective	1 (0.1)	1 (0.1)	2 (0.1)
Candida infection	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Cellulitis	12 (1.2)	8 (0.6)	19 (1.4)
Chronic sinusitis	1 (0.1)	2 (0.2)	3 (0.2)
Chronic tonsillitis	1 (0.1)	1 (0.1)	2 (0.1)
Colonic abscess	0 (0.0)	2 (0.2)	2 (0.1)
Conjunctivitis	28 (2.9)	20 (1.6)	46 (3.4)
Conjunctivitis bacterial	10 (1.0)	2 (0.2)	11 (0.8)
Conjunctivitis viral	2 (0.2)	1 (0.1)	3 (0.2)
Corona virus infection	23 (2.4)	78 (6.2)	95 (7.0)
Cystitis	6 (0.6)	10 (0.8)	15 (1.1)
Cystitis bacterial	1 (0.1)	0 (0.0)	1 (0.1)
Dermatitis infected	0 (0.0)	1 (0.1)	1 (0.1)
Dermatophytosis of nail	0 (0.0)	4 (0.3)	4 (0.3)
Diarrhoea infectious	1 (0.1)	0 (0.0)	1 (0.1)
Diverticulitis	3 (0.3)	2 (0.2)	4 (0.3)
Ear infection	12 (1.2)	7 (0.6)	19 (1.4)
Ear infection bacterial	1 (0.1)	1 (0.1)	2 (0.1)
Ear infection fungal	0 (0.0)	2 (0.2)	2 (0.1)
Ear infection staphylococcal	0 (0.0)	1 (0.1)	1 (0.1)
Eczema impetiginous	0 (0.0)	1 (0.1)	1 (0.1)
Eczema infected	5 (0.5)	4 (0.3)	7 (0.5)
Enteritis infectious	0 (0.0)	1 (0.1)	1 (0.1)
Enterobiasis	0 (0.0)	1 (0.1)	1 (0.1)
Enterocolitis viral	1 (0.1)	0 (0.0)	1 (0.1)
Epididymitis	2 (0.2)	2 (0.2)	3 (0.2)
Erysipelas	5 (0.5)	3 (0.2)	8 (0.6)
Erythema migrans	0 (0.0)	1 (0.1)	1 (0.1)
Escherichia urinary tract infection	1 (0.1)	1 (0.1)	2 (0.1)
Eye infection	0 (0.0)	1 (0.1)	1 (0.1)
Eye infection bacterial	1 (0.1)	0 (0.0)	1 (0.1)
Eyelid folliculitis	3 (0.3)	1 (0.1)	4 (0.3)
Eyelid infection	0 (0.0)	1 (0.1)	1 (0.1)
Folliculitis	40 (4.1)	23 (1.8)	58 (4.3)
Fungal infection	1 (0.1)	1 (0.1)	2 (0.1)
Fungal oesophagitis	1 (0.1)	1 (0.1)	1 (0.1)
Fungal skin infection	8 (0.8)	8 (0.6)	16 (1.2)
Furuncle	4 (0.4)	7 (0.6)	11 (0.8)
Gastritis viral	3 (0.3)	0 (0.0)	3 (0.2)
Gastroenteritis	10 (1.0)	13 (1.0)	23 (1.7)
Gastroenteritis bacterial	0 (0.0)	1 (0.1)	1 (0.1)
Gastroenteritis norovirus	1 (0.1)	0 (0.0)	1 (0.1)
Gastroenteritis rotavirus	1 (0.1)	0 (0.0)	1 (0.1)
Gastroenteritis viral	6 (0.6)	1 (0.1)	7 (0.5)
Gastrointestinal candidiasis	0 (0.0)	1 (0.1)	1 (0.1)
Gastrointestinal infection	1 (0.1)	2 (0.2)	3 (0.2)
Gastrointestinal viral infection	0 (0.0)	3 (0.2)	3 (0.2)
Genital candidiasis	2 (0.2)	1 (0.1)	3 (0.2)
Genital herpes	0 (0.0)	1 (0.1)	1 (0.1)
Genital infection	0 (0.0)	1 (0.1)	1 (0.1)
Genital infection fungal	1 (0.1)	1 (0.1)	2 (0.1)
Genitourinary tract infection	1 (0.1)	0 (0.0)	1 (0.1)
Gingivitis	2 (0.2)	3 (0.2)	5 (0.4)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Groin infection	0 (0.0)	1 (0.1)	1 (0.1)
Helicobacter gastritis	0 (0.0)	1 (0.1)	1 (0.1)
Helicobacter infection	5 (0.5)	2 (0.2)	7 (0.5)
Herpes simplex	3 (0.3)	3 (0.2)	6 (0.4)
Herpes zoster	2 (0.2)	9 (0.7)	11 (0.8)
Herpes zoster oticus	0 (0.0)	1 (0.1)	1 (0.1)
Hordeolum	6 (0.6)	12 (0.9)	17 (1.3)
Impetigo	10 (1.0)	5 (0.4)	14 (1.0)
Infected dermal cyst	0 (0.0)	2 (0.2)	2 (0.1)
Infection	0 (0.0)	1 (0.1)	1 (0.1)
Infective scleritis	0 (0.0)	1 (0.1)	1 (0.1)
Influenza	12 (1.2)	9 (0.7)	21 (1.6)
Kaposi's varicelliform eruption	1 (0.1)	0 (0.0)	1 (0.1)
Laryngitis	1 (0.1)	0 (0.0)	1 (0.1)
Latent tuberculosis	6 (0.6)	4 (0.3)	10 (0.7)
Localised infection	1 (0.1)	2 (0.2)	3 (0.2)
Lower respiratory tract infection	1 (0.1)	0 (0.0)	1 (0.1)
Lung abscess	0 (0.0)	1 (0.1)	1 (0.1)
Lyme disease	2 (0.2)	1 (0.1)	3 (0.2)
Malassezia infection	1 (0.1)	0 (0.0)	1 (0.1)
Molluscum contagiosum	1 (0.1)	0 (0.0)	1 (0.1)
Nail bed infection bacterial	0 (0.0)	1 (0.1)	1 (0.1)
Nail candida	1 (0.1)	0 (0.0)	1 (0.1)
Nasal herpes	1 (0.1)	0 (0.0)	1 (0.1)
Nasopharyngitis	188 (19.4)	135 (10.7)	299 (22.1)
Oesophageal candidiasis	1 (0.1)	2 (0.2)	3 (0.2)
Onychomycosis	3 (0.3)	4 (0.3)	7 (0.5)
Ophthalmic herpes zoster	1 (0.1)	0 (0.0)	1 (0.1)
Oral bacterial infection	0 (0.0)	1 (0.1)	1 (0.1)
Oral candidiasis	158 (16.3)	112 (8.8)	230 (17.0)
Oral fungal infection	19 (2.0)	17 (1.3)	29 (2.1)
Oral herpes	18 (1.9)	14 (1.1)	30 (2.2)
Oral infection	0 (0.0)	2 (0.2)	2 (0.1)
Oral pustule	0 (0.0)	1 (0.1)	1 (0.1)
Orchitis	2 (0.2)	0 (0.0)	2 (0.1)
Orf	0 (0.0)	1 (0.1)	1 (0.1)
Oropharyngeal candidiasis	6 (0.6)	2 (0.2)	8 (0.6)
Otitis externa	17 (1.8)	15 (1.2)	31 (2.3)
Otitis externa candida	1 (0.1)	0 (0.0)	1 (0.1)
Otitis media	15 (1.5)	6 (0.5)	21 (1.6)
Otitis media acute	0 (0.0)	2 (0.2)	2 (0.1)
Paronychia	3 (0.3)	5 (0.4)	8 (0.6)
Parotitis	2 (0.2)	1 (0.1)	3 (0.2)
Pelvic abscess	1 (0.1)	0 (0.0)	1 (0.1)
Perichondritis	1 (0.1)	1 (0.1)	1 (0.1)
Pericoronitis	0 (0.0)	1 (0.1)	1 (0.1)
Periodontitis	6 (0.6)	6 (0.5)	12 (0.9)
Periorbital cellulitis	0 (0.0)	1 (0.1)	1 (0.1)
Periorbital infection	1 (0.1)	0 (0.0)	1 (0.1)
Pharyngitis	21 (2.2)	24 (1.9)	43 (3.2)
Pharyngitis streptococcal	3 (0.3)	6 (0.5)	9 (0.7)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Pharyngotonsillitis	1 (0.1)	0 (0.0)	1 (0.1)
Pilonidal cyst	1 (0.1)	1 (0.1)	2 (0.1)
Pneumonia	4 (0.4)	3 (0.2)	5 (0.4)
Pneumonia bacterial	3 (0.3)	0 (0.0)	3 (0.2)
Pneumonia viral	0 (0.0)	1 (0.1)	1 (0.1)
Pulpitis dental	6 (0.6)	2 (0.2)	7 (0.5)
Rash pustular	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory tract infection	1 (0.1)	1 (0.1)	2 (0.1)
Rhinitis	10 (1.0)	7 (0.6)	17 (1.3)
Sinusitis	20 (2.1)	27 (2.1)	45 (3.3)
Skin bacterial infection	5 (0.5)	4 (0.3)	9 (0.7)
Skin candida	10 (1.0)	8 (0.6)	18 (1.3)
Skin infection	1 (0.1)	1 (0.1)	2 (0.1)
Sporotrichosis	0 (0.0)	1 (0.1)	1 (0.1)
Staphylococcal infection	2 (0.2)	1 (0.1)	3 (0.2)
Staphylococcal skin infection	4 (0.4)	2 (0.2)	6 (0.4)
Streptococcal abscess	1 (0.1)	0 (0.0)	1 (0.1)
Streptococcal infection	1 (0.1)	0 (0.0)	1 (0.1)
Subcutaneous abscess	5 (0.5)	6 (0.5)	11 (0.8)
Sycosis barbae	1 (0.1)	0 (0.0)	1 (0.1)
Tinea capitis	1 (0.1)	0 (0.0)	1 (0.1)
Tinea cruris	3 (0.3)	2 (0.2)	5 (0.4)
Tinea manuum	2 (0.2)	3 (0.2)	4 (0.3)
Tinea pedis	14 (1.4)	16 (1.3)	27 (2.0)
Tinea versicolour	2 (0.2)	6 (0.5)	7 (0.5)
Tongue fungal infection	1 (0.1)	1 (0.1)	2 (0.1)
Tonsillitis	15 (1.5)	9 (0.7)	22 (1.6)
Tonsillitis bacterial	1 (0.1)	0 (0.0)	1 (0.1)
Tooth abscess	3 (0.3)	4 (0.3)	7 (0.5)
Tooth infection	8 (0.8)	4 (0.3)	11 (0.8)
Tracheitis	1 (0.1)	0 (0.0)	1 (0.1)
Upper respiratory tract infection	77 (7.9)	73 (5.8)	142 (10.5)
Urethritis	1 (0.1)	1 (0.1)	2 (0.1)
Urinary tract infection	49 (5.1)	46 (3.6)	88 (6.5)
Urinary tract infection bacterial	1 (0.1)	1 (0.1)	2 (0.1)
Vaginal infection	2 (0.2)	2 (0.2)	3 (0.2)
Viral infection	1 (0.1)	2 (0.2)	3 (0.2)
Viral pharyngitis	1 (0.1)	0 (0.0)	1 (0.1)
Viral tonsillitis	0 (0.0)	1 (0.1)	1 (0.1)
Viral upper respiratory tract infection	9 (0.9)	9 (0.7)	17 (1.3)
Vulvovaginal candidiasis	8 (0.8)	3 (0.2)	11 (0.8)
Vulvovaginal mycotic infection	1 (0.1)	5 (0.4)	6 (0.4)
Wound infection staphylococcal	1 (0.1)	0 (0.0)	1 (0.1)
Injury, poisoning and procedural complications	**96 (9.9)**	**108 (8.5)**	**195 (14.4)**
Accident at work	1 (0.1)	1 (0.1)	2 (0.1)
Anaemia postoperative	0 (0.0)	1 (0.1)	1 (0.1)
Animal bite	3 (0.3)	3 (0.2)	5 (0.4)
Ankle fracture	1 (0.1)	1 (0.1)	2 (0.1)
Arthropod bite	7 (0.7)	8 (0.6)	15 (1.1)
Arthropod sting	2 (0.2)	2 (0.2)	4 (0.3)
Back injury	1 (0.1)	0 (0.0)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Bone contusion	3 (0.3)	1 (0.1)	4 (0.3)
Burns first degree	1 (0.1)	1 (0.1)	2 (0.1)
Burns second degree	0 (0.0)	1 (0.1)	1 (0.1)
Chemical burn of skin	0 (0.0)	1 (0.1)	1 (0.1)
Concussion	0 (0.0)	1 (0.1)	1 (0.1)
Contusion	7 (0.7)	8 (0.6)	15 (1.1)
Corneal abrasion	0 (0.0)	2 (0.2)	2 (0.1)
Dumping syndrome	0 (0.0)	1 (0.1)	1 (0.1)
Epicondylitis	2 (0.2)	2 (0.2)	4 (0.3)
Eye injury	1 (0.1)	0 (0.0)	1 (0.1)
Eyelid contusion	0 (0.0)	1 (0.1)	1 (0.1)
Fall	1 (0.1)	4 (0.3)	5 (0.4)
Femoral neck fracture	1 (0.1)	0 (0.0)	1 (0.1)
Fibula fracture	2 (0.2)	0 (0.0)	2 (0.1)
Foot fracture	1 (0.1)	1 (0.1)	2 (0.1)
Foreign body	1 (0.1)	0 (0.0)	1 (0.1)
Foreign body in eye	0 (0.0)	1 (0.1)	1 (0.1)
Hand fracture	3 (0.3)	4 (0.3)	7 (0.5)
Head injury	2 (0.2)	1 (0.1)	3 (0.2)
Heart injury	1 (0.1)	0 (0.0)	1 (0.1)
Humerus fracture	0 (0.0)	1 (0.1)	1 (0.1)
Incision site erythema	0 (0.0)	1 (0.1)	1 (0.1)
Incision site swelling	0 (0.0)	1 (0.1)	1 (0.1)
Injury	1 (0.1)	0 (0.0)	1 (0.1)
Jaw fracture	0 (0.0)	1 (0.1)	1 (0.1)
Joint dislocation	0 (0.0)	1 (0.1)	1 (0.1)
Joint injury	3 (0.3)	8 (0.6)	11 (0.8)
Laceration	8 (0.8)	6 (0.5)	14 (1.0)
Ligament sprain	9 (0.9)	9 (0.7)	18 (1.3)
Limb crushing injury	1 (0.1)	1 (0.1)	2 (0.1)
Limb fracture	0 (0.0)	1 (0.1)	1 (0.1)
Limb injury	6 (0.6)	5 (0.4)	11 (0.8)
Limb traumatic amputation	0 (0.0)	1 (0.1)	1 (0.1)
Lower limb fracture	1 (0.1)	2 (0.2)	3 (0.2)
Lumbar vertebral fracture	0 (0.0)	2 (0.2)	2 (0.1)
Meniscus injury	0 (0.0)	2 (0.2)	2 (0.1)
Muscle injury	0 (0.0)	1 (0.1)	1 (0.1)
Muscle rupture	2 (0.2)	0 (0.0)	2 (0.1)
Muscle strain	6 (0.6)	6 (0.5)	12 (0.9)
Nail injury	0 (0.0)	1 (0.1)	1 (0.1)
Neck injury	0 (0.0)	1 (0.1)	1 (0.1)
Patella fracture	1 (0.1)	0 (0.0)	1 (0.1)
Pneumothorax traumatic	0 (0.0)	1 (0.1)	1 (0.1)
Post lumbar puncture syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Post procedural contusion	0 (0.0)	1 (0.1)	1 (0.1)
Post procedural inflammation	0 (0.0)	1 (0.1)	1 (0.1)
Post-traumatic neck syndrome	3 (0.3)	0 (0.0)	3 (0.2)
Post-traumatic pain	0 (0.0)	1 (0.1)	1 (0.1)
Procedural pain	0 (0.0)	3 (0.2)	3 (0.2)
Radius fracture	4 (0.4)	0 (0.0)	4 (0.3)
Repetitive strain injury	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Rib fracture	0 (0.0)	1 (0.1)	1 (0.1)
Road traffic accident	3 (0.3)	3 (0.2)	5 (0.4)
Scapula fracture	1 (0.1)	0 (0.0)	1 (0.1)
Scar	1 (0.1)	0 (0.0)	1 (0.1)
Scratch	0 (0.0)	1 (0.1)	1 (0.1)
Skeletal injury	1 (0.1)	0 (0.0)	1 (0.1)
Skin abrasion	4 (0.4)	7 (0.6)	11 (0.8)
Skin injury	0 (0.0)	1 (0.1)	1 (0.1)
Spinal column injury	2 (0.2)	1 (0.1)	3 (0.2)
Spinal compression fracture	0 (0.0)	1 (0.1)	1 (0.1)
Spinal fracture	0 (0.0)	1 (0.1)	1 (0.1)
Sternal fracture	1 (0.1)	2 (0.2)	3 (0.2)
Sunburn	1 (0.1)	2 (0.2)	3 (0.2)
Tendon injury	1 (0.1)	1 (0.1)	2 (0.1)
Tendon rupture	1 (0.1)	6 (0.5)	7 (0.5)
Thermal burn	3 (0.3)	1 (0.1)	4 (0.3)
Tibia fracture	1 (0.1)	1 (0.1)	2 (0.1)
Tooth avulsion	0 (0.0)	1 (0.1)	1 (0.1)
Tooth fracture	3 (0.3)	4 (0.3)	7 (0.5)
Traumatic haematoma	2 (0.2)	0 (0.0)	2 (0.1)
Upper limb fracture	2 (0.2)	0 (0.0)	2 (0.1)
Vaccination complication	0 (0.0)	2 (0.2)	2 (0.1)
Wound	1 (0.1)	3 (0.2)	4 (0.3)
Wrist fracture	1 (0.1)	0 (0.0)	1 (0.1)
Investigations	**82 (8.5)**	**102 (8.1)**	**168 (12.4)**
Alanine aminotransferase increased	7 (0.7)	7 (0.6)	12 (0.9)
Amylase increased	1 (0.1)	0 (0.0)	1 (0.1)
Aortic bruit	1 (0.1)	0 (0.0)	1 (0.1)
Aspartate aminotransferase increased	5 (0.5)	11 (0.9)	15 (1.1)
Bacterial test	1 (0.1)	0 (0.0)	1 (0.1)
Bacterial test positive	1 (0.1)	1 (0.1)	2 (0.1)
Blood bilirubin increased	0 (0.0)	2 (0.2)	2 (0.1)
Blood cholesterol increased	0 (0.0)	1 (0.1)	1 (0.1)
Blood creatinine decreased	0 (0.0)	1 (0.1)	1 (0.1)
Blood creatinine increased	2 (0.2)	3 (0.2)	5 (0.4)
Blood glucose decreased	0 (0.0)	2 (0.2)	2 (0.1)
Blood glucose increased	5 (0.5)	6 (0.5)	11 (0.8)
Blood iron decreased	1 (0.1)	0 (0.0)	1 (0.1)
Blood magnesium decreased	1 (0.1)	0 (0.0)	1 (0.1)
Blood potassium decreased	1 (0.1)	0 (0.0)	1 (0.1)
Blood potassium increased	1 (0.1)	2 (0.2)	3 (0.2)
Blood pressure increased	7 (0.7)	11 (0.9)	17 (1.3)
Blood triglycerides increased	0 (0.0)	1 (0.1)	1 (0.1)
Blood urea increased	1 (0.1)	0 (0.0)	1 (0.1)
Blood uric acid increased	1 (0.1)	0 (0.0)	1 (0.1)
Blood urine present	1 (0.1)	0 (0.0)	1 (0.1)
Body temperature increased	1 (0.1)	1 (0.1)	2 (0.1)
C-reactive protein increased	1 (0.1)	0 (0.0)	1 (0.1)
Cardiac murmur	0 (0.0)	1 (0.1)	1 (0.1)
Chest x-ray abnormal	0 (0.0)	1 (0.1)	1 (0.1)
Coronavirus test positive	3 (0.3)	0 (0.0)	3 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Crystal urine present	1 (0.1)	2 (0.2)	3 (0.2)
Ejection fraction decreased	0 (0.0)	1 (0.1)	1 (0.1)
Electrocardiogram st segment depression	0 (0.0)	1 (0.1)	1 (0.1)
Electrocardiogram st segment elevation	0 (0.0)	1 (0.1)	1 (0.1)
Electrocardiogram t wave amplitude decreased	0 (0.0)	2 (0.2)	2 (0.1)
Electrocardiogram t wave inversion	1 (0.1)	1 (0.1)	2 (0.1)
Eosinophil count increased	1 (0.1)	0 (0.0)	1 (0.1)
False positive tuberculosis test	15 (1.5)	11 (0.9)	24 (1.8)
Gamma-glutamyltransferase increased	7 (0.7)	17 (1.3)	23 (1.7)
Gastric ph decreased	0 (0.0)	1 (0.1)	1 (0.1)
Glucose urine present	1 (0.1)	0 (0.0)	1 (0.1)
Glycosylated haemoglobin increased	0 (0.0)	2 (0.2)	2 (0.1)
Haemoglobin increased	0 (0.0)	2 (0.2)	2 (0.1)
Heart rate irregular	1 (0.1)	0 (0.0)	1 (0.1)
Hepatic enzyme increased	9 (0.9)	10 (0.8)	17 (1.3)
Interferon gamma release assay positive	0 (0.0)	1 (0.1)	1 (0.1)
Liver function test abnormal	0 (0.0)	2 (0.2)	2 (0.1)
Liver function test increased	1 (0.1)	7 (0.6)	8 (0.6)
Lymph node palpable	0 (0.0)	1 (0.1)	1 (0.1)
Lymphocyte count decreased	0 (0.0)	3 (0.2)	3 (0.2)
Mycobacterium tuberculosis complex test positive	0 (0.0)	1 (0.1)	1 (0.1)
Neutrophil count decreased	0 (0.0)	1 (0.1)	1 (0.1)
Occult blood	1 (0.1)	0 (0.0)	1 (0.1)
Occult blood positive	1 (0.1)	0 (0.0)	1 (0.1)
Platelet count decreased	1 (0.1)	0 (0.0)	1 (0.1)
Platelet count increased	1 (0.1)	0 (0.0)	1 (0.1)
Protein urine	1 (0.1)	0 (0.0)	1 (0.1)
Protein urine present	0 (0.0)	2 (0.2)	2 (0.1)
Psychiatric evaluation abnormal	2 (0.2)	2 (0.2)	4 (0.3)
Red blood cell count increased	0 (0.0)	1 (0.1)	1 (0.1)
Stool analysis abnormal	0 (0.0)	1 (0.1)	1 (0.1)
Transaminases increased	3 (0.3)	4 (0.3)	7 (0.5)
Tumour marker increased	0 (0.0)	1 (0.1)	1 (0.1)
Urinary casts present	0 (0.0)	1 (0.1)	1 (0.1)
Urinary sediment present	2 (0.2)	0 (0.0)	2 (0.1)
Urine analysis abnormal	1 (0.1)	1 (0.1)	2 (0.1)
Urine leukocyte esterase	1 (0.1)	0 (0.0)	1 (0.1)
Vitamin b12 decreased	0 (0.0)	1 (0.1)	1 (0.1)
Vitamin d decreased	1 (0.1)	0 (0.0)	1 (0.1)
Weight decreased	2 (0.2)	1 (0.1)	3 (0.2)
Weight increased	0 (0.0)	5 (0.4)	5 (0.4)
White blood cell count decreased	2 (0.2)	2 (0.2)	4 (0.3)
White blood cell count increased	2 (0.2)	0 (0.0)	2 (0.1)
Metabolism and nutrition disorders	**56 (5.8)**	**64 (5.1)**	**114 (8.4)**
Abnormal loss of weight	3 (0.3)	1 (0.1)	4 (0.3)
Decreased appetite	3 (0.3)	1 (0.1)	4 (0.3)
Dehydration	1 (0.1)	1 (0.1)	2 (0.1)
Diabetes mellitus	7 (0.7)	10 (0.8)	16 (1.2)
Diabetes mellitus inadequate control	1 (0.1)	0 (0.0)	1 (0.1)
Diabetic ketoacidosis	0 (0.0)	1 (0.1)	1 (0.1)
Dyslipidaemia	1 (0.1)	2 (0.2)	3 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Folate deficiency	0 (0.0)	1 (0.1)	1 (0.1)
Glucose tolerance impaired	5 (0.5)	2 (0.2)	7 (0.5)
Gout	2 (0.2)	8 (0.6)	9 (0.7)
Hypercholesterolaemia	10 (1.0)	5 (0.4)	15 (1.1)
Hyperglycaemia	2 (0.2)	8 (0.6)	10 (0.7)
Hyperkalaemia	1 (0.1)	1 (0.1)	2 (0.1)
Hyperlipidaemia	5 (0.5)	4 (0.3)	9 (0.7)
Hypertriglyceridaemia	0 (0.0)	2 (0.2)	2 (0.1)
Hyperuricaemia	3 (0.3)	4 (0.3)	7 (0.5)
Hypocalcaemia	0 (0.0)	1 (0.1)	1 (0.1)
Hypoglycaemia	0 (0.0)	2 (0.2)	2 (0.1)
Hyponatraemia	1 (0.1)	1 (0.1)	2 (0.1)
Increased appetite	0 (0.0)	1 (0.1)	1 (0.1)
Insulin resistance	0 (0.0)	1 (0.1)	1 (0.1)
Iron deficiency	1 (0.1)	0 (0.0)	1 (0.1)
Ketoacidosis	1 (0.1)	0 (0.0)	1 (0.1)
Obesity	0 (0.0)	4 (0.3)	4 (0.3)
Type 2 diabetes mellitus	11 (1.1)	12 (0.9)	23 (1.7)
Vitamin b12 deficiency	3 (0.3)	1 (0.1)	4 (0.3)
Vitamin d deficiency	1 (0.1)	4 (0.3)	5 (0.4)
Musculoskeletal and connective tissue disorders	**124 (12.8)**	**162 (12.8)**	**268 (19.8)**
Arthralgia	19 (2.0)	41 (3.2)	57 (4.2)
Arthritis	3 (0.3)	4 (0.3)	7 (0.5)
Arthropathy	2 (0.2)	0 (0.0)	2 (0.1)
Back pain	27 (2.8)	17 (1.3)	42 (3.1)
Bone cyst	0 (0.0)	1 (0.1)	1 (0.1)
Bursitis	4 (0.4)	6 (0.5)	10 (0.7)
Chondropathy	0 (0.0)	1 (0.1)	1 (0.1)
Coccydynia	1 (0.1)	0 (0.0)	1 (0.1)
Costochondritis	2 (0.2)	0 (0.0)	2 (0.1)
Dactylitis	1 (0.1)	1 (0.1)	2 (0.1)
Dupuytren's contracture	0 (0.0)	1 (0.1)	1 (0.1)
Fibromyalgia	1 (0.1)	1 (0.1)	2 (0.1)
Flank pain	1 (0.1)	0 (0.0)	1 (0.1)
Foot deformity	1 (0.1)	0 (0.0)	1 (0.1)
Gouty arthritis	0 (0.0)	1 (0.1)	1 (0.1)
Groin pain	1 (0.1)	0 (0.0)	1 (0.1)
Haemarthrosis	1 (0.1)	0 (0.0)	1 (0.1)
Inclusion body myositis	1 (0.1)	0 (0.0)	1 (0.1)
Intervertebral disc degeneration	0 (0.0)	1 (0.1)	1 (0.1)
Intervertebral disc disorder	0 (0.0)	2 (0.2)	2 (0.1)
Intervertebral disc protrusion	4 (0.4)	3 (0.2)	7 (0.5)
Joint effusion	0 (0.0)	1 (0.1)	1 (0.1)
Joint stiffness	2 (0.2)	2 (0.2)	4 (0.3)
Joint swelling	2 (0.2)	2 (0.2)	4 (0.3)
Kyphosis	0 (0.0)	1 (0.1)	1 (0.1)
Muscle spasms	5 (0.5)	9 (0.7)	13 (1.0)
Muscle tightness	0 (0.0)	1 (0.1)	1 (0.1)
Muscular weakness	3 (0.3)	1 (0.1)	4 (0.3)
Musculoskeletal chest pain	2 (0.2)	3 (0.2)	5 (0.4)
Musculoskeletal discomfort	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Musculoskeletal pain	12 (1.2)	7 (0.6)	18 (1.3)
Musculoskeletal stiffness	0 (0.0)	2 (0.2)	2 (0.1)
Myalgia	3 (0.3)	9 (0.7)	12 (0.9)
Myositis	1 (0.1)	0 (0.0)	1 (0.1)
Neck pain	2 (0.2)	5 (0.4)	7 (0.5)
Nodal osteoarthritis	0 (0.0)	1 (0.1)	1 (0.1)
Osteitis	1 (0.1)	0 (0.0)	1 (0.1)
Osteoarthritis	8 (0.8)	11 (0.9)	18 (1.3)
Osteochondrosis	1 (0.1)	0 (0.0)	1 (0.1)
Osteoporosis	1 (0.1)	0 (0.0)	1 (0.1)
Pain in extremity	6 (0.6)	15 (1.2)	20 (1.5)
Periarthritis	0 (0.0)	4 (0.3)	4 (0.3)
Peripheral arthritis	0 (0.0)	1 (0.1)	1 (0.1)
Plantar fascial fibromatosis	1 (0.1)	0 (0.0)	1 (0.1)
Plantar fasciitis	1 (0.1)	2 (0.2)	3 (0.2)
Psoriatic arthropathy	5 (0.5)	14 (1.1)	19 (1.4)
Rhabdomyolysis	0 (0.0)	2 (0.2)	2 (0.1)
Rheumatoid arthritis	0 (0.0)	1 (0.1)	1 (0.1)
Rotator cuff syndrome	1 (0.1)	2 (0.2)	3 (0.2)
Scoliosis	1 (0.1)	1 (0.1)	2 (0.1)
Spinal column stenosis	1 (0.1)	3 (0.2)	4 (0.3)
Spinal osteoarthritis	5 (0.5)	5 (0.4)	10 (0.7)
Spinal pain	4 (0.4)	7 (0.6)	11 (0.8)
Spondylolisthesis	0 (0.0)	2 (0.2)	2 (0.1)
Synovial cyst	0 (0.0)	2 (0.2)	2 (0.1)
Tendinous contracture	0 (0.0)	1 (0.1)	1 (0.1)
Tendon pain	0 (0.0)	1 (0.1)	1 (0.1)
Tendonitis	9 (0.9)	3 (0.2)	12 (0.9)
Tenosynovitis	2 (0.2)	1 (0.1)	3 (0.2)
Torticollis	1 (0.1)	0 (0.0)	1 (0.1)
Trigger finger	0 (0.0)	3 (0.2)	3 (0.2)
Upper extremity mass	0 (0.0)	1 (0.1)	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**35 (3.6)**	**52 (4.1)**	**79 (5.8)**
Acanthoma	1 (0.1)	0 (0.0)	1 (0.1)
Acrochordon	4 (0.4)	1 (0.1)	5 (0.4)
Adenocarcinoma of colon	0 (0.0)	1 (0.1)	1 (0.1)
Basal cell carcinoma	1 (0.1)	5 (0.4)	6 (0.4)
Benign neoplasm of thyroid gland	1 (0.1)	1 (0.1)	2 (0.1)
Benign renal neoplasm	0 (0.0)	1 (0.1)	1 (0.1)
Bladder transitional cell carcinoma	1 (0.1)	0 (0.0)	1 (0.1)
Breast cancer	0 (0.0)	1 (0.1)	1 (0.1)
Colon adenoma	0 (0.0)	1 (0.1)	1 (0.1)
Colon cancer	1 (0.1)	1 (0.1)	2 (0.1)
Colon cancer metastatic	0 (0.0)	1 (0.1)	1 (0.1)
Colorectal cancer metastatic	0 (0.0)	1 (0.1)	1 (0.1)
Fibroma	1 (0.1)	2 (0.2)	3 (0.2)
Fibrous histiocytoma	0 (0.0)	2 (0.2)	2 (0.1)
Gastrointestinal tract adenoma	0 (0.0)	1 (0.1)	1 (0.1)
Haemangioma	2 (0.2)	0 (0.0)	2 (0.1)
Haemangioma of bone	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Haemangioma of liver	1 (0.1)	1 (0.1)	2 (0.1)
Haemangioma of skin	0 (0.0)	1 (0.1)	1 (0.1)
Invasive breast carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Leiomyoma	0 (0.0)	1 (0.1)	1 (0.1)
Lip and/or oral cavity cancer	0 (0.0)	1 (0.1)	1 (0.1)
Lipoma	0 (0.0)	2 (0.2)	2 (0.1)
Malignant melanoma	0 (0.0)	1 (0.1)	1 (0.1)
Malignant melanoma in situ	1 (0.1)	1 (0.1)	1 (0.1)
Melanocytic naevus	1 (0.1)	1 (0.1)	2 (0.1)
Metastatic bronchial carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Nodular fasciitis	1 (0.1)	0 (0.0)	1 (0.1)
Papillary thyroid cancer	0 (0.0)	1 (0.1)	1 (0.1)
Parathyroid tumour benign	0 (0.0)	1 (0.1)	1 (0.1)
Penile wart	1 (0.1)	0 (0.0)	1 (0.1)
Prostate cancer	0 (0.0)	1 (0.1)	1 (0.1)
Prostatic adenoma	0 (0.0)	1 (0.1)	1 (0.1)
Pyogenic granuloma	1 (0.1)	0 (0.0)	1 (0.1)
Seborrhoeic keratosis	9 (0.9)	2 (0.2)	11 (0.8)
Skin papilloma	9 (0.9)	13 (1.0)	21 (1.6)
Squamous cell carcinoma	0 (0.0)	1 (0.1)	1 (0.1)
Squamous cell carcinoma of lung	1 (0.1)	0 (0.0)	1 (0.1)
Squamous cell carcinoma of skin	1 (0.1)	2 (0.2)	3 (0.2)
Thyroid cancer	0 (0.0)	1 (0.1)	1 (0.1)
Thyroid neoplasm	0 (0.0)	1 (0.1)	1 (0.1)
Uterine leiomyoma	1 (0.1)	0 (0.0)	1 (0.1)
Vulvovaginal warts	1 (0.1)	0 (0.0)	1 (0.1)
Nervous system disorders	**58 (6.0)**	**81 (6.4)**	**135 (10.0)**
Amnesia	1 (0.1)	0 (0.0)	1 (0.1)
Carpal tunnel syndrome	2 (0.2)	4 (0.3)	6 (0.4)
Cerebral infarction	1 (0.1)	0 (0.0)	1 (0.1)
Cerebral ischaemia	1 (0.1)	0 (0.0)	1 (0.1)
Cerebrovascular accident	1 (0.1)	1 (0.1)	2 (0.1)
Cerebrovascular disorder	1 (0.1)	0 (0.0)	1 (0.1)
Cervical radiculopathy	0 (0.0)	1 (0.1)	1 (0.1)
Cervicobrachial syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Dizziness	5 (0.5)	6 (0.5)	11 (0.8)
Drop attacks	0 (0.0)	1 (0.1)	1 (0.1)
Dysgeusia	2 (0.2)	1 (0.1)	3 (0.2)
Headache	23 (2.4)	38 (3.0)	59 (4.4)
Hemiplegic migraine	1 (0.1)	0 (0.0)	1 (0.1)
Hypersomnia	1 (0.1)	0 (0.0)	1 (0.1)
Hypoaesthesia	1 (0.1)	2 (0.2)	3 (0.2)
Hyporeflexia	1 (0.1)	0 (0.0)	1 (0.1)
Intercostal neuralgia	0 (0.0)	1 (0.1)	1 (0.1)
Intracranial pressure increased	1 (0.1)	0 (0.0)	1 (0.1)
Lethargy	0 (0.0)	1 (0.1)	1 (0.1)
Leukoencephalopathy	0 (0.0)	1 (0.1)	1 (0.1)
Loss of consciousness	1 (0.1)	2 (0.2)	3 (0.2)
Migraine	3 (0.3)	2 (0.2)	5 (0.4)
Multiple sclerosis	0 (0.0)	1 (0.1)	1 (0.1)
Nerve compression	1 (0.1)	1 (0.1)	2 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Neuropathy peripheral	1 (0.1)	5 (0.4)	6 (0.4)
Paraesthesia	1 (0.1)	4 (0.3)	5 (0.4)
Parosmia	0 (0.0)	1 (0.1)	1 (0.1)
Periodic limb movement disorder	1 (0.1)	0 (0.0)	1 (0.1)
Peroneal nerve palsy	1 (0.1)	0 (0.0)	1 (0.1)
Presyncope	2 (0.2)	1 (0.1)	3 (0.2)
Relapsing-remitting multiple sclerosis	0 (0.0)	1 (0.1)	1 (0.1)
Sciatica	1 (0.1)	7 (0.6)	8 (0.6)
Seizure	2 (0.2)	1 (0.1)	3 (0.2)
Sinus headache	0 (0.0)	1 (0.1)	1 (0.1)
Spondylitic myelopathy	1 (0.1)	0 (0.0)	1 (0.1)
Syncope	1 (0.1)	0 (0.0)	1 (0.1)
Tension headache	2 (0.2)	0 (0.0)	2 (0.1)
Toxic encephalopathy	0 (0.0)	1 (0.1)	1 (0.1)
Transient ischaemic attack	1 (0.1)	1 (0.1)	2 (0.1)
Tremor	1 (0.1)	1 (0.1)	2 (0.1)
Trigeminal neuralgia	0 (0.0)	1 (0.1)	1 (0.1)
Vertebrobasilar insufficiency	1 (0.1)	0 (0.0)	1 (0.1)
Pregnancy, puerperium and perinatal conditions	**2 (0.2)**	**0 (0.0)**	**2 (0.1)**
Abortion spontaneous	1 (0.1)	0 (0.0)	1 (0.1)
Pregnancy on oral contraceptive	1 (0.1)	0 (0.0)	1 (0.1)
Product issues	**1 (0.1)**	**0 (0.0)**	**1 (0.1)**
Device failure	1 (0.1)	0 (0.0)	1 (0.1)
Psychiatric disorders	**27 (2.8)**	**28 (2.2)**	**52 (3.8)**
Adjustment disorder with depressed mood	0 (0.0)	1 (0.1)	1 (0.1)
Alcohol abuse	1 (0.1)	3 (0.2)	4 (0.3)
Alcohol withdrawal syndrome	1 (0.1)	0 (0.0)	1 (0.1)
Anxiety	2 (0.2)	3 (0.2)	4 (0.3)
Anxiety disorder	1 (0.1)	0 (0.0)	1 (0.1)
Attention deficit/hyperactivity disorder	0 (0.0)	1 (0.1)	1 (0.1)
Bipolar disorder	3 (0.3)	1 (0.1)	4 (0.3)
Bipolar i disorder	1 (0.1)	0 (0.0)	1 (0.1)
Completed suicide	1 (0.1)	0 (0.0)	1 (0.1)
Depressed mood	2 (0.2)	0 (0.0)	2 (0.1)
Depression	4 (0.4)	8 (0.6)	12 (0.9)
Drug dependence	1 (0.1)	0 (0.0)	1 (0.1)
Generalised anxiety disorder	1 (0.1)	2 (0.2)	3 (0.2)
Initial insomnia	0 (0.0)	1 (0.1)	1 (0.1)
Insomnia	9 (0.9)	6 (0.5)	15 (1.1)
Mental status changes	0 (0.0)	1 (0.1)	1 (0.1)
Neurosis	0 (0.0)	1 (0.1)	1 (0.1)
Panic attack	1 (0.1)	1 (0.1)	2 (0.1)
Post-traumatic stress disorder	0 (0.0)	1 (0.1)	1 (0.1)
Sleep disorder	1 (0.1)	0 (0.0)	1 (0.1)
Stress	0 (0.0)	1 (0.1)	1 (0.1)
Suicidal ideation	0 (0.0)	2 (0.2)	2 (0.1)
Tension	1 (0.1)	0 (0.0)	1 (0.1)
Renal and urinary disorders	**37 (3.8)**	**38 (3.0)**	**67 (5.0)**
Acute kidney injury	4 (0.4)	1 (0.1)	5 (0.4)
Calculus urinary	1 (0.1)	0 (0.0)	1 (0.1)
Crystalluria	1 (0.1)	0 (0.0)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Cystitis haemorrhagic	1 (0.1)	0 (0.0)	1 (0.1)
Cystitis noninfective	0 (0.0)	1 (0.1)	1 (0.1)
Diabetic nephropathy	1 (0.1)	0 (0.0)	1 (0.1)
Dysuria	0 (0.0)	2 (0.2)	2 (0.1)
Glycosuria	3 (0.3)	4 (0.3)	6 (0.4)
Haematuria	5 (0.5)	5 (0.4)	10 (0.7)
Haemoglobinuria	0 (0.0)	1 (0.1)	1 (0.1)
Hypertonic bladder	2 (0.2)	2 (0.2)	3 (0.2)
Micturition urgency	0 (0.0)	1 (0.1)	1 (0.1)
Nephrolithiasis	6 (0.6)	6 (0.5)	11 (0.8)
Nitrituria	0 (0.0)	1 (0.1)	1 (0.1)
Nocturia	1 (0.1)	1 (0.1)	2 (0.1)
Pollakiuria	1 (0.1)	0 (0.0)	1 (0.1)
Proteinuria	5 (0.5)	10 (0.8)	14 (1.0)
Renal colic	0 (0.0)	1 (0.1)	1 (0.1)
Renal cyst	4 (0.4)	6 (0.5)	10 (0.7)
Renal failure	1 (0.1)	1 (0.1)	2 (0.1)
Renal impairment	1 (0.1)	0 (0.0)	1 (0.1)
Urethral disorder	1 (0.1)	0 (0.0)	1 (0.1)
Urinary hesitation	0 (0.0)	1 (0.1)	1 (0.1)
Urinary retention	1 (0.1)	0 (0.0)	1 (0.1)
Urinary tract inflammation	1 (0.1)	0 (0.0)	1 (0.1)
Reproductive system and breast disorders	**16 (1.7)**	**23 (1.8)**	**38 (2.8)**
Amenorrhoea	1 (0.1)	0 (0.0)	1 (0.1)
Bartholin's cyst	1 (0.1)	0 (0.0)	1 (0.1)
Benign prostatic hyperplasia	2 (0.2)	5 (0.4)	7 (0.5)
Breast cyst	0 (0.0)	1 (0.1)	1 (0.1)
Breast mass	0 (0.0)	1 (0.1)	1 (0.1)
Cervical dysplasia	0 (0.0)	1 (0.1)	1 (0.1)
Cervical polyp	0 (0.0)	1 (0.1)	1 (0.1)
Dysmenorrhoea	0 (0.0)	1 (0.1)	1 (0.1)
Endometriosis	1 (0.1)	2 (0.2)	3 (0.2)
Erectile dysfunction	1 (0.1)	0 (0.0)	1 (0.1)
Fibrocystic breast disease	1 (0.1)	0 (0.0)	1 (0.1)
Genital haemorrhage	0 (0.0)	1 (0.1)	1 (0.1)
Gynaecomastia	1 (0.1)	0 (0.0)	1 (0.1)
Menorrhagia	1 (0.1)	1 (0.1)	2 (0.1)
Menstruation irregular	1 (0.1)	0 (0.0)	1 (0.1)
Metrorrhagia	0 (0.0)	1 (0.1)	1 (0.1)
Ovarian cyst	0 (0.0)	1 (0.1)	1 (0.1)
Pelvic cyst	0 (0.0)	1 (0.1)	1 (0.1)
Polycystic ovaries	2 (0.2)	0 (0.0)	2 (0.1)
Prostatic calcification	0 (0.0)	1 (0.1)	1 (0.1)
Prostatitis	0 (0.0)	5 (0.4)	5 (0.4)
Pruritus genital	1 (0.1)	0 (0.0)	1 (0.1)
Scrotal mass	0 (0.0)	1 (0.1)	1 (0.1)
Testicular pain	1 (0.1)	1 (0.1)	2 (0.1)
Uterine polyp	1 (0.1)	1 (0.1)	2 (0.1)
Uterine prolapse	1 (0.1)	0 (0.0)	1 (0.1)
Uterovaginal prolapse	0 (0.0)	1 (0.1)	1 (0.1)
Vaginal haemorrhage	1 (0.1)	0 (0.0)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Respiratory, thoracic and mediastinal disorders	**80 (8.3)**	**83 (6.6)**	**156 (11.5)**
Acute respiratory failure	1 (0.1)	1 (0.1)	2 (0.1)
Allergic bronchitis	0 (0.0)	1 (0.1)	1 (0.1)
Allergic cough	3 (0.3)	0 (0.0)	3 (0.2)
Asthma	3 (0.3)	3 (0.2)	6 (0.4)
Bronchitis chronic	2 (0.2)	1 (0.1)	3 (0.2)
Chronic obstructive pulmonary disease	1 (0.1)	6 (0.5)	6 (0.4)
Cough	22 (2.3)	20 (1.6)	41 (3.0)
Dysphonia	0 (0.0)	2 (0.2)	2 (0.1)
Dyspnoea	1 (0.1)	2 (0.2)	3 (0.2)
Dyspnoea exertional	0 (0.0)	2 (0.2)	2 (0.1)
Emphysema	1 (0.1)	1 (0.1)	2 (0.1)
Epistaxis	1 (0.1)	1 (0.1)	2 (0.1)
Haemothorax	0 (0.0)	1 (0.1)	1 (0.1)
Hypoxia	0 (0.0)	1 (0.1)	1 (0.1)
Interstitial lung disease	1 (0.1)	0 (0.0)	1 (0.1)
Laryngeal ulceration	1 (0.1)	0 (0.0)	1 (0.1)
Lung cyst	0 (0.0)	1 (0.1)	1 (0.1)
Lung disorder	0 (0.0)	2 (0.2)	2 (0.1)
Nasal congestion	4 (0.4)	1 (0.1)	5 (0.4)
Nasal discomfort	0 (0.0)	1 (0.1)	1 (0.1)
Nasal obstruction	1 (0.1)	0 (0.0)	1 (0.1)
Nasal polyps	1 (0.1)	0 (0.0)	1 (0.1)
Nasal septum deviation	2 (0.2)	0 (0.0)	2 (0.1)
Oropharyngeal discomfort	1 (0.1)	1 (0.1)	2 (0.1)
Oropharyngeal pain	19 (2.0)	12 (0.9)	31 (2.3)
Pharyngeal oedema	0 (0.0)	1 (0.1)	1 (0.1)
Pharyngeal ulceration	1 (0.1)	0 (0.0)	1 (0.1)
Pleurisy	1 (0.1)	0 (0.0)	1 (0.1)
Pneumonitis	0 (0.0)	1 (0.1)	1 (0.1)
Pneumothorax	1 (0.1)	0 (0.0)	1 (0.1)
Productive cough	0 (0.0)	1 (0.1)	1 (0.1)
Pulmonary cavitation	1 (0.1)	0 (0.0)	1 (0.1)
Pulmonary embolism	3 (0.3)	0 (0.0)	3 (0.2)
Pulmonary granuloma	0 (0.0)	1 (0.1)	1 (0.1)
Pulmonary mass	0 (0.0)	1 (0.1)	1 (0.1)
Rales	1 (0.1)	0 (0.0)	1 (0.1)
Respiratory disorder	0 (0.0)	1 (0.1)	1 (0.1)
Respiratory failure	1 (0.1)	0 (0.0)	1 (0.1)
Rhinalgia	0 (0.0)	1 (0.1)	1 (0.1)
Rhinitis allergic	5 (0.5)	14 (1.1)	19 (1.4)
Rhinorrhoea	6 (0.6)	5 (0.4)	11 (0.8)
Sinus congestion	2 (0.2)	0 (0.0)	2 (0.1)
Sleep apnoea syndrome	4 (0.4)	7 (0.6)	11 (0.8)
Tonsillar inflammation	0 (0.0)	1 (0.1)	1 (0.1)
Upper-airway cough syndrome	2 (0.2)	0 (0.0)	2 (0.1)
Skin and subcutaneous tissue disorders	**187 (19.3)**	**214 (16.9)**	**352 (26.0)**
Acne	9 (0.9)	8 (0.6)	15 (1.1)
Actinic keratosis	0 (0.0)	9 (0.7)	9 (0.7)
Alopecia	7 (0.7)	5 (0.4)	12 (0.9)
Alopecia areata	1 (0.1)	2 (0.2)	3 (0.2)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Androgenetic alopecia	2 (0.2)	1 (0.1)	3 (0.2)
Angiokeratoma	1 (0.1)	0 (0.0)	1 (0.1)
Blister	2 (0.2)	0 (0.0)	2 (0.1)
Chloasma	1 (0.1)	0 (0.0)	1 (0.1)
Chronic pigmented purpura	0 (0.0)	1 (0.1)	1 (0.1)
Chronic spontaneous urticaria	3 (0.3)	1 (0.1)	4 (0.3)
Decubitus ulcer	0 (0.0)	1 (0.1)	1 (0.1)
Dermal cyst	4 (0.4)	5 (0.4)	9 (0.7)
Dermatitis	12 (1.2)	7 (0.6)	18 (1.3)
Dermatitis acneiform	3 (0.3)	2 (0.2)	5 (0.4)
Dermatitis allergic	5 (0.5)	8 (0.6)	13 (1.0)
Dermatitis atopic	6 (0.6)	5 (0.4)	11 (0.8)
Dermatitis contact	30 (3.1)	30 (2.4)	58 (4.3)
Dermatosis	0 (0.0)	1 (0.1)	1 (0.1)
Diabetic foot	1 (0.1)	1 (0.1)	2 (0.1)
Diffuse alopecia	1 (0.1)	0 (0.0)	1 (0.1)
Drug eruption	0 (0.0)	1 (0.1)	1 (0.1)
Dry skin	7 (0.7)	4 (0.3)	11 (0.8)
Dyshidrotic eczema	3 (0.3)	5 (0.4)	8 (0.6)
Ecchymosis	0 (0.0)	1 (0.1)	1 (0.1)
Eczema	24 (2.5)	35 (2.8)	54 (4.0)
Eczema asteatotic	7 (0.7)	12 (0.9)	17 (1.3)
Eczema nummular	4 (0.4)	2 (0.2)	6 (0.4)
Erythema	2 (0.2)	6 (0.5)	8 (0.6)
Erythema ab igne	0 (0.0)	1 (0.1)	1 (0.1)
Erythrodermic psoriasis	1 (0.1)	0 (0.0)	1 (0.1)
Haemorrhage subcutaneous	1 (0.1)	0 (0.0)	1 (0.1)
Hand dermatitis	0 (0.0)	4 (0.3)	4 (0.3)
Hidradenitis	4 (0.4)	2 (0.2)	6 (0.4)
Hyperhidrosis	1 (0.1)	2 (0.2)	3 (0.2)
Hyperkeratosis	6 (0.6)	2 (0.2)	8 (0.6)
Idiopathic urticaria	0 (0.0)	1 (0.1)	1 (0.1)
Ingrowing nail	2 (0.2)	2 (0.2)	4 (0.3)
Ingrown hair	1 (0.1)	0 (0.0)	1 (0.1)
Intertrigo	7 (0.7)	10 (0.8)	17 (1.3)
Keratosis pilaris	0 (0.0)	1 (0.1)	1 (0.1)
Lentigo	1 (0.1)	0 (0.0)	1 (0.1)
Leukoplakia	0 (0.0)	1 (0.1)	1 (0.1)
Lichen sclerosus	1 (0.1)	0 (0.0)	1 (0.1)
Lichen striatus	1 (0.1)	0 (0.0)	1 (0.1)
Mechanical urticaria	3 (0.3)	0 (0.0)	3 (0.2)
Milia	0 (0.0)	1 (0.1)	1 (0.1)
Miliaria	3 (0.3)	4 (0.3)	7 (0.5)
Myxoid cyst	0 (0.0)	1 (0.1)	1 (0.1)
Nail bed inflammation	0 (0.0)	1 (0.1)	1 (0.1)
Nail discolouration	0 (0.0)	1 (0.1)	1 (0.1)
Nail pigmentation	0 (0.0)	1 (0.1)	1 (0.1)
Nail psoriasis	1 (0.1)	0 (0.0)	1 (0.1)
Neurodermatitis	1 (0.1)	0 (0.0)	1 (0.1)
Night sweats	1 (0.1)	1 (0.1)	2 (0.1)
Onychoclasis	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Onycholysis	1 (0.1)	1 (0.1)	1 (0.1)
Palmoplantar keratoderma	2 (0.2)	0 (0.0)	2 (0.1)
Photosensitivity reaction	1 (0.1)	0 (0.0)	1 (0.1)
Pityriasis	2 (0.2)	0 (0.0)	2 (0.1)
Pityriasis rosea	0 (0.0)	1 (0.1)	1 (0.1)
Polymorphic light eruption	1 (0.1)	0 (0.0)	1 (0.1)
Post inflammatory pigmentation change	1 (0.1)	0 (0.0)	1 (0.1)
Prurigo	0 (0.0)	2 (0.2)	2 (0.1)
Pruritus	10 (1.0)	10 (0.8)	19 (1.4)
Pruritus generalised	1 (0.1)	0 (0.0)	1 (0.1)
Pseudofolliculitis barbae	0 (0.0)	1 (0.1)	1 (0.1)
Psoriasis	16 (1.7)	22 (1.7)	37 (2.7)
Purpura	0 (0.0)	1 (0.1)	1 (0.1)
Pustular psoriasis	2 (0.2)	0 (0.0)	2 (0.1)
Pyoderma gangrenosum	0 (0.0)	1 (0.1)	1 (0.1)
Rash	5 (0.5)	6 (0.5)	11 (0.8)
Rhinophyma	0 (0.0)	1 (0.1)	1 (0.1)
Rosacea	0 (0.0)	2 (0.2)	2 (0.1)
Seborrhoeic dermatitis	12 (1.2)	12 (0.9)	24 (1.8)
Skin burning sensation	0 (0.0)	1 (0.1)	1 (0.1)
Skin depigmentation	0 (0.0)	1 (0.1)	1 (0.1)
Skin discolouration	0 (0.0)	1 (0.1)	1 (0.1)
Skin erosion	0 (0.0)	1 (0.1)	1 (0.1)
Skin exfoliation	0 (0.0)	4 (0.3)	4 (0.3)
Skin fissures	2 (0.2)	2 (0.2)	4 (0.3)
Skin hypertrophy	0 (0.0)	1 (0.1)	1 (0.1)
Skin irritation	1 (0.1)	1 (0.1)	2 (0.1)
Skin lesion	1 (0.1)	1 (0.1)	2 (0.1)
Skin maceration	1 (0.1)	0 (0.0)	1 (0.1)
Skin ulcer	2 (0.2)	0 (0.0)	2 (0.1)
Solar dermatitis	0 (0.0)	1 (0.1)	1 (0.1)
Solar lentigo	1 (0.1)	0 (0.0)	1 (0.1)
Stasis dermatitis	1 (0.1)	1 (0.1)	2 (0.1)
Swelling face	0 (0.0)	1 (0.1)	1 (0.1)
Toxic skin eruption	1 (0.1)	2 (0.2)	3 (0.2)
Transient acantholytic dermatosis	0 (0.0)	1 (0.1)	1 (0.1)
Urticaria	9 (0.9)	11 (0.9)	19 (1.4)
Urticaria chronic	1 (0.1)	1 (0.1)	2 (0.1)
Urticaria contact	1 (0.1)	0 (0.0)	1 (0.1)
Vitiligo	0 (0.0)	1 (0.1)	1 (0.1)
Xeroderma	0 (0.0)	1 (0.1)	1 (0.1)
Social circumstances	**0 (0.0)**	**4 (0.3)**	**4 (0.3)**
Menopause	0 (0.0)	3 (0.2)	3 (0.2)
Stress at work	0 (0.0)	1 (0.1)	1 (0.1)
Surgical and medical procedures	**0 (0.0)**	**1 (0.1)**	**1 (0.1)**
Dental implantation	0 (0.0)	1 (0.1)	1 (0.1)
Uncoded	**0 (0.0)**	**2 (0.2)**	**2 (0.1)**
Vascular disorders	**52 (5.4)**	**50 (3.9)**	**99 (7.3)**
Aortic aneurysm	2 (0.2)	1 (0.1)	3 (0.2)
Aortic aneurysm rupture	0 (0.0)	1 (0.1)	1 (0.1)
Aortic dilatation	0 (0.0)	1 (0.1)	1 (0.1)

Summary of TEAEs

System Organ Class - Preferred Term	BKZ Q4W (N=969) n (%)	BKZ Q8W (N=1267) n (%)	BKZ Total (N=1353) n (%)
Aortic stenosis	1 (0.1)	0 (0.0)	1 (0.1)
Arteriosclerosis	1 (0.1)	1 (0.1)	2 (0.1)
Circulatory collapse	0 (0.0)	1 (0.1)	1 (0.1)
Deep vein thrombosis	2 (0.2)	1 (0.1)	3 (0.2)
Femoral artery embolism	1 (0.1)	0 (0.0)	1 (0.1)
Haematoma	1 (0.1)	2 (0.2)	3 (0.2)
Hot flush	1 (0.1)	0 (0.0)	1 (0.1)
Hypertension	37 (3.8)	40 (3.2)	74 (5.5)
Hypotension	2 (0.2)	1 (0.1)	3 (0.2)
Hypovolaemic shock	1 (0.1)	0 (0.0)	1 (0.1)
Orthostatic hypotension	1 (0.1)	0 (0.0)	1 (0.1)
Peripheral artery occlusion	1 (0.1)	0 (0.0)	1 (0.1)
Peripheral artery stenosis	1 (0.1)	0 (0.0)	1 (0.1)
Peripheral venous disease	1 (0.1)	1 (0.1)	2 (0.1)
Spider vein	0 (0.0)	1 (0.1)	1 (0.1)
Varicose vein	2 (0.2)	0 (0.0)	2 (0.1)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRTIAN = 5 to 5 (BKZ Q4W); TRTIAN = 6 to 6 (BKZ Q8W); TRTIAN = 7 to 7 (BKZ Total); TRTEMFL = "Y" (Adverse Events).

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

MELINDA L MCCORD
10/16/2023 08:32:00 AM
Signing for myself and Kevin Clark, MD

KELLEY A BURRIDGE
10/16/2023 10:12:26 AM

EUGENIO ANDRACA-CARRERA
10/16/2023 10:13:28 AM

SHAMIR N KALARIA
10/16/2023 10:14:55 AM

BERNARD A FISCHER
10/16/2023 10:36:57 AM

GORDANA DIGLISIC
10/16/2023 10:43:09 AM

NIKOLAY P NIKOLOV
10/17/2023 12:56:09 PM

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	BLA
Application Number(s)	761151
Priority or Standard	Standard
Submit Date(s)	July 15, 2020
Received Date(s)	July 15, 2020
PDUFA Goal Date	October 15, 2021 (Action deferred until facility inspections were completed)
Division/Office	Dermatology and Dentistry
Review Completion Date	May 11, 2022
Established/Proper Name	Bimekizumab-bkzx
(Proposed) Trade Name	BIMZELX
Pharmacologic Class	a humanized interleukin-17A and F antagonist
Code name	UCB4940 (CDP4940)
Applicant	UCB, Inc.
Dosage form	injection
Applicant proposed Dosing Regimen	320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For some patients, a dose of 320 mg every 4 weeks after week 16 may be considered.
Applicant Proposed Indication(s)/Population(s)	For the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	200965009 |Plaque psoriasis (disorder)
Recommendation on Regulatory Action	Complete Response
Recommended Indication(s)/Population(s) (if applicable)	BIMZELX is indicated for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	200965009 |Plaque psoriasis (disorder)
Recommended Dosing Regimen	320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For patients weighing ≥120 kg, a dose of 320 mg every 4 weeks after Week 16 may be considered.

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CDRH=Center for Devices and Radiological Health
DCN=Division of Cardiology and Nephrology
DCOA=Clinical Outcomes Assessment
DEPI= Division of Epidemiology
DG= Division of Gastroenterology
DHN= Division of Hepatology and Nutrition
DMEPA=Division of Medication Error Prevention and Analysis
DP=Division of Psychiatry
DPMH=Division of Pediatric and Maternal Health
DRM=Division of Risk Management
OBP= Office of Biotechnology Products
OPDP=Office of Prescription Drug Promotion
OPRO= Office of Program and Regulatory Operations
OSE= Office of Surveillance and Epidemiology
OPQ=Office of Pharmaceutical Quality
OSI=Office of Scientific Investigations
PLT=Patient Labeling Team

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Glossary

AC	advisory committee
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AMS	active medication set
AR	adverse reaction
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BSA	Body Surface Area
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CI	confidence interval
CMC	chemistry, manufacturing, and controls
CMH	Cochran-Mantel-Haenszel
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DHOT	Division of Hematology Oncology Toxicology
DMC	data monitoring committee
ECG	electrocardiogram
eCTD	electronic common technical document
ESS	escape subject set
ETASU	elements to assure safe use
FAS	full analysis set
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice
ICH	International Conference on Harmonisation
IGA	Investigator Global Assessment
IND	Investigational New Drug
ISE	integrated summary of effectiveness

ISS	integrated summary of safety
LOCF	last observation carried forward
MCMC	Markov Chain Monte Carlo
MedDRA	Medical Dictionary for Regulatory Activities
MI	multiple imputation
MS	maintenance set
MTP	Multiplicity Testing Procedure
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NI	non-inferiority
NME	new molecular entity
NRI	non-responder imputation
OC	Observed cases
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PASI	Psoriasis Area and Severity Index
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PPS	per protocol set
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PSD	Patient Symptom Diary
PSUR	Periodic Safety Update report
Q4W	every 4 weeks
Q8W	every 8 weeks
RS	randomized set
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SC	subcutaneously
SGE	special government employee
SOC	standard of care
SS	Safety Set
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

BIMZELX (bimekizumab-bkzx, hereafter referred to as bimekizumab) is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) that binds to IL-17A and IL-17F. IL-17 is a naturally occurring cytokine that is involved in inflammatory and immune responses.

BLA 761151 is an original BLA for bimekizumab and was submitted on July 15, 2020. The proposed indication is the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The proposed dosing regimen is 320 mg (given as 2 subcutaneous [SC] injections of 160 mg each) at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For patients weighing ≥120 kg, a dosage of 320 mg every 4 weeks after Week 16 may be considered. The proposed commercial presentations for bimekizumab drug product (160 mg/ml) are a single-dose pre-filled syringe and a single-dose pre-filled autoinjector, each with a 1 ml fill volume.

The Agency concluded that the proposed proprietary name, BIMZELX, was acceptable from both a promotional and safety perspective under BLA 761151 (Proprietary Name Review by Madhuri Patel, PharmD, Division of Medication Error Prevention and Analysis [DMEPA] dated October 13, 2020.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (PS0009 and PS0013), which provided evidence of the effectiveness of bimekizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The trials assessed the changes from Baseline to Week 16 compared to placebo for the co-primary endpoints:

- Proportion of subjects achieving Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from Baseline to Week 16
- Proportion of subjects achieving ≥90% improvement in the Psoriasis Area and Severity Index (PASI) from Baseline to Week 16 (PASI90)

Bimekizumab was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials. The Applicant has demonstrated that bimekizumab is effective for its intended use in the target population and has met the evidentiary standard required by 21 CFR 314.126(a)(b) to support approval.

However, because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356) by the Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing (OPMA/DBM), the application cannot be approved at this time. Refer to Section 4.2 (Product Quality) of this review for more detailed information regarding the deficiencies identified and steps needed to correct the deficiencies. The review team recommends a Complete Response for BLA 761151. Satisfactory resolution of the identified deficiencies is required before the application may be approved.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Psoriasis is a chronic, inflammatory disease that primarily affects the skin and is characterized by erythematous, scaly plaques and substantial impairment of quality of life. BIMZELX (bimekizumab) injection, for subcutaneous use is proposed for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Bimekizumab, the active ingredient in BIMZELX, is an original biologic product. Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) that binds to IL-17A and IL-17F. IL-17 is a naturally occurring cytokine that is involved in inflammatory and immune responses. Bimekizumab inhibits the release of proinflammatory cytokines and chemokines that have been implicated in the pathogenesis of psoriasis. Bimekizumab is available as 160 mg/ml in a single-dose pre-filled syringe and a single-dose pre-filled autoinjector, each with a 1 ml fill volume.

For the treatment of moderate to severe plaque psoriasis, current therapeutic options include phototherapy and photochemotherapy with methoxsalen, systemic small molecule drugs (acitretin, apremilast, cyclosporine, methotrexate), and biologic products (adalimumab, etanercept, infliximab, ustekinumab, secukinumab, ixekizumab, brodalumab, guselkumab, tildrakizumab, and risankizumab). Although the efficacy varies, no product produces a response in all patients or provides a permanent cure. Phototherapy and photochemotherapy may be impractical due to office-based administration requirements. All the systemic products may have one or more serious adverse reactions, including malignancy, serious infections, teratogenicity, depression, nephrotoxicity, hepatotoxicity, and bone marrow suppression (Menter, et. al., 2008). Because of these limitations, there is a recognizable need for additional therapeutic options despite the number of available therapies.

Substantial evidence of efficacy was demonstrated in 2 pivotal trials. In Trials PS0009 and PS0013, 670 subjects 18 years of age and older with moderate to severe plaque psoriasis who were eligible for systemic therapy or phototherapy were treated with bimekizumab and 169 with placebo. Moderate-to-severe plaque psoriasis was defined as a body surface area (BSA) involvement of ≥10%, an Investigator's Global Assessment (IGA) score of ≥3 ("moderate") in the overall assessment of psoriasis on a severity scale of 0 to 4, and a Psoriasis Area and Severity Index (PASI) score ≥12. In Trial PS0009, subjects were randomized to treatment with bimekizumab 320 mg Q4W, ustekinumab (for subjects weighing ≤100kg, 45 mg initially and 4 weeks later, then every 12 weeks; for subjects weighing >100kg, 90 mg initially and 4 weeks later, then every 12 weeks), or placebo. In Trial PS0013, subjects were randomized to bimekizumab 320 mg Q4W or placebo. In Trial PS0009, US-licensed ustekinumab was used in all sites in the US; all other sites received EU-approved ustekinumab. Because the Applicant did not provide an adequate scientific bridge between U.S. licensed and EU-approved ustekinumab, these products are considered distinct products.

The co-primary endpoints were assessed at Week 16 and included i) the proportion of subjects achieving Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from Baseline to Week 16, and ii) the proportion of subjects achieving ≥90% improvement in the Psoriasis Area and Severity Index (PASI) from Baseline to Week 16 (PASI90). In these trials, bimekizumab was superior to placebo on both PASI90 (Trial PS0009: 85% vs 5% and Trial PS0013: 91% vs 1%; p-values < 0.001) and IGA response (Trial PS0009: 84% vs 5% and Trial PS0013: 93% vs 1%; p-values < 0.001). Key secondary endpoints for both trials included the proportion of subjects achieving i) PASI100 response at Week 16, ii) IGA score of 0 ("clear") with at least a 2-grade improvement from Baseline at Week 16, iii) Scalp IGA score of 0 ("clear") or 1 ("almost clear") with a 2-grade improvement from Baseline at Week 16, and iv) PASI75 at Week 16. In addition, key secondary endpoints included assessment of psoriasis symptoms (itching, pain, and scaling) measured by the Patient Symptom Diary (PSD) at Week 16. In both trials, bimekizumab was statistically superior to placebo (p-values < 0.001) for all of these key secondary efficacy endpoints.

To evaluate maintenance and durability of response, subjects in Trial PS0013 who achieved a PASI90 response at Week 16 entered into a 40-week, double-blind, placebo-controlled, randomized-withdrawal period. During the randomized-withdrawal period, subjects initially randomized to bimekizumab 320mg Q4W who achieved a PASI 90 were re-randomized 1:1:1 to either bimekizumab 320mg Q4W or bimekizumab 320mg Q8W or placebo. Relapse was defined as not achieving a PASI75 response at Week 20 or later during the Randomized-Withdrawal Period. At Week 56, 87% of the subjects who continued treatment with bimekizumab 320 mg Q4W and 91% of subjects who were re-randomized to bimekizumab 320 mg Q8W maintained PASI90 response compared to 16% of subjects who were re-randomized to placebo and withdrawn from bimekizumab. In addition, for subjects who were IGA 0/1 responders at Week 16, at Week 56 87% of the subjects who continued treatment with bimekizumab 320 mg Q4W and 90% of subjects who were re-randomized to bimekizumab 320 mg Q8W maintained IGA 0/1 response compared to 24% of subjects who were re-randomized to placebo and withdrawn from bimekizumab. For responders at Week 16 who were re-randomized to treatment withdrawal, the median time to loss of PASI-90 was approximately 24 weeks. In addition, for subjects who were re-randomized to treatment withdrawal and also had IGA score of 0 or 1 at Week 16, the median time to loss of IGA score of 0 or 1 was approximately 24 weeks.

The overall safety database consisted of subjects enrolled in the phase 2 and phase 3 trials (Pool S2). The primary analysis dataset (Pool S1) for the review of safety of bimekizumab included pooled data from the Initial Treatment Period (Week 0-16) of the placebo-controlled phase 3 Trials PS0009 and PS0013. The safety database was adequate to characterize the safety profile of bimekizumab. Based on the analysis of the submitted data, treatment with bimekizumab did not appear to increase the risk of mortality. In Pool S1, serious adverse events (SAEs) were reported in 1.6% of subjects treated with bimekizumab and 2.4% of subjects treated with placebo. Treatment with bimekizumab was not associated with an increased risk of malignancy, suicidal ideation and behavior (SIB), major adverse cardiovascular events (MACE), or serious drug-related hypersensitivity reactions.

Infections were reported more frequently in subjects treated with bimekizumab than placebo. In Pool S1, TEAEs from the SOC of Infections and Infestations were reported in 36% of subjects treated with bimekizumab and 23% of subjects treated with placebo. A total of 14 subjects with latent TB were enrolled in the phase 3 trials and received prophylactic treatment for TB. None of these subjects developed active TB. Information regarding the need for pretreatment evaluation for tuberculosis will be conveyed in product labeling. Other adverse reactions (ARs) reported in ≥1% of subjects treated with bimekizumab and more frequently than in subjects treated with placebo included upper respiratory infections (15%), oral candidiasis (9%), headache (3%), injection site reactions (3%), Tinea infections (3%), gastroenteritis (2%), Herpes simplex infections (1%), acne (1%), folliculitis (1%), other Candida infections (1%), and fatigue (1%). These ARs will be conveyed in product labeling.

During the review of safety data, the review team discovered potential cases of drug-induced liver injury (DILI) associated with treatment with bimekizumab. There were no fatalities due to hepatic injury and no liver transplants. In Pool S1, elevations of transaminases >3 times the upper limit of normal (ULN) were reported in 1.0% of subjects treated with bimekizumab and 0.6% of subjects treated with placebo. Dr. Paul Hayashi and Dr. Mark Avigan from the DILI team of the Division of Hepatology and Nutrition (DHN) and Office of Surveillance and Epidemiology (OSE) identified 5 subjects who were considered to have possible or probable DILI by the DILI team or the Applicant's Hepatology Assessment Committee. Based on recommendations from the DILI team, labeling for bimekizumab will include Liver biochemical Abnormalities in Section 5 (Warnings and Precautions), including a statement advising prescribers to avoid use use of bimekizumab in patients with acute liver disease or cirrhosis because such patients may be at increased risk for severe hepatic injury. Labeling will also include recommendations for testing of liver enzymes, alkaline phosphatase, and bilirubin prior to and periodically during treatment with bimekizumab. Data from Pool S1 for elevated transaminases will be conveyed in Section 6.1 of product labeling. In addition, elevated liver enzymes/DILI will be evaluated as an outcome of interest in a prospective, observational, long-term safety study.

The DILI team also noted that reactivation of Hepatitis B virus (HBV) has been reported in postmarketing studies of secukinumab, which is an IL-17A blocker. This risk was also evaluated by consultants from the Division of Pharmacovigilance I (DPV) and Division of Epidemiology I (DEPI). Based on their analyses, consultants from the DILI team, DPV, and DEPI recommended inclusion of a recommendation for pretreatment evaluation for HBV infection in labeling for bimekizumab. However, because subjects with serologic evidence of HBV infection were excluded from clinical trials in the development program for bimekizumab, no data are available regarding the potential risk of HBV reactivation in patients treated with bimekizumab. As such, a recommendation for pretreatment evaluation for HBV will not be included in product labeling at this time. However, HBV reactivation will be included as an outcome of interest in an observational, long-term postmarketing safety study.

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. Subjects with a history of IBD could be enrolled in the clinical trials as long as they had no active symptomatic disease at Screening or Baseline. In the phase 2 and phase 3 trials, one subject (1/1789, exposure-adjusted incidence rate [EAIR] 0.05/100 subject-years) treated with bimekizumab 320 mg Q4W developed

new-onset ulcerative colitis which was serious, led to discontinuation, and was considered related to treatment by the investigator. IBD will be included in Sections 5 (Warnings and Precautions) and 6 (Adverse Reactions) of labeling for bimekizumab and will be evaluated as an outcome of interest in a prospective, observational, long-term safety study.

Product labeling and patient labeling, including a Medication Guide, as well as routine pharmacovigilance are adequate to manage the risk of BIMZELX in the postmarketing milieu. A Risk Evaluation and Mitigation Strategy (REMS) is not needed. Postmarketing requirements under 505(o) will include: studies to evaluate maternal, fetal, and infant outcomes of women exposed to bimekizumab during pregnancy, a lactation study, and a prospective, observational long term safety study to assess for malignancy and other serious adverse reactions (e.g., serious infection [including opportunistic infection], reactivation of Hepatitis B, tuberculosis, gastrointestinal [including inflammatory bowel disease, elevated liver enzymes/hepatotoxicity], cardiovascular, and hematologic events). Required pediatric assessments, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) will include: a PK, safety, and efficacy trial in subjects 12 years to <18 years of age, and a safety, efficacy, and PK trial in subjects ages 6 years to <18 years of age.

The available safety and efficacy data support the approval of BIMZELX (bimekizumab) injection, for subcutaneous use, for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Although there are a number of FDA-approved products with an acceptable benefit-risk profile for this indication, none of these treatments provides a permanent cure or universal response and all of these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

The Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing (OPMA/DBM) completed the compliance reviews of the pre-license inspections conducted at (b) (4) Drug Substance Manufacturing Facility (FEI: (b) (4) & UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356). Because of Good Manufacturing Practices (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility, the application cannot be approved at this time. The review team recommends a Complete Response for BLA 761151. Satisfactory resolution of the identified deficiencies is required before the application may be approved.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Psoriasis is a common, chronic, inflammatory multi-system disorder which primarily affects the skin and joints and is associated with substantial impairment of quality of life. The prevalence of psoriasis in the U.S. is approximately 4.6 %, of which an estimated 20% have moderate to severe disease. One third of patients have concomitant arthritis. Other comorbidities include depression/suicide, autoimmune disease, cardiovascular disease, and metabolic syndrome.	Moderate to severe plaque psoriasis is a serious disease because of its chronicity, impact on quality of life, and co-morbidities.
Current Treatment Options	• FDA approved drugs for the treatment of moderate to severe psoriasis include anti-metabolites (methotrexate), tumor necrosis factor (TNF) inhibitors (etanercept, adalimumab and infliximab), IL-12/23 blockers (ustekinumab), IL-17A blockers (secukinumab and ixekizumab), an IL-17A receptor antagonist (brodalumab), IL-23 blockers (guselkumab, tildrakizumab, risankizumab), a T cell inhibitor (cyclosporine), retinoids (acitretin) and phosphodiesterase 4 inhibitors (apremilast). Other treatment options include phototherapy with either PUVA (UVA light combined with methoxsalen) or UVB light (narrow or broadband). • All approved therapeutic options may be associated with the risk of serious adverse reactions or administration challenges. The use of phototherapy and photochemotherapy are limited by the need for office administration and additional photoprotection. Teratogenicity and hyperlipidemia are labeled risks with acitretin. Depression and weight loss are safety concerns with apremilast. The primary risks of cyclosporine use are nephrotoxicity and hypertension. Methotrexate has teratogenic, hepatotoxic, and nephrotoxic effects and may cause bone marrow toxicity and pulmonary fibrosis. Other systemic products may cause immunosuppression, serious infections and	There are several FDA-approved products with an acceptable benefit-risk profile for the treatment of moderate-to-severe plaque psoriasis in adults. None of these treatments provides a permanent cure or universal response and all these products are associated with one or more serious risks. Because treatment may be complicated by inadequate response, loss of response, adverse reactions, and the presence of comorbidities or concomitant illnesses, there is a need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	malignancy. All biologic products may be associated with loss of effect and serious hypersensitivity reactions. See the Summary of Treatment Armamentarium for Moderate to Severe Psoriasis for the specific labeled safety issues for each product.	
Benefit	• Data from Trial PS0009 and PS0013 provided substantial evidence of the effectiveness of bimekizumab for the treatment of moderate to severe plaque psoriasis. During these trials, 670 adult subjects with moderate to severe plaque psoriasis were treated with bimekizumab and 169 with placebo. Moderate-to-severe plaque psoriasis was defined as a BSA involvement of ≥10%, IGA score of ≥3 ("moderate") in the overall assessment of psoriasis on a severity scale of 0 to 4, and a PASI score ≥12. In both trials, subjects were initially randomized to bimekizumab 320 mg Q4W or placebo. In trial PS0009, subjects were also randomized to ustekinumab. The co-primary endpoints were assessed at Week 16 and included i) the proportion of subjects achieving Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from Baseline to Week 16, and ii) the proportion of subjects achieving ≥90% improvement in the Psoriasis Area and Severity Index (PASI) from Baseline to Week 16 (PASI90). • In both trials, bimekizumab was superior to placebo on both PASI90 (Trial PS0009: 85% vs 5% and Trial PS0013: 91% vs 1%; p-values < 0.001) and IGA response (Trial PS0009: 84% vs 5% and Trial PS0013: 93% vs 1%; p-values < 0.001). Key secondary endpoints for both trials included the proportion of subjects achieving i) PASI100 response at Week 16, ii) IGA score of 0 ("clear") with at least a 2-grade improvement from Baseline at Week 16, iii) Scalp IGA score of 0	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive. Achievement of clear or almost-clear skin is an intrinsically meaningful outcome for a cutaneous disease such as psoriasis. The data demonstrates that a patient with moderate-to-severe plaque psoriasis treated with bimekizumab 320 mg Q4W is likely to achieve clear or almost clear skin by Week 16, and to maintain this effect with continued treatment to Week 56. In addition, the data demonstrates that patients who respond to treatment with bimekizumab at Week 16 and discontinue treatment thereafter maintain response for approximately 24 weeks.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	("clear") or 1 ("almost clear") with a 2-grade improvement from Baseline at Week 16, and iv) PASI75 at Week 16. In addition, secondary endpoints included assessment of psoriasis symptoms (itching, pain, and scaling) measured by the Patient Symptom Diary (PSD) at Week 16. In both trials, bimekizumab was statistically superior to placebo (p-values < 0.001) for all of these key secondary efficacy endpoints. • To evaluate maintenance and durability of response, subjects in Trial PS0013 who achieved a PASI90 response at Week 16 entered into a 40-week, double-blind, placebo-controlled, randomized-withdrawal period. At Week 56, 87% of subjects treated with bimekizumab 320 mg Q4W and 91% of subjects treated with bimekizumab 320 mg Q8W maintained PASI90 response compared to 16% of subjects re-randomized to placebo. In addition, at Week 56, 87% of subjects treated with bimekizumab 320 mg Q4W and 90% of subjects treated with bimekizumab 320 mg Q8W maintained IGA 0/1 response compared to 24% of subjects who were re-randomized to placebo. For responders at Week 16 who were re-randomized to treatment withdrawal, the median time to loss of PASI-90 was approximately 24 weeks. The median time to loss of IGA score of 0/1 was also 24 weeks.	
Risk and Risk Management	• The primary safety database consisted of subjects enrolled in the phase 2 and phase 3 trials (Pool S2) and included 1789 subjects exposed to bimekizumab, including 1591 subjects for ≥8 months and 1371 for ≥12 months. The primary analysis dataset (Pool S1) for the review of safety of bimekizumab included pooled data from the Initial Treatment Period (Week 0-16) of the placebo-controlled phase 3 Trials PS0009 and PS0013 and included 670 subjects treated with bimekizumab 320 mg Q4W and 169 subjects treated with placebo.	The safety profile of bimekizumab has been adequately characterized. The safety profiles for all the approved therapies are informed by postmarketing data, which are not yet available for bimekizumab. However, in view of the premarket safety database for bimekizumab and the mechanism of action, it is unlikely that postmarketing exposure will

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	• In Pool S1, serious adverse events (SAEs) were reported in 1.6% of subjects treated with bimekizumab and 2.4% of subjects treated with placebo. • Infections were reported more frequently in subjects treated with bimekizumab (36%) than placebo (23%). The most common infections were upper respiratory infections. • A total of 14 subjects with latent TB were enrolled in the phase 3 trials and received prophylactic treatment for TB. None of these subjects developed active TB. Subjects were screened for TB prior to enrollment in the pivotal trials, and pre-treatment screening will be recommended in product labeling. • Treatment with bimekizumab was not associated with an increased risk of malignancy, suicidal ideation and behavior (SIB), major adverse cardiovascular events (MACE), or serious drug-related hypersensitivity reactions. • In Pool S1, elevations of transaminases >3 times the upper limit of normal (ULN) were reported in 1.0% of subjects treated with bimekizumab and 0.6% of subjects treated with placebo. There were 5 subjects who were considered to have possible or probable DILI by the DILI team or the Applicant's Hepatology Assessment Committee. Based on recommendations from the DILI team, labeling for bimekizumab will include Liver biochemical Abnormalities in Section 5 (Warnings and Precautions), including a statement advising prescribers to avoid use use of bimekizumab in patients with acute liver disease or cirrhosis because such patients may be at increased risk for serious hepatic injury. Labeling will also include	identify risks for malignancy or specific organ toxicities of a magnitude that would alter the benefit-risk conclusion. Prescription labeling, patient labeling (including Medication Guide), Instructions for Use, and routine pharmacovigilance, in conjunction with the post marketing requirements, are adequate to manage the risks of the product.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recommendations for testing of liver enzymes, alkaline phosphatase, and bilirubin prior to and periodically during treatment with bimekizumab. Data from Pool S1 for elevated transaminases will be conveyed in Section 6.1 of product labeling. In addition, elevated liver enzymes/DILI will be evaluated as an outcome of interest in a prospective, observational, long-term safety study. • Because HBV reactivation has been identified in post-marketing studies for the IL-17A inhibitor secukinumab, HBV reactivation will also be included as an outcome of interest in an observational, long-term postmarketing safety study. • New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. In the phase 2 and phase 3 trials, one subject (1/1789, EAIR 0.05/100 subject-years) treated with bimekizumab 320 mg Q4W developed new-onset ulcerative colitis which was serious, led to discontinuation, and was considered related to treatment. IBD will be included in Sections 5 (Warnings and Precautions) and 6 (Adverse Reactions) of labeling for bimekizumab and will be evaluated as an outcome of interest in a prospective, observational, long-term safety study. • There are insufficient data regarding the use of bimekizumab in pregnant women. An enhanced pre- and postnatal developmental toxicity study conducted with bimekizumab in pregnant monkeys revealed no maternal toxicity and no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. There were no observed adverse effects observed at 38 times the maximum	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	recommended human dose. A postmarketing study will be required to characterize the risk of fetal exposure to bimekizumab. • The following studies will be included in postmarketing requirements (PMRs): 1. Conduct a multicenter, open-label trial to assess the PK, safety, and efficacy of bimekizumab in adolescents (12 to <18 years of age) with moderate to severe chronic plaque psoriasis 2. Conduct a multicenter, randomized, parallel-group, blinded active-controlled study to assess the efficacy, safety, and PK of bimekizumab in pediatric subjects 6 to <18 years old with moderate to severe chronic plaque psoriasis 3. Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Bimzelx during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life. 4. Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations, spontaneous abortions, stillbirths, and small for gestational age and	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	preterm birth in women exposed to Bimzelx during pregnancy compared to an unexposed control population. 5. Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Bimzelx to assess concentrations of bimekizumab-bkzx in breastmilk using a validated assay and to assess the effects on the breastfed infant. 6. Conduct a prospective observational study to assess the long-term safety of bimekizumab treatment in U.S. adult patients with moderate to severe plaque psoriasis. Fully ascertain and centrally verify malignancy (including lymphoma), opportunistic infections, reactivation of Hepatitis B, tuberculosis, and serious infections. Other outcomes include hypersensitivity, gastrointestinal events (including inflammatory bowel disease, elevated liver enzymes/drug-induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), hematologic events, and neuropsychiatric (suicidal ideation/behavior) adverse events. For each adverse-event outcome separately, compare incidence in bimekizumab-treated patients against reference rates internally derived from analyses conducted in patients treated with other chronic systemic treatments for moderate-to-severe plaque psoriasis. Regardless of treatment discontinuation or switch to a different treatment for plaque psoriasis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events in representative U.S. patients who start treatment with bimekizumab for plaque psoriasis in the setting of	

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with bimekizumab. Enroll patients over a 4-year period and plan to follow for a minimum of 8 years from time of enrollment. • Labeling: Product labeling adequately addresses the risks identified during product development and conveys the lack of data from human exposure during pregnancy. A Medication Guide for the proposed presentation is included in patient labeling and is appropriate to inform patients of potential risks. Instructions for Use will convey information regarding self-administration of bimekizumab by patents or administration by caregivers. • A REMS is not recommended. Precedent biologic products with comparable safety profiles have a similar approach to post-marketing risk management.	

1.4. Patient Experience Data

Patient Experience Data Relevant to this Application (check all that apply)

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		8
		X	Patient reported outcome (PRO)	8.1.7
		□	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	8.1.2
		□	Performance outcome (PerfO)	
	□	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		
	□	Patient-focused drug development or other stakeholder meeting summary reports		
	□	Observational survey studies designed to capture patient experience data		
	□	Natural history studies		
	□	Patient preference studies (e.g., submitted studies or scientific publications)		
	□	Other: (Please specify):		
X	Patient experience data that were not submitted in the application, but were considered in this review:			
	□	Input informed from participation in meetings with patient stakeholders		
	X	Patient-focused drug development or other stakeholder meeting summary reports		2.2
	□	Observational survey studies designed to capture patient experience data		
	□	Other: (Please specify):		
□	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Psoriasis is a common, chronic, immune-mediated skin disorder. The characteristic lesion is a sharply demarcated erythematous plaque with micaceous scale, and the plaques may be localized or widespread in distribution (Feldman 2015). Psoriasis is a complex autoimmune inflammatory disease that occurs in genetically susceptible individuals. The pathophysiology of psoriasis involves the activation of innate immune cells in the skin, which produce proinflammatory cytokines that trigger and perpetuate the inflammatory cascade (Blauvelt and Ehst 2015).

In the United States and Canada, prevalences as high as 4.6% and 4.7% have been reported, respectively (Blauvelt and Ehst 2015). It is estimated that approximately 7.5 million people in the United States have psoriasis. Approximately 80% of those affected by psoriasis have mild-to-moderate disease, and 20% have moderate-to-severe psoriasis affecting more than 5% of the body surface area (BSA). The most common form of psoriasis is plaque psoriasis, affecting about 80% to 90% of patients with psoriasis (Menter et al. 2008).

Psoriasis can first appear at any age, from infancy to the eighth decade of life. Two peaks in age of onset have been reported: one at 20 to 30 years of age and a second peak at 50 to 60 years. In approximately 75% of patients, the onset is before the age of 40 years, and in 35% to 50%, it is before the age of 20 years. The age of onset is earlier in women than in men (Blauvelt and Ehst 2015).

The natural history of psoriasis is chronic with intermittent remissions. Plaque psoriasis is the most common presentation; other forms include guttate, pustular, erythrodermic, and inverse psoriasis. Psoriasis may affect fingernails and toenails, most frequently in association with psoriatic arthritis. A diagnosis of psoriasis can be made by history taking and physical examination in the vast majority of cases. The differential diagnosis of psoriasis may include seborrheic dermatitis, lichen simplex chronicus, atopic dermatitis, and nummular eczema. Occasionally, a skin biopsy is performed to rule out other conditions (Blauvelt and Ehst 2015).

The presentation of psoriasis in the pediatric population can be different from that in adults. Psoriasis in infants often presents with involvement of the diaper area. Infants with diaper-area involvement typically develop symmetrical, well-demarcated erythematous patches with little scale. Maceration may be present. Unlike irritant diaper dermatitis, the inguinal folds are usually involved. Affected infants may also have psoriatic plaques in other body areas. These plaques are often smaller and thinner than the psoriatic plaques in adult patients. In children, scalp involvement is a common and often initial presentation of chronic plaque psoriasis. In addition, children with chronic plaque psoriasis are more likely to have facial involvement than are adults (Blauvelt and Ehst 2015).

A number of comorbid systemic conditions occur more frequently in patients with psoriasis. Examples of these conditions include cardiovascular disease, malignancy, diabetes, hypertension, metabolic syndrome, inflammatory bowel disease, serious infections, and autoimmune disorders. Psychiatric comorbidities associated with psoriasis include depression and suicidal ideation; neurotic, stress-related, or somatoform disorders; and personality and behavioral disorders (Korman 2017).

The impact of psoriasis on the daily lives of patients was among the topics discussed at a Patient-Focused Drug Development Meeting for psoriasis held by the Agency on March 17, 2016. Patients who attended the meeting described severe physical, social, and emotional effects, including depression, anxiety, limitations on activities, embarrassment, stigma, and social discrimination. Patients shared their experiences with currently available therapies, and they described varying degrees of success in managing symptoms with these therapies.

Psoriasis is a chronic, debilitating disease with significant impacts on the lives of affected patients. At the Patient-Focused Drug Development meeting, patients discussed current challenges with variability in effectiveness, tolerability, access to available treatments, and uncertainty regarding long-term effects of available treatments. Therefore, development of additional safe and effective therapies continues to be an important goal. This is especially true for certain subgroups of patients with psoriasis, such as children and pregnant women.

2.2. Analysis of Current Treatment Options

Although there are multiple topical therapies available for the treatment of psoriasis, topical therapies are not typically used alone for the treatment of moderate to severe disease. Approved systemic therapies for the treatment of moderate to severe plaque psoriasis are described in the table below.

Table 1: Summary of Treatment Armamentarium for Moderate-to-Severe Plaque Psoriasis

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Antimetabolite/ Immuno-suppressant	Methotrexate 1972	Severe, recalcitrant, disabling, psoriasis not adequately responsive to other forms of therapy; but only when diagnosis established by biopsy and/or dermatologic consultation. Must rule out undiagnosed concomitant disease affecting immune responses	Starting dose schedules: 1. Weekly single oral, IM or IV dose: 10 to 25 mg per week until adequate response is achieved 2. Divided oral dose: 2.5 mg at 12 hr intervals for three doses 30 mg/week should not ordinarily be exceeded	No efficacy information for psoriasis in labeling	BW: potentially fatal toxic reactions including bone marrow suppression, aplastic anemia, and gastrointestinal toxicity with concomitant NSAID tx; hepatotoxicity, pulmonary toxicity, kidney toxicity, opportunistic infections, malignant lymphoma, tumor lysis syndrome, severe skin toxicity, fetal death and anomalies "should not be used in pregnant women with psoriasis"	Major AE derm dosing: ↑Liver enzymes stomatitis, diarrhea, nausea and vomiting, lymphopro-liferative disorders Recommend periodic liver biopsy if tx long-term Pregnancy: X
Tumor Necrosis Factor Inhibitor	Infliximab (Remicade) 2006	Chronic severe (extensive or disabling) plaque psoriasis, candidates for phototherapy or systemic therapy and when other systemic therapies are medically less appropriate	5 mg/kg IV at 0, 2 and 6 weeks, then every 8 weeks	From labeling: 3 R, DB, PC trials PASI 75 at week 10 1. Inflix (5 mg/kg)-80% vs. 3% placebo 2. Inflix (5 mg/kg)-75% vs. 2% placebo 3. Inflix (5 mg/kg)-88% vs. Inflix (3 mg/kg) 72% vs. 6% placebo	BW: risk of serious infection (bacterial sepsis, TB, invasive fungal and opportunistic), malignancies including hepatosplenic T-cell lymphomas (adolescents and young adults) Warnings: Hepatitis B reactivation, heart failure, hepatotoxicity, cytopenias, hypersensitivity events, malignancy	Pregnancy: B

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Tumor Necrosis Factor Inhibitor	Adalimumab (Humira) 2008	Moderate to severe chronic plaque psoriasis, candidates for phototherapy or systemic therapy	80 mg via SC initial dose, followed by 40 mg SC every other week starting 1 week after initial dose	From labeling: 2 R, DB, PC trials PASI 75 at Week 16 1. Ada-71% vs. 7% placebo 2. Ada-78% vs. 19% placebo	BW: risk of serious infections (bacterial sepsis, TB, invasive fungal and opportunistic), malignancy including hepatosplenic T-cell lymphoma Warnings: hypersensitivity reactions, hepatitis B reactivation, demyelinating disease, cytopenias, heart failure, Lupus-like syndrome	Pregnancy: B
Tumor Necrosis Factor Inhibitor	Etanercept (Enbrel) 2004; 2016	Chronic moderate to severe psoriasis, candidates for phototherapy or systemic therapy; 11/2016–approved for patients 4 years of age and older	50 mg SC twice weekly for 3 months, followed by 50 mg once weekly; <63 kg (138 lb)- 0.8 mg/kg SC weekly.	From labeling: 2 R, DB, PC trials PASI 75 at 3 months 1. Etan-47% vs. 4% placebo 2. Etan-46% vs. 3% placebo	BW: risk of serious infection (bacterial sepsis, TB, invasive fungal and opportunistic), lymphomas, other malignancies Warnings: demyelinating disease, worsen CHF, pancytopenia, malignancy, hepatitis B reactivation	Pregnancy: B
IL-12 and IL-23 Blocker	Ustekinumab (Stelara) 2009	Moderate to severe psoriasis, candidates for phototherapy or systemic therapy	Patients weighing <100 kg: 45 mg SC initially and 4 weeks later, followed by 45 mg SC every 12 weeks; patients weighing >100 kg: 90 mg SC initially and 4 weeks later, followed by 90 mg SC every 12 weeks	From labeling: 2 R, DB, PC trials PASI 75 at Week 12 1. Uste (90 mg)-66% vs. uste (45 mg)-67% vs. 3% placebo 2. Uste (90 mg)-76% vs. uste (45 mg)-67% vs. 4% placebo	W&Ps: infections (serious bacterial, fungal and viral), theoretical risk for serious infections, malignancy, reversible posterior leukoencephalopathy syndrome, pretreatment eval for TB	Pregnancy: B

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-17A Blocker	Secukinumab (Cosentyx) 2015	Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy	300 mg SC at weeks 0, 1, 2, 3 and 4 followed by 300 mg SC every 4 weeks. For some patients, a dose of 150 mg may be acceptable	From labeling: 4 R, DB, PC trials PASI 75 at Week 12 1. Sec (300 mg)-82% vs. sec (150 mg)-71% vs. 4% placebo 2. Sec (300 mg)-76% vs. sec (150 mg)-67% vs. 5% placebo 3. Sec (300 mg)-75% vs. sec (150 mg)-69% vs. 0% placebo 4. Sec (300 mg)-87% vs. sec (150 mg)-70% vs. 3% placebo	W&Ps: infections (serious bacterial, fungal and viral), theoretical risk for serious infections, Crohn's disease, hypersensitivity reactions, pretreatment eval for TB	Pregnancy: B
IL-17A Blocker	Ixekizumab (Taltz) 2016	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	160 mg (two 80 mg injections) SC at week 0, followed by 80 mg at weeks 2, 4, 6, 8, 10, and 12, then 80 mg every 4 weeks	From labeling: 3 R, DB, PC trials PASI75 at Week 12 1. Ixe (80 mg q2wk) 89% vs. 4% placebo 2. Ixe (80 mg q2wk) 90% vs. 2% placebo 3. Ixe (160 mg × 1, then 80 mg q2wk) 87% vs. 7% placebo	W&Ps: infections (upper respiratory tract, oral candidiasis, conjunctivitis and tinea infections; inflammatory bowel disease (Crohn's disease and ulcerative colitis); hypersensitivity reactions; pretreatment eval for TB	
IL-17 Receptor A Antagonist	Brodalumab (Siliq) 2017	Moderate-to-severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and who have failed to respond or have lost response to other systemic therapies	210 mg by SC injection at weeks 0, 1, and 2 followed by 210 mg every 2 weeks	From labeling: 3 R, DB, PC trials PASI 75 and sPGA of 0 (clear) or 1 (almost clear) at Week 12 1. Bro (210 mg q2wk) PASI 75 83% vs. 3% placebo; sPGA 0 or 1 bro 76% vs. 1% placebo 2. Bro (210 mg q2wk) PASI 75 86% vs. 8% placebo; sPGA 0 or 1 bro 79% vs. 4% placebo; PASI 100 bro 44% vs. uste 22% 3. Bro (210 mg q2wk) PASI 75 85% vs. 6% placebo; sPGA 0 or 1 bro 80% vs. 4% placebo; PASI 100 bro 37% vs. uste 19%	BW for suicidal ideation and behavior W&Ps: Suicidal ideation and behavior; infections (serious infections and fungal infections); Crohn's disease; pretreatment eval for TB; avoid live vaccines	REMS requires prescribers and pharmacies to be certified; patients must sign a patient-prescriber agreement form

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
IL-23 Blocker	Guselkumab (Tremfya) 2017	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	100 mg by SC injection at week 0, week 4, and every 8 weeks thereafter	From labeling: 3 R, DB, PC, AC trials; 1 & 2: PASI 90 and sPGA of 0 ("cleared") or 1 ("minimal") at Week 16 1. Gus (100 mg weeks 0 & 4 then q8wk) PASI 90 73% vs. 3% placebo; IGA 0 or 1 85% vs. 7% placebo 2. Gus (100 mg Weeks 0 & 4 then q8wk) PASI 90 70% vs. 2% placebo; IGA 0 or 1 84% vs. 8% placebo 3. Subjects began tx with uste; at wk16 subjects with IGA ≥2 R to gus or continued uste; endpoint at Week 28 IGA 0 or 1 with ≥2 grade improvement; gus 31% vs. 14% uste	W&Ps: infections (upper respiratory tract infections, gastroenteritis, tinea infections, and herpes simplex infections); pretreatment eval for TB; avoid live vaccines	
IL-23 Blocker	Risankizumab (Skyrizi) 2019	Moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy	150 mg by SC injection at week 0, week 4, and every 12 weeks thereafter	From Labeling: 4 R, DB, PC trials; PASI 90 and sPGA of 0 ("clear") or 1 ("almost clear") at Week 16. 1. RKZ 150 mg (150 mg weeks 0 & 4 then q12wk) PASI 90 75% vs. 5% placebo; IGA 0 or 1 88% vs. 8% placebo 2. RKZ 150 mg (150 mg weeks 0 & 4 then q12wk) PASI 90 75% vs. 2% placebo; IGA 0 or 1 84% vs. 5% placebo 3. RKZ 150 mg (150 mg weeks 0 & 4 then q12wk) PASI 90 73% vs. 2% placebo; IGA 0 or 1 84% vs. 7% placebo	W&Ps: infections (upper respiratory tract infections, tinea infections); pretreatment eval for TB; avoid live vaccines	

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
T-Cell Inhibitor/ Immuno-suppressant	Cyclosporine 1997	Adult, nonimmuno-compromised patients with severe recalcitrant disabling psoriasis who have failed at least one systemic therapy	Starting dose: 2.5 mg/kg/day, taken twice daily, dosage ↑ by 0.5 mg/kg/day at 2-week intervals, to a maximum of 4.0 mg/kg/day	From labeling: PASI 75 - 51% at 8 weeks, 79% at 16 weeks	BW: Should only be used by MDs experienced in management of systemic immunosuppressive Rx, ↑ susceptibility to infections and development of neoplasia including lymphoma, also hypertension, nephrotoxicity which ↑ with ↑ doses. In psoriasis patients with history of PUV-A, UV-B, coal tar or radiation Rx-↑ risk of skin malignancies Warnings: Hepatotoxicity, hyperkalemia, thrombotic microangiopathy, progressive multifocal leukoencephalopathy, malignancies, serious infection, neurotoxicity	Pregnancy category: C

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Retinoid	Acitretin (Soriatane) 1996	Severe psoriasis unresponsive to other therapies or whose clinical condition contraindicates the use of other treatments	Starting dose: 25 to 50 mg orally (PO) per day, maintenance doses of 25 to 50 mg per day may be given dependent upon an individual patient's response to initial Rx	From labeling: 2 DB, PC trials-Mean change in PGA at 8 weeks A. Acitretin (50 mg)-2 vs. -0.29 on placebo B. Acitretin (50 mg)-1.57 vs. Acitretin (25 mg)-1.06 vs. -0.06 on placebo (no multiplicity adjustment for trial B)	BW: pregnancy must be prevented during Rx and for 3 years following because of teratogenicity, no ethanol ingestion by FOCBP because of metabolism to etretinate and ↑ 1/2life, REMS (Do Your P.A.R.T.) participation required for FOCBP-see Drugs @FDA for details. Patients cannot donate blood for 3 years post-Rx; see label for data on pregnancies in partners of male patients on acitretin	W&P: hepatotoxicity, skeletal abnormalities, lipids ↑, cardiovascular risk ↑, ophthalmologic effects, pancreatitis, capillary leak syndrome, pseudotumor cerebri, exfoliative dermatitis, depression Pregnancy category: X
Phosphodiesterase 4 (PDE4) Inhibitor	Apremilast (Otezla) 2014	Moderate-to-severe psoriasis, candidates for phototherapy or systemic therapy	To reduce risk of gastrointestinal symptoms, titrate to recommended dose of 30 mg per oral twice daily	From labeling: 2 R, DB, PC trials PASI 75 at 16 weeks 1. Aprem 33% vs. 5% in placebo 2. Aprem 28.8% vs. 5.8% in placebo	W&Ps: depression, weight decrease, drug interactions with strong P450 enzyme inducers (rifampin, phenobarbital, carbamazepine phenytoin)	Diarrhea, nausea, URI, headache Pregnancy category: C

FDA-Approved Treatment	Product(s) Name/Year Approved	Relevant Indication	Dosage and Administration	Efficacy Information	Important Safety and Tolerability Issues	Other Comments
Phototherapy	PUVA-8-MOP (methoxsalen) + UV-A therapy	Severe, recalcitrant, disabling psoriasis not responsive to other forms of therapy	20-70 mg per oral (based on weight) taken 2-4 hr before exposure to UV-A light	No efficacy information for psoriasis in the labeling	BW: should only be used by MDs who have special competence in psoriasis management. Warnings: serious skin burning, ocular damage, aging of the skin, skin cancer (including melanoma)	Nausea, erythema, pruritus, must avoid all exposure to sunlight (even through windows) of eyes and skin for 24 hr after ingestion Pregnancy category: C

Source: Reviewer's table from the Unireview of BLA 761067
Abbreviations: AC, active comparator; ada, adalimumab; aprem, apremilast; bro, brodalumab; BW, boxed warning; DB, double-blind; etan, etanercept; gus, guselkumab; inflix, infliximab; Ixe, ixekizumab; NSAID, nonsteroidal anti-inflammatory drug; PASI, Psoriasis Area Severity Index; PC, placebo-controlled; R, randomized; sec, secukinumab; uste, ustekinumab; RKZ, risankizumab; W&Ps, warnings and precautions; FDA, U.S. Food and Drug Administration; sPGA, static Physician's Global Assessment; REMS, risk evaluation and mitigation strategy; IM, intramuscular; IV, intravenous; MD, Doctor of Medicine; AE, adverse event; UV, ultraviolet; CHF, congestive heart failure; SC, subcutaneous injection; FOCBP, females of childbearing potential; IGA, Investigator's Global Assessment; IL, interleukin; TB, tuberculosis; URI, upper respiratory infection; tx, treatment; q8wk, every 8 weeks

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

Because bimekizumab is an original biologic product and is not currently marketed in the US, this section is not applicable.

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant developed bimekizumab injection under IND 128707. On May 2, 2016, the Agency held a pre-IND Meeting with the Applicant, and the Applicant opened the IND on June 14, 2016. After the pre-IND meeting, the Applicant interacted with the Agency at the following milestones/meetings during the development program: guidance meetings (written responses only) April 18, 2017, August 8, 2017, May 23, 2018, and August 20, 2018; CMC pre-BLA meeting September 24, 2019, and pre-BLA meeting December 9, 2019.

The Agency conducted a pre-IND meeting with the Applicant on May 2, 2016. The Applicant proposed to conduct a phase 2 dose-ranging trial (PS0010) followed by an open-label extension trial (PS0011). The Agency recommended that the duration of the maintenance period (open label Trial PS0011) be at least 48 weeks and that dose ranging should continue during Trial PS011. The Agency also advised the Applicant to conduct a prospective assessment for neuropsychiatric adverse events (AEs), including anxiety, depression, and suicidal ideation and behavior (SIB). Advice was also provided regarding the proposed patient-reported outcome (PRO) measures.

In addition, the Applicant proposed to conduct a "seamless" development program with the phase 3 trials immediately following phase 2 trials PS0010 and PS0011. The Agency replied that because the available clinical database was limited, we could not concur that the proposed operationally seamless program is adequate to support the dose selection and benefit-risk assessment. The Agency advised the Applicant to assess all elements of dose ranging to inform dose and dosing frequencies and the primary timepoint for efficacy evaluation for the phase 3 trials. The Applicant was also advised to request an End-of-Phase 2 (EOP2) meeting after completion of the phase 2 trials to inform discussion and planning for the phase 3 program.

The Applicant opened the IND with the submission of phase 2 Protocol PS0010 on June 14, 2016. In a Study May Proceed letter dated August 16, 2016, the Agency advised the Applicant regarding the recommended co-primary efficacy endpoints for the treatment of plaque psoriasis. The Agency also recommended that a mental health professional be involved in the screening process, as well as to evaluate any depression or SIB during the trial. The Applicant was also advised to screen for neuropsychiatric AEs at every visit. The Agency also advised the Applicant regarding screening instruments appropriate for this purpose. The Agency also

recommended that assessment of severity of nail and scalp involvement be based on an acceptable Investigator Global Assessment (IGA) scale.

On August 17, 2016, the Applicant submitted a protocol for phase 2 Trial PS0011. In an advice letter dated November 2, 2016, the Agency advised the Applicant that subjects who discontinued treatment after meeting stopping criteria should remain in the study and be monitored until the adverse event resolves or stabilizes. The Agency also provided additional advice regarding screening, monitoring, and stopping criteria related to depression/SIB. In addition, the Applicant was advised regarding documentation and adjudication of major adverse cardiovascular events (MACE).

On April 18, 2017, the Agency sent written responses from a guidance meeting which conveyed advice regarding the Applicant's proposed phase 3 program. No formal End-of-Phase 2 meeting was requested by the Applicant. The Agency advised the Applicant regarding the information needed to support the use of non-US-licensed active comparator products in US trial sites. The Applicant was also advised of the need to establish a scientific bridge between the non-US-licensed comparator and the US-licensed comparator if they intended to rely on data from a non-US-licensed comparator to support a labeling claim.

Further comments regarding the phase 3 program included the following. The Agency advised the Applicant to propose a clinically meaningful threshold of change for defining treatment response for pain, itch and scaling as assessed by the Patient Symptom Diary (PSD). The Applicant was also advised to conduct active assessment for injection site reactions at every visit, and to include escape criteria for non-responders based on the IGA response. The Agency also stated that during the randomized-withdrawal trial, the definition of relapse should be based on the IGA response. The Agency also provided advice regarding information needed to support inclusion of patient-reported outcome (PRO) data in labeling as well as the size of the safety database.

In an advice letter dated June 22, 2017, the Agency provided recommendations regarding phase 2 protocol PS0016 and extension study PS0018. The Agency reiterated the recommended co-primary endpoints should be the IGA response (i.e., the proportion of subjects who achieve "clear" or "almost clear" [score of 0 or 1 with 2-grade improvement from baseline on acceptable 5-point IGA scale]) and the Psoriasis Area and Severity Index (PASI) (e.g., PASI 75, PASI 90). The letter also conveyed additional advice regarding assessment of PROs using the PSD. Specifically, subjects should have a sufficient baseline PSD score in each of the items (pain, itch and scaling) in order to observe a clinically meaningful response.

Written responses from a guidance meeting were sent on August 8, 2017. The responses provided advice regarding the immunogenicity evaluation, manufacturing process, human factors studies, and development of the safety syringe (SS) and autoinjector (AI) devices. Regarding the human factors validation studies, the Applicant was advised to record use errors, operational difficulties, and close calls for each attempt for each participant and collect

subjective feedback, perform a root cause analysis, and determine if additional mitigations are needed to further mitigate user errors observed in the study. The Agency also advised the Applicant to conduct the human factors validation studies with the to-be-marketed commercial product. The Agency also provided advice regarding the proposed clinical use study to evaluate the ability of subjects to perform self-injections using the SS and AI presentations. Specifically, the Agency advised the Applicant to identify the intended injection site (e.g., arm, thigh, and/or abdomen) and injection angle for each of the product presentations and to enroll subjects across a spectrum of body weights in the study. In addition, the Applicant was advised to collect a minimum of 100 devices per presentation and examine the devices for any evidence of failure.

The Applicant submitted phase 3 Protocols PS0008, PS0009, and PS0013 on November 16, 2017. In an advice letter sent February 3, 2018, the Agency provided advice regarding the protocols. Advice pertinent to all 3 protocols included reiteration of previous comments regarding the assessment of MACE and injection site reactions, as well as the need to provide escape criteria for non-responders based on IGA response. In addition, the Agency provided comments regarding inclusion and exclusion criteria for depression and SIB. The Agency also advised the Applicant that the proposed concomitant use of intra-articular or topical corticosteroids should be avoided because such use may confound the assessment of safety and efficacy. Regarding PRO assessments, the Applicant was advised to evaluate itch, pain, and scaling separately, and that a reduction of 4 or more points on a numerical rating scale (NRS) for itch is generally considered clinically significant.

The Applicant proposed the inclusion of an active comparator for Trials PS0008 (adalimumab) and PS0009 (ustekinumab). The Agency reiterated previous advice regarding the need to establish a scientific bridge between US-licensed and EU-approved products if the Applicant intended to pursue labeling claims against the comparator products. The Agency also advised the Applicant that risks listed in the Warnings and Precautions section of labeling for each of the comparator products should be addressed in the withdrawal criteria for the respective trials. In addition, the Agency reiterated that during the randomized withdrawal period of Trial PS0013, relapse should be defined based on IGA response. The Applicant was also advised to define and assess for rebound during the randomized withdrawal period.

In written responses dated May 23, 2018, the Agency provided additional advice regarding the development program for the SS and AI devices. Specifically, the Agency agreed that the design of the proposed study to evaluate the PK comparability of the SS and AI presentations with the pre-filled syringe (PFS) used in the phase 3 trials appeared reasonable. For the clinical use study, the Applicant proposed (b) (4) The Applicant addressed previous advice by providing information regarding the injection sites, a proposal to evaluate subjects across a spectrum of body weights, and a proposal to examine >100 devices per presentation for failure after use. The Agency recommended that subjects return to the study site (e.g., 24 hours after performing self-

injection) for evaluation of injection site reactions (e.g., erythema, edema, etc.) as well as a query for injection site pain. Otherwise, the Agency agreed that the Applicant's proposals appeared reasonable.

The Applicant submitted a Human Factors Validation Protocol on April 2, 2018. In an advice letter sent June 22, 2018, the Agency advised the Applicant that the study protocol should reflect real-world use. In addition, the Applicant received advice regarding recording errors of use by subjects, as well as the preferred format for presentation of human factors data to the Agency.

The Applicant submitted amendments to phase 3 protocols PS0008, PS0009, and PS0013 on April 13, 2018. In an advice letter dated July 20, 2018, the Agency advised the Applicant that in general, to support a comparative claim against an active comparator, replication of study findings from two adequate and well-controlled studies are needed. The Agency also provided information regarding the criteria required for a single study submission for cases where a single study submission can be acceptable. The Agency also reiterated comments regarding the need for adequate scientific bridge between EU-approved and US-licensed active comparator to justify the relevance of these data to a demonstration of superiority. In addition, the Agency reiterated previous comments advising the Applicant to propose a clinically meaningful threshold for change for pain, itch, and scaling assessed by the PSD. The Agency also reiterated the recommendation that the definition of relapse in Trial PS0013 be based on loss of success, defined as an IGA score ≥2.

The Agency sent written responses from a guidance meeting August 20, 2018, which provided advice to the Applicant regarding a proposed study in healthy subjects to evaluate the effect of a single dose of bimekizumab on the response to the influenza vaccine. The Agency agreed that the proposed inclusion criteria and use of the hemagglutinin inhibition assay to measure serotype-specific antibodies were reasonable. However, the Agency also advised the Applicant to consider evaluating vaccine effectiveness in subjects with psoriasis treated with bimekizumab in a clinical trial setting.

On July 16, 2018, the Applicant submitted the protocol for open-label extension Trial PS0014. In an advice letter dated September 19, 2018, the Agency advised the Applicant to base treatment assignments in Trial PS0014 on IGA rather than PASI response in the feeder trials. The Applicant was also advised that concomitant use of topical or systemic corticosteroids or topical Vitamin D analogs may confound the assessment of safety and efficacy. However, the Agency also advised that concomitant limited use of low potency topical corticosteroids (e.g., to intertriginous areas) may be acceptable provided that such use was documented, and the effect considered in the evaluation of safety and efficacy. The Agency also provided advice regarding the statistical evaluation of efficacy response based on dosing regimen in the feeder and extension trials.

On August 6, 2018, the Applicant submitted protocols UP0033 and DV0002. Trial UP0033 was a clinical pharmacology trial to evaluate the comparative PK of bimekizumab administered by the PFS and AI presentations. Trial DV0002 was a sub-study of Trial PS0014 and was designed to evaluate the ability of subjects with psoriasis to perform self-injection with the PFS and AI presentations. In an advice letter dated October 26, 2018, the Agency advised the Applicant to develop a mechanism to record and evaluate damaged or dysfunctional devices within the trial. In addition, the Applicant was advised to evaluate injection site pain using an NRS rather than a visual analog scale.

On November 28, 2018, the Applicant submitted the protocol for Trial UP0034, which was designed to evaluate the effect of a single dose of bimekizumab 320 mg on the response to influenza vaccine in healthy subjects. In an advice letter dated May 31, 2019, the Agency advised that conducting the study in the target population exposed to multiple doses of bimekizumab would be more relevant. The Agency also expressed concerns about inferring effectiveness in this patient population based on non-inferiority of hemagglutination inhibition (HI) responses because other immune factors besides HI antibodies may be important for protection against influenza. The Agency also advised that the proposed inclusion of only subjects who were influenza seronegative and exclusion of subjects who received any vaccination within the previous 52 weeks were not representative of the general US population and may limit the ability to extrapolate study findings to the general population. Furthermore, the Agency also advised the exclusion of subjects with known diagnosis of immunodeficiency or use of immunomodulatory agents other than bimekizumab (e.g., systemic steroids, cyclophosphamide, chemotherapy, radiation therapy).

On December 9, 2019, the Agency held a pre-BLA meeting with the Applicant. The Applicant proposed to submit foreign data supporting information only for US sites that did not sign FDA Form 1572s; the Agency agreed that this was reasonable. The Agency provided advice regarding the submission of a Request for Proprietary Name Review. The Agency agreed that from a technical perspective, the proposed format and content of the BLA submission was acceptable. The Applicant was also advised that the immunogenicity assays used for the detection and confirmation of anti-drug binding and neutralizing antibodies should be adequately validated prior to analysis of phase 3 clinical samples. In addition, clinical serum samples should be appropriately stored until suitable immunogenicity assays are developed

and fully validated. The Agency agreed that the Applicant's proposal to submit interim clinical study reports for Trials PS0008, PS0009, and PS0013 and the interim data cutoff of Trial PS0014 appeared reasonable. The Agency disagreed with the Applicant's proposal to submit neutralizing antibody data with the 120-day safety update and advised that the data should be included with the original BLA submission. The Agency also provided advice regarding the Applicant's planned pooling strategy for safety data from the phase 2 and phase 3 trials.

The Agency also agreed with the Applicant's proposal to provide shift tables for hematology and biochemistry lab data based on Common Terminology Criteria for Adverse Events (CTCAE) grade. However, the Agency also requested the Applicant to provide shift tables including the raw values, along with the normal reference range. The Agency also agreed with the Applicant's proposal to provide narratives for deaths, premature termination adverse events (PTAEs), serious adverse events (SAEs), AEs that have been identified for special monitoring, and pregnancies. The Agency clarified that PTAEs should include all subjects who discontinued from the trials because of an AE, whether or not the AE was considered treatment related.

The Applicant also proposed to pool safety data from studies across multiple indications. The Agency responded that interpretation of findings from such pooling may be limited because different patient populations may be susceptible to different adverse events to result in a different safety profile. The Agency also agreed with the information proposed by the Applicant for inclusion in the 120-day safety update and advised that narratives for pregnancies be included in the update as well. The Applicant was asked to submit evidence to support the proposed thresholds for the PSD response score for itch, pain, and scaling. The Agency also asked the Applicant to provide the coding dictionary used for mapping investigator verbatim terms to preferred terms, as well as an analysis of ECG data.

The review team discovered evidence of possible drug-induced liver injury (DILI) in subjects treated with bimekizumab and consulted the DILI team from the Division of Hepatology and Nutrition. On March 22, 2021, an Information Request was sent to the Applicant requesting the establishment of an independent Hepatology Assessment Committee (HAC) to provide an overall summary of the risk of DILI associated with treatment with bimekizumab. On April 16, 2021 (SDN 48), the Applicant submitted the report from the HAC. The review team considered the HAC report to be a Major Amendment, and the user fee goal date was extended to October 15, 2021 (letter dated April 26, 2021).

Refer to Section 8.2.9 for a discussion of the pediatric development plan for bimekizumab for the treatment of moderate to severe plaque psoriasis.

4 Significant Issues from Other Review Disciplines Pertinent to Clinical Conclusions on Efficacy and Safety

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The sites were selected for inspection by the Office of Scientific Investigations based on number of enrolled subjects, prior inspectional history, site efficacy, filing of financial disclosure, and common site/investigator for multiple phase 3 clinical trials. The findings of the clinical inspection summary (review by Phuc Nguyen, MD dated July 15, 2021) are summarized in the table below.

Table 2: Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification
Andrew Blauvelt, MD Oregon Medical Research Center 9495 SW Locust St Suite G Portland, OR 97223	PS0008, PS0013	PS0008- 18 PS0013- 20	NAI
Abel Jarrell, MD ActivMed Practices and Research, Inc. 110 Corporate Drive Suite 2 Portsmouth, NH 03801	PS0009, PS0013	PS0009- 12 PS0013- 6	NAI

Source: Reviewer's table
Abbreviation: ID, identification; MD, Doctor of Medicine; NAI, no action indicated

The clinical sites of Dr. Jacek Szepietowski (Site 365 in Trials PS0008 and PS0013, Poland) and Dr. Dagmara Witkowska (Site 370 in Trials PS0009 and PS0013, Poland) were also initially selected for inspection. However, because of travel restrictions related to the coronavirus disease-2019 (COVID-19) pandemic, the need for this inspection was reevaluated. Following discussion between the Office of Scientific Investigations and the Division of Dermatology and Dentistry, the decision was made that assessment of the application could proceed without inspection of these sites.

The review team concluded that the conduct of the trials appears to be adequate, and that the data generated appear to be acceptable to support the use of this product for the proposed indication. Refer to the Clinical Inspection Summary by Phuc Nguyen, MD, for further information regarding the findings of the Clinical Site Inspections.

4.2. Product Quality

Bimekizumab-bkzx, an interleukin-17 A and F antagonist, is an immunoglobulin G1 (IgG1) monoclonal antibody produced by recombinant DNA technology in Chinese Hamster Ovary cells. Bimekizumab-bkzx is a humanized IgG1/κ monoclonal antibody that selectively binds to

human interleukin 17A (IL-17A), interleukin 17F (IL-17F), and interleukin 17-AF cytokines, and inhibits their interaction with the IL-17 receptor complex. IL-17A and IL-17F are naturally occurring cytokines involved in normal inflammatory and immune responses. Bimekizumab-bkzx inhibits the release of proinflammatory cytokines and chemokines.

BIMZELX (bimekizumab-bkzx) injection is a sterile, preservative-free, clear to slightly opalescent and pale brownish-yellow solution for subcutaneous use. Each BIMZELX prefilled syringe or prefilled autoinjector delivers 1 mL containing 160 mg bimekizumab-bkzx, (b) (4) (1.23 mg), glycine (16.5 mg), polysorbate 80 ((b) (4) mg), sodium acetate (b) (4) and Water for Injection, USP at pH (b) (4) Liquid drug product contained within a glass pre-filled syringe (PFS) is further packaged into one of two commercial presentations, a safety syringe (SS) or an autoinjector (AI).

This application will not be approved during this assessment cycle due to GMP deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356) by the Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing (OPMA/DBM). At this time, there are no outstanding module 3 review issues from either OBP or OPMA for STN 761151 for BIMZELX (bimekizumab-bkzx) manufactured by UCB, Inc. Because the application will not be approved in this cycle, the facility issue listed below will be communicated to the Applicant in the FDA Complete Response (CR) letter. If manufacturing changes are made before the Applicant submits their responses to the CR deficiencies, additional assessment may be needed during the next assessment cycle. See the separate Quality Executive Summary in DARRTS dated May 6, 2022.

OPMA/DBM has completed the compliance reviews of the pre-license inspections conducted at (b) (4) Drug Substance Manufacturing Facility (b) (4) & UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356). The inspectional recommendation will be a withhold for the UCB Braine Drug Product site as a result of the inadequate 483 responses. The (b) (4) DS site 483 responses were deemed adequate and the site is acceptable. The Overall Manufacturing Inspection Recommendation (OMIR) for this BLA will be "Withhold" due to the withhold approval recommendation for the UCB Braine Drug Product manufacturing site.

<u>UCB Pharma SA Inspection Observations</u>:

1) Failure to establish process controls designed to assure that the drug product you manufacture has the identity, strength, quality, and purity that it purports or is represented to possess;
2) Control procedures are not established which monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristic of in-process material and the drug product;
3) A utility is of inadequate design; and
4) A facility is not adequately maintained.

From a CMC standpoint, OPQ is recommending a Complete Response letter be issued to UCB, Inc. to convey the information below regarding facility issues.

Complete Response Language:

> We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.
>
> FACILITY INSPECTIONS
>
> During a recent inspection of the UCB Pharma SA (FEI: 3003909356) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

Post-Action Application Letter

The Office of Pharmaceutical Manufacturing Assessment (OPMA) will send a Post-Application Action Letter (PAL) to the facility after the Complete Response Letter is issued. The PAL will inform the facility that OPMA does not consider the facility ready to support commercial operations of the subject drug application and convey the outstanding facility deficiencies that need to be addressed. Corrective actions, quality system improvements, and supportive studies completed to address the deficiencies will be evaluated during the next review cycle and may be verified during a future on-site evaluation of the facility.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

There are two single-use devices that are part of the BLA761151 submission:

- Safety Syringe (SS - PFS); i.e., accessorized pre-filled syringe (PFS)
- Autoinjector (AI)

The original “container closure” for the device is a prefilled and prestaked prefilled syringe, intended to deliver 1 mL of bimekizumab to the patient. The following regarding the device “container closure” is taken from doc: drug-product-container-closure-system-maa:

The primary packaging for the bimekizumab drug product consists of a 1mL long Type (b) (4) glass pre-filled syringe (PFS) fitted with a staked 27G, ½" special thin wall needle. The syringe is closed using a grey (b) (4) rubber stopper and a rigid needle shield (RNS) consisting of a (b) (4) elastomer needle cover and a (b) (4) rigid shield.

The PFS is assembled with functional secondary packaging to produce one of two finished product presentations: the bimekizumab-SS-1mL or the bimekizumab-AI-1mL. The final product device components, excluding the primary packaging components, do not have any fluid path and therefore do not have any contact with the drug product contained within the PFS.

The device design, including the essential performance requirements were adequately verified and validated. Details regarding the design verification and validation review that was conducted by the Center for Devices and Radiological Health (CDRH) can be found in CDRH's full review memo, dated March 17, 2021.

A pre-approval inspection (PAI) recommendation related to the device constituent of the final device manufacturer, UCB Pharma SA, was communicated to the Office of Regulatory Affairs (ORA) on 8/14/2020. Due to the ongoing national health emergency the PAI has not been inspected as of 8/16/2021.
On 3/17/2021 CDRH recommended that the device constituent parts of the combination product (Autoinjector and Safety Syringe) be approved pending an adequate pre-approval inspection at UCB Pharma SA.

Human Factors

The Applicant conducted a human factors (HF) validation study to evaluate their PFS and AI presentations. The study enrolled 75 participants including health care providers (HCPs), caregivers, and patients with psoriasis (PSO), psoriatic arthritis (PsA), or axial spondyloarthritis (axSpA). There were 15 participants evaluated in each user group and no training was provided in the HF validation study. The investigator used a simulated use methodology and use scenarios include home and office settings (for HCPs) with a radio for a distraction. A knowledge test was included to evaluate users' understanding of the appropriate injection sites, dosing regimen, the storage conditions in the IFU, the bimekizumab labeling, when a full dose is delivered, and bimekizumab disposal.

The HF validation study was reviewed by the Division of Medication Error Prevention and Analysis (DMEPA). In a review dated May 4, 2021, Lissa C. Owens, PharmD of DMEPA stated that the results of the HF validation study identified failures, close calls, and use difficulties with critical tasks. In addition, the evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors.

The DMEPA review concluded that these issues could be mitigated with revisions to the carton/container label, IFU, and Quick Start Guide (QSG) prior to approval. DMEPA also concluded that the revisions could be implemented without the submission of additional HF validation testing data. Recommendations regarding the revisions were communicated to the Applicant in an Information Request dated May 10, 2021. The Applicant submitted the revisions as requested. In reviews dated May 27, 2021 and August 19, 2021, DMEPA stated that the Applicant had satisfactorily implemented the recommendations. Overall, DMEPA concluded that the results of the HF validation study were acceptable.

5 Nonclinical Pharmacology/Toxicology

5.1. Executive Summary

The Applicant has submitted an original BLA under section 351(a) of the Public Health Service Act for bimekizumab for subcutaneous injection for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. The only relevant species for nonclinical testing is the nonhuman primate. The Applicant has conducted repeat dose toxicity studies in cynomolgus monkeys with weekly doses administered by subcutaneous injection for up to 26 weeks, followed by a treatment-free recovery period of up to 21 weeks to assess potential recovery and/or late developing effects of treatment. The effects on male and female fertility were assessed by examination of reproductive organs, menstrual cycle lengths, or sperm analysis in the 26-week repeat-dose toxicity study in monkeys. In a pre- and postnatal developmental study, bimekizumab was administered to pregnant cynomolgus monkeys from gestation day 20 to parturition and maternal and infant cynomolgus monkeys were monitored for 6 months after delivery.

No genetic toxicology or carcinogenicity studies were conducted with bimekizumab. The Applicant provided a carcinogenic risk assessment, using information from the published literature. The nonclinical information does not suggest an increased carcinogenic risk associated with clinical use of bimekizumab.

Bimekizumab is approvable from a pharmacology/toxicology perspective. There are no recommended nonclinical postmarketing commitments or postmarketing requirements for this BLA.

5.2. Referenced NDAs, BLAs, DMFs

All the pivotal nonclinical studies have been previously reviewed under the corresponding IND (128707). Pivotal nonclinical studies are summarized in this review.

5.3. Pharmacology

Primary pharmacology

Bimekizumab is a purified recombinant, humanized, full length IgG1 antibody with high affinity for human interleukin (IL)-17 A and IL-17F, inhibiting their interaction with the IL-17 receptor complex. The affinity of bimekizumab for human IL-17A and IL-17F have been determined with dissociation constant (K_D) values of 3.5 pM and 28 pM, respectively. The corresponding K_D values for bimekizumab and cynomolgus monkey IL-17A and IL-17F were higher at 12 pM and 345 pM, respectively. This represents around 3.5-fold and 12-fold lower affinity of bimekizumab for IL-17A and IL-17F, respectively, in monkeys compared to humans.

The ability of bimekizumab to inhibit the activity of natural human IL-17A and IL-17F was determined in a NIH-3T3 cell bioassay. The results show that the T helper 17 (Th17)-stimulated release of IL-6 was potently inhibited by bimekizumab. Only partial inhibition of IL-6 release was achieved by neutralization of either IL-17A or IL-17F alone. These results support the hypothesis that bimekizumab, which targets both IL-17A and IL-17F, may show increased clinical efficacy.

Both IL-17A and IL-17F were able to stimulate a dose dependent IL-6 response from NIH-3T3 cells. The concentration of bimekizumab required to inhibit the IL-6 response by 50% (IC_{50}) for IL-17A at concentrations capable of inducing 75%, 50% and 25% of maximal effect (EC_{75}, EC_{50}, EC_{25}) were 4.15 ng/mL, 1.21 ng/mL and 0.50 ng/mL, respectively. The IC_{50} values of bimekizumab for IL-17F tested at EC_{75}, EC_{50}, and EC_{25} were 96.49 ng/mL, 44.25 ng/mL and 6.16 ng/mL, respectively. The IC_{50} value of bimekizumab against natural human Th17 cell-derived IL-17A and IL-17F from two donors was approximately 40 ng/mL.

The capacity of bimekizumab to cross-react with cynomolgus monkey IL-17A and IL-17F was also determined using the NIH-3T3 cell bioassay. NIH-3T3 cells were stimulated with human or cynomolgus cytokines in combination with human TNF-α. The mean K_D values of bimekizumab for human and cynomolgus IL-17A were 8 pM and 5 pM, respectively. The values for human and cynomolgus monkey IL-17F were 310 pM and 640 pM, respectively.

The Applicant conducted a tissue cross-reactivity study using human and cynomolgus monkey tissue samples. No cross-reactive binding of bimekizumab conjugated to fluorescein isothiocyanate was observed in any human or monkey tissue at any concentration tested (0, 0.1, 1, and 5 µg/mL).

A study was conducted in whole blood from humans and cynomolgus monkeys to evaluate the hemolytic potential of bimekizumab. Both bimekizumab and the formulation vehicle (b) (4)) were found to be non-hemolytic in human and monkey blood.

Safety Pharmacology

No dedicated safety pharmacology studies have been conducted with bimekizumab. Clinical observations from the repeat-dose toxicity studies conducted in cynomolgus monkeys indicate bimekizumab does not induce central nervous system or respiratory effects. No ECG or blood pressure effects were observed in cynomolgus monkeys treated subcutaneously for 26 weeks with up to 200 mg/kg/week bimekizumab. Toxicokinetics verified adequate exposure to bimekizumab during treatment to ensure neutralization of IL-17A and IL-17F.

5.4. ADME/PK

Toxicokinetics were evaluated during the repeat dose toxicity studies conducted in cynomolgus monkeys with subcutaneous administration (0, 50, or 200 mg/kg/week). Exposure was comparable between male and female monkeys and increased in a slightly less than dose proportional manner.

5.5. Toxicology

5.5.1. General Toxicology

Study title/ number: An 8-week study of CDP4940 by intravenous/subcutaneous injection in cynomolgus monkeys with a 12 week recovery period / 521779. This study was conducted in accordance with the Good Laboratory Practice (GLP) standards required by the US FDA GLP regulations.

Bimekizumab was administered once weekly by intravenous (0 [redacted] (b) (4) 20 or 200 mg/kg) or subcutaneous (0, 50, or 200 mg/kg) injection to 2-year old cynomolgus monkeys (2/sex/group) for 8 weeks followed by a 12-week recovery phase. No significant toxicity and no immunomodulation of the humoral immune system were observed. Toxicokinetics were evaluated on Day 50 and exposure increased slightly less than proportionally, with steady state reached after six doses. The NOAEL was determined to be 200 mg/kg/week, based on the lack of toxicity.

Nonrodent toxicity studies are typically conducted with 3 animals/sex/group. The Applicant has conducted the pivotal repeat-dose toxicity study with the recommended number of animals.

Study title/ number: 26-Week subcutaneous administration toxicity study in the cynomolgus monkey followed by a 21-week recovery phase/ 8284146. This study was conducted in accordance with the GLP standards required by the US FDA GLP regulations.

Once weekly subcutaneous administration of bimekizumab (0 [redacted] (b) (4) 50, 200 mg/kg/week) to sexually mature cynomolgus monkeys (3/sex/group) for 26 weeks followed by a 21-week recovery phase had no effect on body weight, clinical pathology, ECG measurements or blood pressure.

No effects on fertility parameters such as histopathology of reproductive organs, menstrual cycle lengths, or sperm analysis were observed. There was no bimekizumab-related effect on relative or absolute numbers of CD3+ T-cells, CD3+, CD8+ cytotoxic T-cells, CD3+CD4+ helper T-cells, CD20+ B cells, or CD16+ NK-cells.

Two animals dosed with 50 mg/kg/week bimekizumab died during the course of the treatment or recovery phase of the study, and their necropsies revealed inflammation and/or

microabscesses in the gastrointestinal tract. Acanthosis, spongiosis, exocytosis, inflammatory cell infiltrates, epidermal pustules and skin ulcers were observed in all bimekizumab dose groups, with severity increasing with dose. Low dose skin changes were not observed after the recovery period. Based on the cutaneous and intestinal effects a NOAEL could not be established.

The systemic exposure of bimekizumab (C_{max} and $AUC_{0\text{-}7days}$) increased in a sub-proportional manner after 26 weeks of treatment (50, 200 mg/kg/week). Exposure was comparable between male and female monkeys. The exposure at the high dose was $AUC_{0\text{-}7days}$ of 23967 µg●day/mL and Cmax of 4303 µg/mL.

Bimekizumab specifically inhibits IL-17A and IL-17F and as such muco-epidermal infections are considered to be related to exaggerated pharmacology, leading to decreased muco-epidermal immunity. Infections and microorganism-related changes are not directly translatable from non-human primates to humans.

The NOAEL in an 8-week study in which monkeys were dosed weekly either subcutaneously or intravenously was 200 mg/kg/week.

5.5.2. Genetic Toxicology

As per ICH Guidance S6 R1, *Preclinical safety evaluation of biotechnology-derived pharmaceuticals* (Section 4.7 Genotoxicity Studies), no genetic toxicology testing is warranted for bimekizumab.

5.5.3. Carcinogenicity

Bimekizumab is not pharmacologically active in rodents and no anti-rodent IL-17 A/F surrogate is available. Thus, conventional rodent carcinogenicity studies were not conducted for evaluation of the carcinogenic potential of bimekizumab. The Executive Carcinogenicity Assessment Committee of CDER agreed that rodent carcinogenicity studies are not feasible and the Applicant was granted a waiver for their conduct (March 28, 2018). The Applicant provided a weight-of-evidence analysis of the available literature to address the carcinogenic potential of bimekizumab-related inhibition of IL-17A and IL-17F. Some literature suggests that IL-17 may have a role in tumor formation, tumor proliferation, metastasis and chemoresistance; therefore, neutralization of IL-17 with bimekizumab could be protective against tumors. Other studies suggest that IL-17 protects against tumors via recruitment of immune cells such as cytotoxic T cells and NK cells, which implies that neutralization of IL-17 with bimekizumab may enhance tumor expression. In conclusion, the literature does not suggest a clear concern that inhibition of IL-17A and IL-17F would lead to carcinogenicity or tumor development.

Additionally, no tumors or evidence of pre-neoplastic changes were observed in organs or tissues examined histologically following once weekly subcutaneous administration of bimekizumab to monkeys at doses up to 200 mg/kg for 26 weeks followed by a 21-week post-dosing observational period.

Data from the literature and animal data from the Applicant will be sufficient to adequately address labeling at this time. Additional data from post-marketing patient monitoring of malignancy will be available in the future.

5.5.4. Reproductive and Developmental Toxicology

Embryofetal Development and Prenatal and Postnatal Development

Study title/ number: Enhanced study for effects on pre- and postnatal development in cynomolgus monkeys with a six-months lactation/maturation phase / NCD2676. This study was conducted in accordance with the GLP standards required by the US FDA GLP regulations.

In a pre- and postnatal developmental study, doses of 0 (b) (4) 20 or 50 mg/kg/week bimekizumab were administered subcutaneously to pregnant cynomolgus monkeys from gestation day 20 to parturition. The cynomolgus monkeys (mother and infants) were monitored for 6 months after delivery. No bimekizumab-related adverse effects were observed on maternal parameters such as body weight, pregnancy duration, pregnancy outcome or clinical pathology. There were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development. Concentrations in infant animals and their mothers were consistent on postnatal Day (PND) 7 with mean infant over maternal animal ratio of bimekizumab concentrations of 0.955 and 0.841 in Group 2 and Group 3 animals, respectively. Mean concentrations in maternal animals decreased faster than in infant animals, with mean infant over maternal animal ratios increasing to a maximum of 6.61 on PND 56 in Group 2 and 14.43 on PND 84 in Group 3. The no observed adverse effect level (NOAEL) for both maternal and developmental toxicity was identified as 50 mg/kg/week which is 38 times (based on mg/kg comparison) the maximum recommended human dose (MRHD; 1.33 mg/kg/week based on administration of a 320 mg dose to a 60 kg individual once every 4 weeks).

Juvenile Animal Toxicology Studies

No juvenile animal toxicology studies were conducted with bimekizumab. The placental transfer of IgGs increases progressively during the second half of pregnancy to reach levels close to maternal levels in the infant at birth. Therefore, the fetus is well exposed by maternal dosing of IgGs in general during organ development and immune system maturation. On PND 7, serum concentrations of bimekizumab were comparable in maternal animals and infants,

confirming placental transfer and intra-utero exposure for bimekizumab. No additional juvenile animal toxicology studies are needed to support potential dosing in a pediatric population.

6 Clinical Pharmacology

6.1. Executive Summary

Bimekizumab (formerly known as UCB4940 and CDP4940) 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 interleukin-17A (IL-17A), IL-17F, and IL-17AF cytokines. This submission (BLA 761151) is in support of bimekizumab subcutaneous (SC) administered a dose of 320 mg administered every 4 weeks (Q4W) until Week 16 for the induction phase and then 320 mg every 8 weeks (Q8W) thereafter for the maintenance phase for the treatment of moderate and severe plaque psoriasis (PSO) in adult patients.

This original BLA submission contains 16 clinical pharmacology studies and 3 population pharmacokinetic (Pop-PK) & Exposure-response reports.

The key review findings with specific recommendations/comments are summarized below.

Table 3: Summary of Clinical Pharmacology Review

Review issue	Recommendations and Comments
Pivotal or supportive evidence of effectiveness	The efficacy of bimekizumab SC injection for the treatment of moderate and severe PSO was established in the phase 3 trials (PS0008, PS0009 and PS0013). The positive exposure-response relationship for efficacy based on data from the phase 3 trials provides supportive evidence of effectiveness.
General dosing instructions	The proposed dosing regimen of bimekizumab 320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter is acceptable.
Dosing in patient subgroups (intrinsic and extrinsic factors)	For body weight $\geq$ 120 kg, a dose of 320 mg every 4 weeks treatment after week 16 may be considered.
Bridge between the to-be-marketed and clinical trial formulations	In Study UP0033, the to-be-marketed safety syringe (SS) and auto-injector (AI) presentations have been demonstrated to have comparable PK with the presentation of prefilled syringe containing bimekizumab drug product and the (b) (4) functional secondary packaging that was used in the phase 3 trial in PSO patients. A bioanalytical inspection was conducted by

Review issue	Recommendations and Comments
	the Office of Study Integrity and Surveillance (OSIS) and while there were objectionable conditions, the OSIS reviewer concluded that those observations do not impact the reliability of data from Study UP0033 (See review by Dr. Kara Scheibner, dated 06/07/2021 in DARRTS). Thus, the bridge between the to-be-marketed and clinical trial formulations are deemed to be established.
Immunogenicity	The PK of bimekizumab was impacted in the presence of ADAb, with a slightly lower bimekizumab plasma concentration 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. However, ADAb status had no impact on efficacy and no clinically relevant impact on safety.

6.1.1. Recommendations

The Office of Clinical Pharmacology has reviewed this submission and found it acceptable for approval from a Clinical Pharmacology standpoint.

6.1.2. Post-Marketing Requirements and Commitments

- PMR: PREA-PMRs for 1) conducting an open-label study to assess the PK, safety and efficacy of bimekizumab in adolescents (12 to <18 years of age) with moderate to severe chronic plaque psoriasis and 2) conducting a randomized, parallel-group, double-blind, placebo-controlled and single-blind active-controlled study to assess the efficacy, safety, and PK of bimekizumab in pediatric subjects 6 to <18 years old with moderate to severe chronic plaque psoriasis.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Pharmacology and Clinical Pharmacokinetics

<u>Absolute bioavailability of bimekizumab SC injection</u>

The absolute bioavailability of bimekizumab following SC injection in healthy subjects was estimated to be 65.6% and 63.1% for the bimekizumab 80 mg and bimekizumab 160mg doses, respectively.

PK Comparability Between the to-be-marketed (TBM) SS-1 mL and AI-1 mL Presentations and the PFS/(b) (4) Presentation Used in the Phase 3 Trial

The PK comparability between the proposed commercial device presentations (a safety syringe [bimekizumab-SS-1mL] and an auto-injector [bimekizumab-AI-1mL]) and the device used in the phase 3 trials (ie, (b) (4) device presentation [referred to as bimekizumab-(b) (4)) presentations was demonstrated in Study UP0033. In this PK comparability study, the point estimates and 90% confidence interval for geometric mean ratio of C_{max}, AUC_{last}, and AUC_{inf} were all within the no effect boundary of 80% to 125%.

Bioanalytical site inspection: A remote record review of the analytical portion of Study UP0033 was conducted by Dr. Kara Scheibner in OSIS (see review dated 06/07/2021 in DARRTS). In her audit, Dr. Scheibner observed objectionable conditions in the ADAb method validation and study such as use of inconsistent acceptance criteria, use of a sub-optimal low positive control and an absence of established criteria to investigate non-monotonic assay signals in the titer assay. However, Dr. Scheibner concluded that based on her review and the Applicant's response, these observations do not impact the reliability of the PK and ADA data from Study UP0033. Thus, from a clinical pharmacology perspective, the bridge between the to-be-marketed and clinical trial formulations are deemed to be established. These findings were communicated to OBP for their assessment.

PK of Bimekizumab SC Injection in Patients With PSO

Bimekizumab concentrations observed for the bimekizumab 320mg Q4W group were higher compared with the bimekizumab 320mg Q4W/Q8W group at Week 24. The systemic concentrations were at steady state by Week 12 and the steady state C_{trough} values ranged from 16.76-19.85 µg/mL for Q4W treatment for all three pivotal phase 3 trials (PS0008, 0009, and 0013). In contrast, the steady state C_{trough} values were 8.13-8.66 ug/mL at Week 24 after switching to Q8W dosing at Week 16 and were 5.27-6.13 µg/mL at week 56 for trials of PS0008 and PS0013. Summary of the C_{trough} concentrations is shown in Table 4 below.

Table 4: Summary of Ctrough values (µg/mL, CV%) of three pivotal phase 3 studies from Week 12 to Week 56

Study number	BKZ dose and dosing regimen	Week 12 (Steady state)	Week 16 (switch week)	Week 24	Week 36	Week 56
PS0008	320 mg Q4W	17.74 (73.7%)	18.23 (75.7%)	17.26 (70.9%)	16.76 (77.5%)	18.34 (89.5%)
	320 mg Q4W/Q8W	17.47 (58.4%)	16.89 (89.0%)	8.13 (101.4%)	13.41 (58.1%)	5.27 (90.3%)

PS0009	320 mg Q4W	19.34 (52.7%)	19.57 (57.3%)	18.11 (64.5%)	Week 40 17.99 (52.3%)	Week 52 17.48 (69.3%)
PS0013	320 mg Q4W	19.27 (51.8%)	19.15 (62.2%)	19.85 (51.3%)	Week 48 19.22 (48.2%)	Week 52 19.38 (54.8%)
	320 mg Q8W		18.55 (109.2%)	8.66 (82.5%)	Week 48 5.40 (129.4%)	6.13 (69.8%)

Source: data summary by reviewer based on Ctrough data of PS0008, 0009, 0013 CSRs.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant has proposed a bimekizumab SC dosing regimen of 320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter is acceptable.

The proposed dosing regimen is supported by the overall efficacy and safety data from the phase 3 trials (Trials PS0008, PS0009, PS0013) and is acceptable. See Section 8 for efficacy results.

Therapeutic Individualization

For body weight $\geq$ 120 kg, a dose of 320 mg every 4 weeks treatment may be considered. Originally, there was no body weight cutoff value proposed for high body weight patients, after review, the cutoff of 120 kg is recommended for this specific population.

Body weight was found to be an intrinsic factor that could impact clinical response. Patients with a higher body weight may have a lower clinical response due to lower plasma concentrations with the same dose compared to a lower body weight patient.

Figure 1: Boxplots of the simulated PASI response rate versus WT categories at Week 56

Source: Figure 35 of CL 0446 PKPD report

Outstanding Issues
None

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

A summary of the general clinical pharmacology, pharmacokinetics and immunogenicity of bimekizumab is provided in Table 5.

Table 5: Summary of Pharmacology, Pharmacokinetics, and Immunogenicity of Bimekizumab

Pharmacology	
Mechanism of action	Bimekizumab is an engineered, humanized, full-length immunoglobulin (Ig) G1 anti-IL-17 monoclonal antibody that selectively and potently bind and neutralize interleukin-17A (IL-17A), IL-17F, and IL-17AF cytokines.
General information	
Bioanalysis	Bimekizumab concentrations in human serum were quantified using a validated electrochemiluminescence immunoassay (ECLIA) assay. The assay was well validated, and the calibration range is 0.25-20 µg/mL. See Section 15.4 for additional details.
Clinical Pharmacokinetics	
PK in healthy subjects	In single-dose studies in healthy subjects, bimekizumab exhibited dose-proportional PK in the tested range of 80 mg to 320 mg, and the median terminal elimination half-life (t1/2) ranged between 19 and 26 days.
PK in PSO subjects	The plasma concentration of bimekizumab increased in a dose proportional fashion in the tested dose range (64 to 480mg) following multiple SC administrations in subjects with PSO. The PK parameters such

	as apparent clearance (CL/F) and apparent volume of distribution (V/F) did not change with time and dose. The estimated population CL/F and V/F for a typical patient of 87kg (median body weight in the PK/PD dataset) with moderate to severe PSO were 0.337L/day and 11.2L, respectively. The t1/2 in the study participants with moderate to severe PSO was 23 days.
Immunogenicity	The positive anti-drug antibody (ADAb) and neutralized antibody (NAb) slightly reduced the systemic exposure (less than 10% in week 56). The impact of immunogenicity on efficacy, and safety is not considered to be clinically meaningful, and hence no dose adjustment based on ADAb and NAb status is necessary.
Incidence	There was a tendency for higher incidences of ADAb in study participants receiving lower doses of bimekizumab (ie, <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. Similar incidences of ADAb were observed in Japanese and Caucasian study participants.
Impact on PK	The PK of bimekizumab was impacted in the presence of ADAb, with a slightly lower bimekizumab plasma concentration observed in ADAb-positive study participants. The presence of neutralizing antibody (Nab) had a larger impact on the PK of bimekizumab than presence of ADAb, but there were too few samples in the groups of study participants who were NAb positive for only IL-17AA (n=10) or only IL-17FF (n=1) to draw meaningful conclusions.
Impact on efficacy and safety	Overall, the clinical impact of the formation of anti-bimekizumab antibodies on efficacy or safety outcomes is low. In addition, ADAb are assumed to have no clinical consequences given the overall low impact of immunogenicity on clinical outcomes.

6.3.2. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

Yes. The overall phase 3 efficacy results provide evidence that bimekizumab is effective for the treatment of adult patients with moderate to severe psoriasis (see details under Section 8). The

dose-response and exposure-response relationships for PASI 90 and IGA 0/1 have provided supportive evidence of effectiveness.

Is the proposed dosing regimen appropriate for the general patient population for which the indication is being sought?

Yes. The proposed dosing regimen of bimekizumab 320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter (Q4W/Q8W) is acceptable for PSO adult patients. The proposed dosing regimen is supported by PK, efficacy and safety results in study PS0008, PS0009 and PS0013 which evaluated bimekizumab SC 320 mg Q4W/Q8W vs. adalizumab, and bimekizumab SC 320 mg Q4W/Q8W vs. placebo, and bimekizumab SC 320 mg Q4W treatment vs. ustekinumab.

Phase 3 Dose Selection Rationale

The recommended dose and dosing regimens tested in the phase 3 trials of bimekizumab were selected based on safety, efficacy, and PK data from the 2 phase 2 trials (PS0010 and PS0016) in adult patients with plaque PSO, as well as PK/PD analyses performed at the end of phase 2b (CL0446).

- In the phase 2b trial PS0010, 5 SC doses of bimekizumab at Q4W for 12 weeks were studied. Specifically, 64mg, 160mg, 320mg loading dose was administered at Baseline followed by 160mg, 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 160 mg with no loading dose of 320 mg. For PASI100, the 320mg dose had a 2-fold higher response compared to the 160mg dose, indicating a clinically meaningful additional benefit with the 320mg dose.
- PK/PD analysis (CL0446) confirmed that 320mg Q4W was predicted to have a clinically meaningful benefit on both the PASI90 and PASI100 response compared to both the 160mg and 160mg with a loading dose. Additionally, the 16-week Initial Treatment Period in phase 3 was chosen given the observation that PASI100 tended to increase beyond Week 12, which was confirmed in the PK/PD model.
- A phase 2 trial (PS0016) was conducted to assess the impact of dosing interval. In this trial, the dosing regimen was 1) Bimekizumab 320mg+placebo where bimekizumab 320mg was administered via SC route at Baseline and Week 4, and placebo was administered at Week 16 and 2) Bimekizumab 320mg where bimekizumab 320mg was administered via SC route at Baseline and Weeks 4 and 16 showed that a loss of PASI100 response had begun by Week 16 in the first cohort (ie, 12 weeks after the second dose at Week 4 in the study) indicating dosing intervals greater than Q8W would result in loss of PASI response. This is further supported by PASI90 data from the bimekizumab 320mg group in the second cohort (where a dose was received at Week 16), where maintenance of PASI90 response was achieved for an additional 8 weeks (ie, through

Week 24) following the Week 16 dose and the response was reduced 12 weeks after the Week 16 dosing (ie, Week 28).

- Simulations from the PK/PD model showed that a Q8W regimen would maintain PASI90 response in a majority of patients and a longer duration between the doses such as a Q12W would lead to more study participants losing PASI90 response.
- Based on a combination of clinical data and PK/PD analysis, a 320mg Q4W regimen was selected as the dose in the Initial Treatment Period up to Week 16 and 320mg Q4W and 320mg Q8W were selected as the maintenance regimens for the phase 3 studies.

Exposure-response for efficacy

A dose-exposure-response relationship between bimekizumab plasma concentration and PASI and IGA has been established and supports a dose of 320mg given every 4 weeks (Q4W) until Week 16 and then 320mg every 8 weeks (Q8W) thereafter in patients with PSO. A dose-exposure-response simulation showed that no dose adjustment is necessary among different race populations even though race was a statistically significant covariate on CL/F in the population PK model. It was noted that the lower plasma concentrations with 8 week interval treatments had no effect on overall PASI response. However, there is an effect of body weight on the response with the Q4W versus Q8W dosing and this is discussed below.

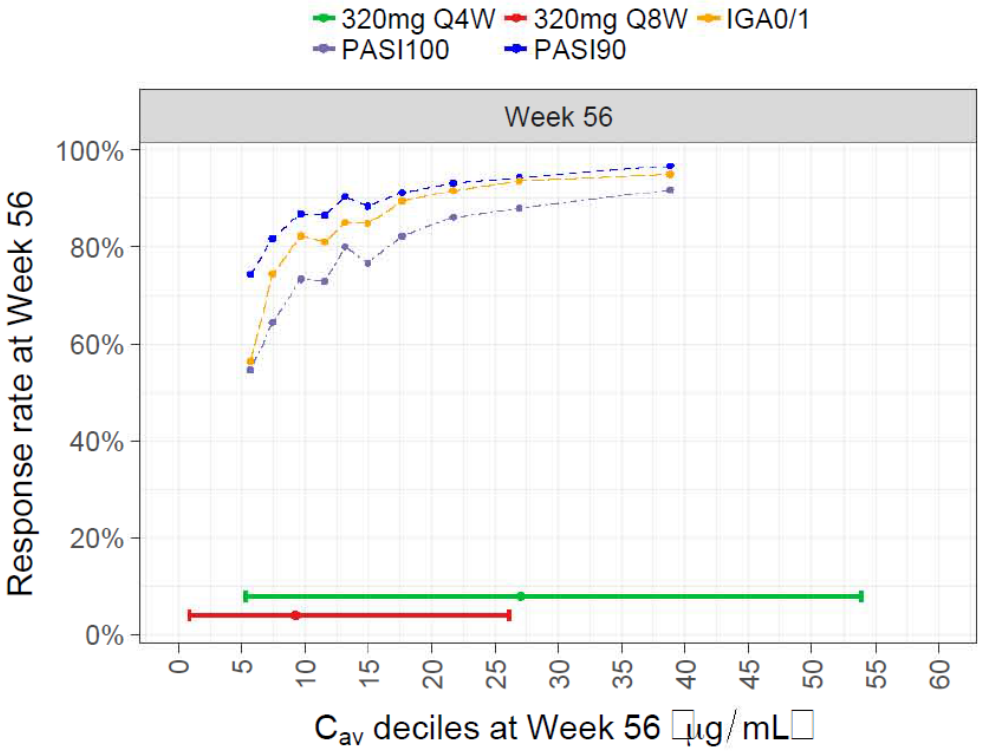
Table 6: Summary of Responder Rate by Visit (Randomized Sets) of CSR PS0008, PS0009, PS0013

Study No.	Dose regimen	PASI75		PASI90		PASI100		IGA 0/1	
		Week 16	Week 56	Week 16	Week 56	Week 16	Week 56	Week 16	Week 56
PS0008	320 mg Q4W	92.4%	88.0%	87.3%	84.8%	60.1%	72.2%	87.7%	82.3%
	320 mg Q4W/Q8W	92.5%	86.3%	85.1%	82.6%	61.5%	70.2%	83.2%	83.2%
PS0009	320 mg Q4W	92.2%	85.0% (w 52)	85.0%	81.6% (w 52)	58.6%	64.2% (w 52)	84.1%	77.9% (w 52)
PS0013	320 mg Q4W	100.0%	88.7%	100.0%	86.8%	68.9%	70.8%	99.1%	86.8%
	320 mg Q4W/Q8W	99.0%	91.0%	99.0%	91.0%	82.0%	83.0%	99.0%	90.0%

Source: Reviewer's analysis

Simulations were performed to illustrate the effect of clinically significant covariates on PASI and IGA responder rates, and to support the selection of bimekizumab dose in moderate to severe PSO patients. The simulation results for PASI and IGA responder rates, presented in Figure 2, indicated 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 2: Simulated PASI90, PASI100 and IGA0/1 response rates versus bimekizumab Cav deciles at Week 56 based on the final bimekizumab exposure response model



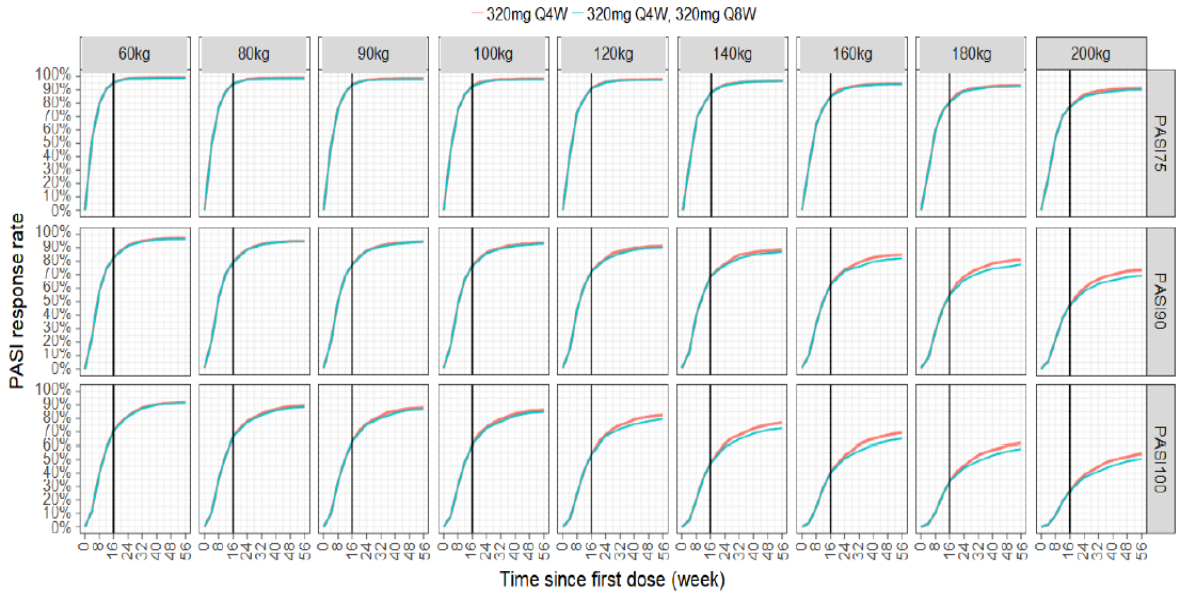
Source: CL0485 figure S6, pg 10.

The lines connect the simulated median response rates and are colored by the response variable types. The horizontal lines represent the median, and 5th and 95th percentiles of Cav at Week 56 (irrespective of PASI or IGA response variable type), colored by different treatment groups. PASI90: 90% improvement from baseline in PASI; PASI100: 100% improvement from baseline in PASI; IGA0/1: IGA score of 1; Cav: average concentration; Q4W: every 4 weeks; Q8W: every 8 weeks.

Is an alternative dosing regimen or management strategy required for subpopulations based on intrinsic patient factors?

For some patients (patients with body weight ≥120kg), continued dosing with 320mg Q4W after Week 16 may be considered. Body weight was found to be an intrinsic factor that could impact clinical response. Patients with a higher body weight may have a lower clinical response with the Q8W dosing compared to the Q4W dosing due to lower plasma concentrations. Therefore, Q4W interval is the recommended dosing regimen in body weight ≥ 120 kg PSO adult patients (see Figure 3 and Figure 4 below).

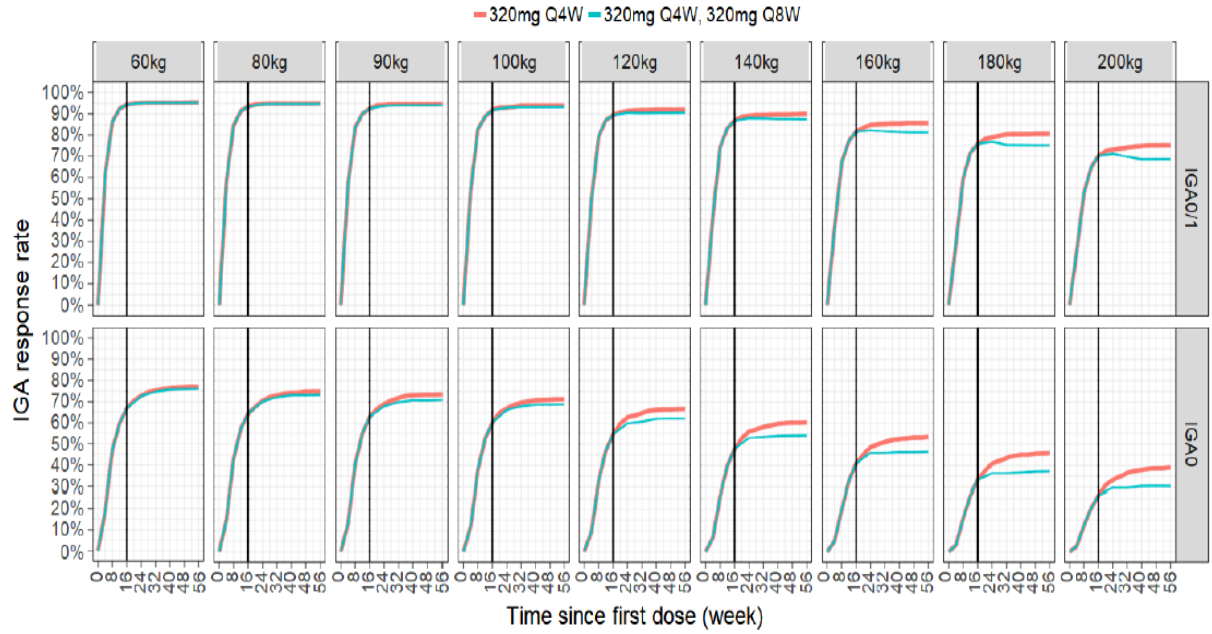
Figure 3: PASI response rate vs time for different weight categories based on the final exposure response model for PASI (CL0485)



Data source: CL0485 Figure 34. Simulation was conducted based on a 65-year-old non-Asian male from Central/Eastern Europe with ADAb negative status and a Baseline PASI of 18.5.

Note: Data is 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 (CL0485)

Figure 4: Simulated IGA response rate vs time for different body weight categories based on the final exposure response model for IGA (CL0485)



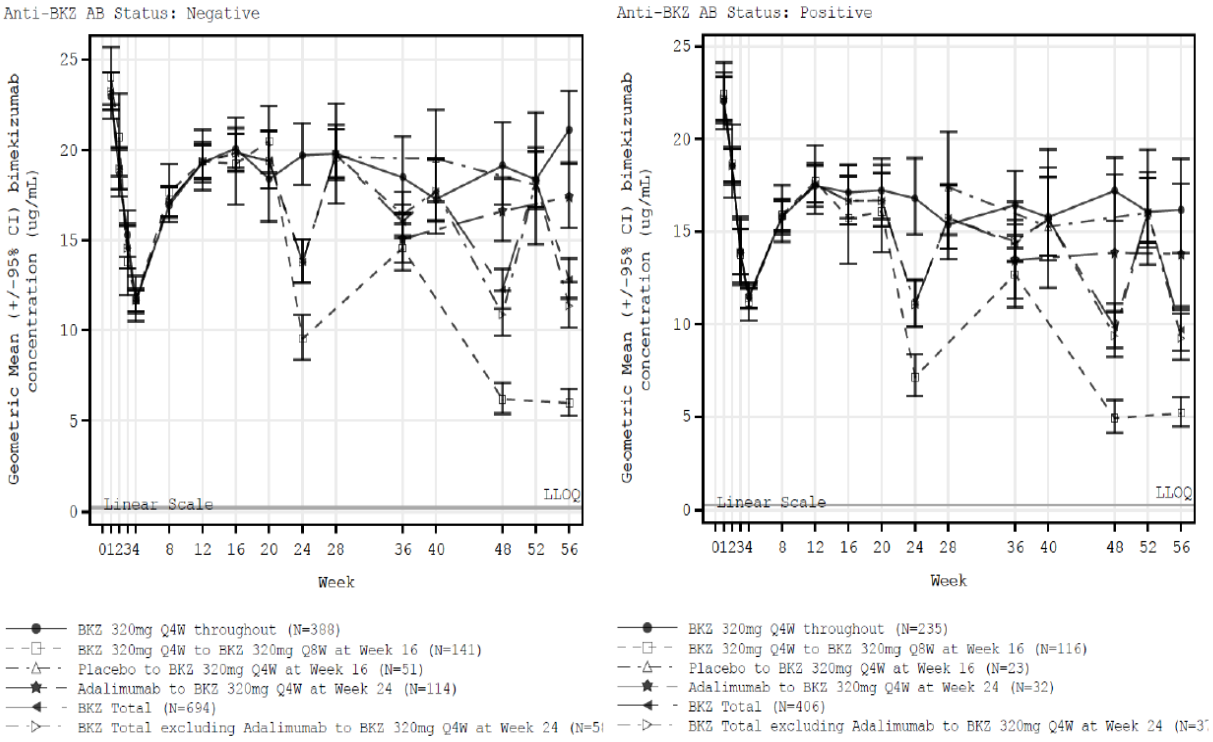
Data source: CL0485 Figure 53

Note: Data is 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 (CL0485)

Effect of Immunogenicity on PK and Efficacy

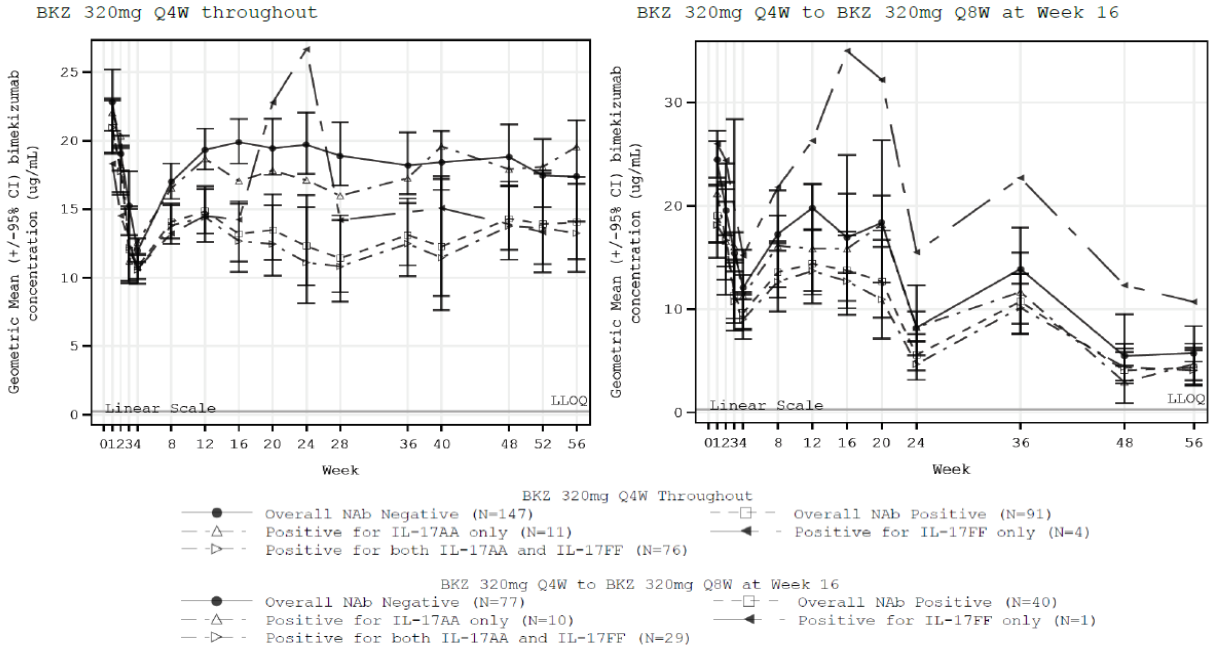
The geometric mean bimekizumab plasma concentration in ADAb-positive study participants in initial and maintenance period was slightly lower compared with ADAb-negative participants. In both bimekizumab treatment regimens, a lower plasma concentration was observed in overall NAb-positive study participants compared with overall NAb-negative participants. This impact of NAb status on PK seems to be larger than in the analysis by ADAb status. There were too few samples in the groups of study participants who were NAb positive for only IL-17AA or only IL-17FF to draw any meaningful conclusions.

Figure 5: Geometric mean of BKZ plasma concentration over time by anti-BKZ antibody status in the Initial and Maintenance Period



Source: Summary of Clin Pharm, ISS Figure 6.2a

Figure 6: Geometric mean of BKZ plasma concentration over time by NAb status in the Initial and Maintenance Period



Source: Summary of Clin Pharm, Figure 6-9, pg 79

Analysis of the impact of ADAb titer group on PASI and IGA response in the pooled Phase 3 studies indicated that ADAb titer had a limited impact on efficacy at both Weeks 16 and 52/56, respectively. However, given the small number of study participants in the titer groups, results are difficult to interpret, and no firm conclusions can be drawn. Similarly, at Week 16, responder rates in the bimekizumab 320mg Q4W group were higher in NAb-negative participants compared with NAb-positive participants, including PASI75, 90, and PASI100 responder rates. However, no impact of NAb status on efficacy was observed after longer exposures.

Figure 7: Summary of responders at Week 16 by treatment group and anti-BKZ antibody titer group category

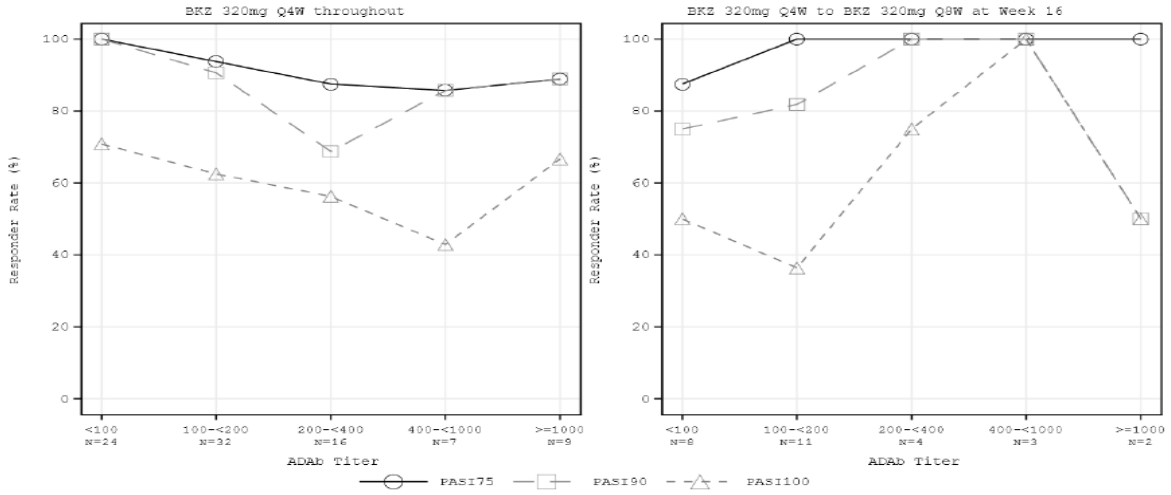
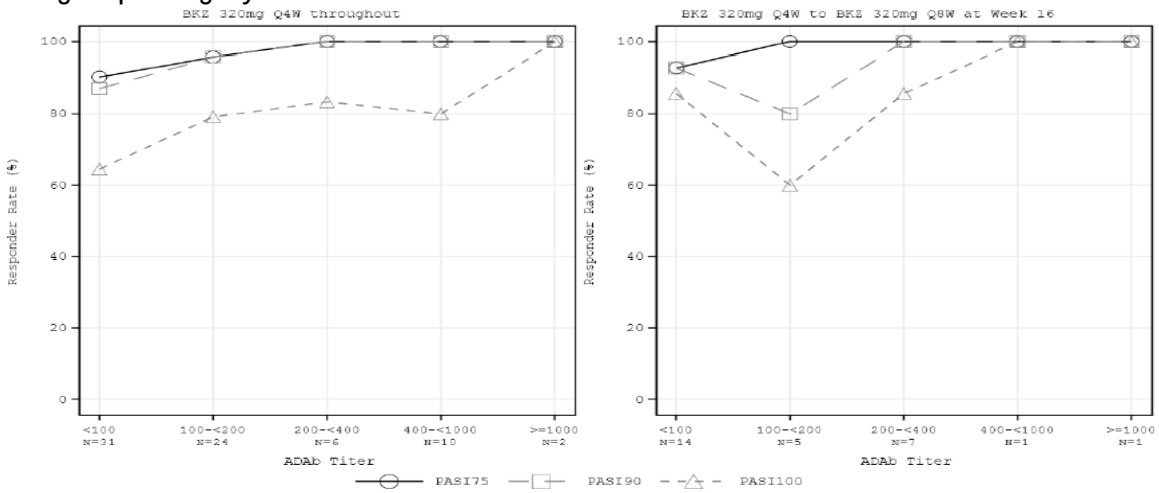


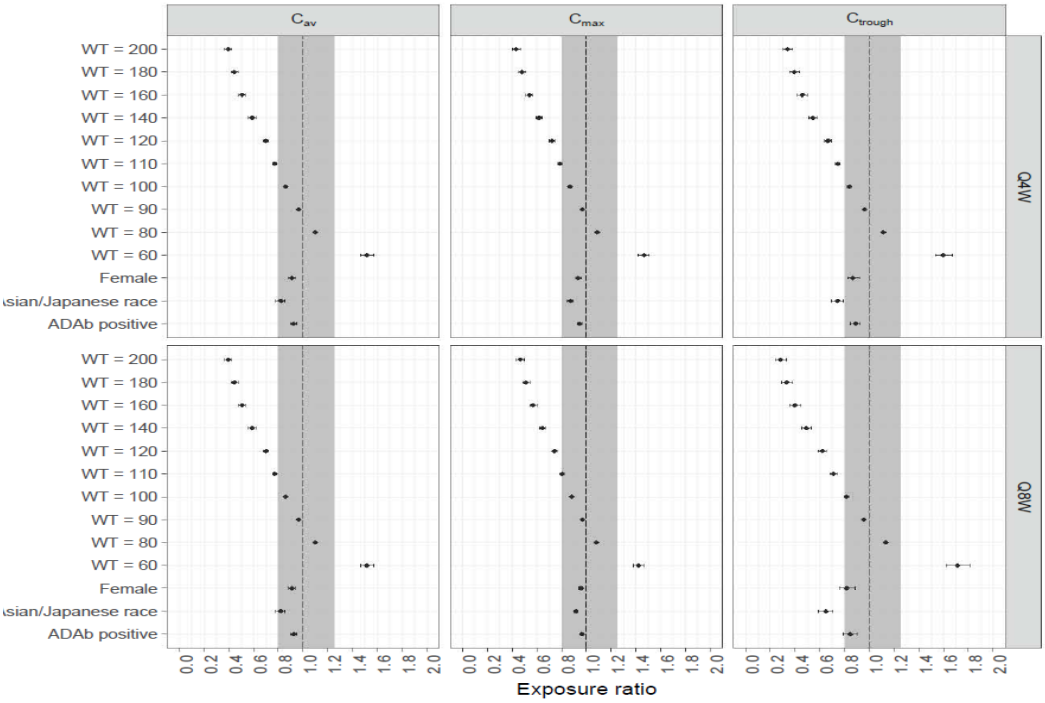
Figure 8: Summary of responders at Week 52/56 by treatment group and anti-BKZ antibody titer group category



Source: Summary of Clin Pharm, Figure 6-9, pg 79

A Forest plot (Figure 9) showed that only body weight is the covariate factor to have an effect on PK, while ADAb (shown above) or other factors such as gender and race did not.

Figure 9: Forest plot of the final bimekizumab population PK model illustrating the ratio of exposure metrics (Cav, Cmax and Ctrough) for the statistically significant covariates stratified by 320mg Q4W and 320mg Q8W regimens

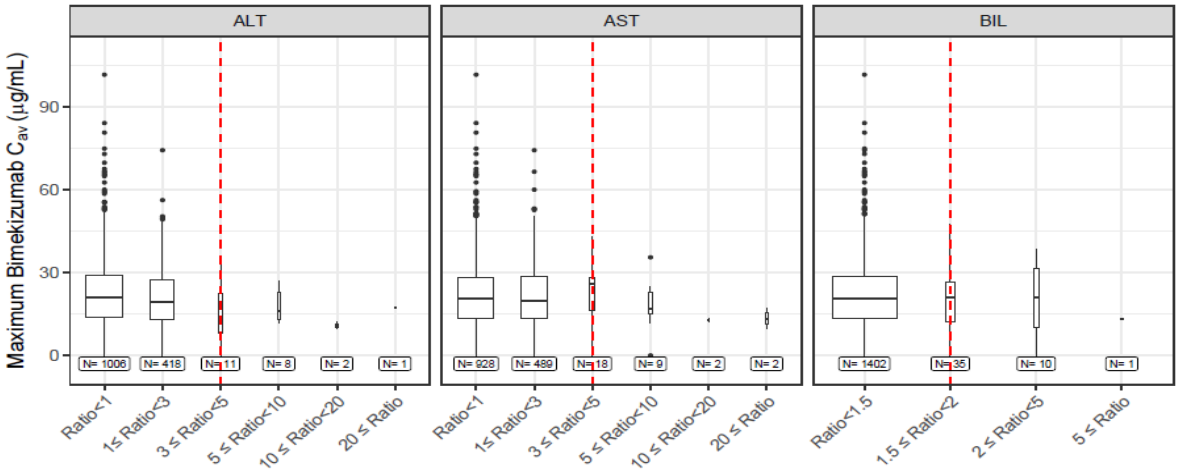


Source: Figure 22, pg 89, CL0485

Note: The data are based on 200 bootstrap samples. The points and the horizontal error bars represent the median and 95% CI of the exposure metric ratio for different covariate groups. The vertical dashed line indicates a ratio of 1. The vertical grey shaded area shows the range from x=0.8 to x=1.25. Six bootstrap samples failed due to rounding errors (NONMEM error code = 134) but were retained in the calculations. Cav: average concentration; Cmax: maximum concentration; Ctrough: trough concentration; CI: confidence interval; Q4W: every 4 weeks; Q8W: every 8 weeks.

<u>Exposure response analysis on ALT/AST and Bilirubin:</u>
Regarding the drug-induced liver injury, the drug exposure was analyzed for the correlation with alanine transaminase (ALT), aspartate transaminase (AST) and bilirubin (BIL) response after treatment with Bimekizumab or placebo in a pool of six different phase 2/3 studies (19000 values for each liver enzyme). The results showed that the number of patients with elevations >3xULN for ALT (1.5%), or >3xULN for AST (2.0%), or >1.5xULN (3.2%) for BIL was low. There is no clear relationship between exposure and ALT, AST or BIL elevations. In addition, liver function elevations in the 4th quartile, where maximum Cav ranged from 29.7 to 102 µg/mL, tended to be lower than quartiles 1 to 3 where Cav was lower. In the below figure, the few subjects with ratio to ULN >=3 for ALT and AST and >=1.5 for BIL do not present higher bimekizumab exposure than the subjects with ratio lower than this threshold.

Figure 10: Maximum Cav of bimekizumab for different maximum ratios of ALT, AST and BIL to ULN categories in the analysis ALT, AST and BIL data sets.



Source: CL0518 report, pg 13, figure 3

The vertical dotted line in red indicates the cut-off of 3 times the ULN for AST and ALT and 1.5 times the ULN for BIL. AST: asparate aminotransferase; ALT: alanine aminotransferase.

Are there clinically relevant food-drug or drug-drug interactions, and what is the appropriate management strategy?

It is unknown at this time whether there are any clinically relevant drug-drug interactions (DDI) as the Applicant has not provided information about the drug interaction potential for bimekizumab.

Because monoclonal antibodies are not metabolized by CYP450 enzymes, conventional drug-drug interaction studies for small molecule drugs are not considered necessary for bimekizumab. However, patients with PSO have elevated levels of proinflammatory cytokines which can suppress the expression of some cytochrome P450 (CYP) enzymes. The suppression of the CYP enzymes could be normalized upon the disease improvement following treatment with bimekizumab. As a result, the exposure of CYP substrates could be altered when the disease condition is improved and the levels of proinflammatory cytokines are normalized. The lack of DDI assessment will be handled by labeling.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7: Listing of Clinical Trials Relevant to BLA 761151

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
PS0008	03412747	Phase 3, randomized, double-blind, active-controlled, parallel-group	BKZ 320 mg SC every 4 weeks (Q4W) BKZ 320 mg SC Q4W Wk 0-16, then 320 mg Q8W ADA 80 mg SC loading dose, then 40 mg SC Q2W until Wk 24, then BKZ 320 mg SC Q4W through Wk 52	Co-primary efficacy: PASI90 response (defined as subject achieving 90% reduction from Baseline in the PASI score) at Week 16) and IGA 0/1 response (defined as 0 ("Clear") or 1 ("Almost Clear") with at least a 2-category improvement from Baseline) at Week 16.)	56 weeks for BKZ; 24 weeks for ADA	478	Moderate to severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for ADA or for systemic PSO therapy and/or phototherapy	77; Australia, Canada, Germany, Hungary, Poland, Republic of Korea, Russian Federation, Taiwan, and US
PS0009	03370133	Phase 3 , randomized, double-blind, placebo- and active-controlled, parallel-group	BKZ 320 mg SC Q4W Ustekinumab 45 mg or 90 mg (based on weight) SC at BL, Wk 4, then Q12W PBO SC Q4W BL- Wk 16, then BKZ 320 mg SC Q4W through Wk 48	Co-primary efficacy: PASI90 response (defined as subject achieving 90% reduction from Baseline in the PASI score) at Week 16 and IGA 0/1 response (defined as 0 ("Clear") or 1 ("Almost Clear") with at least a 2-category improvement from Baseline) at Week 16.	56 weeks	56	Moderate to severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for ustekinumab or for systemic PSO therapy and/or phototherap	105; Australia, Belgium, Canada, Germany, Hungary, Italy, Japan, Poland, Russian Federation, UK, and US

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							y	
PS0013	03410992	Phase 3, randomized, double-blind, placebo-controlled	Initial Treatment Period (16 weeks): BKZ 320mg or PBO SC Q4W 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 320mg Q4W or Q8W, or PBO (i.e., treatment withdrawal)	Co-primary efficacy: PASI90 response (defined as subject achieving 90% reduction from Baseline in the PASI score) at Week 16 and IGA 0/1 response (defined as 0 ("Clear") or 1 ("Almost Clear") with at least a 2-category improvement from Baseline) at Week 16.	56 weeks	435	Moderate to severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for systemic PSO therapy and/or phototherapy	77; Australia, Canada, Germany, Hungary, Poland, Republic of Korea, Russian Federation, UK, and US
		Studies to Support Safety						
PS0014	03598790	Open-label extension (ongoing)	BKZ 320mg SC Q4W or Q8W (Dependent on subject's treatment regimen and PASI response in the feeder study)	Primary (safety): Incidence of TEAEs adjusted by duration of subject exposure to treatment. Secondary (efficacy): IGA response and PASI90 at Week 144	144 weeks	1343	Moderate to Severe plaque PSO who completed 1 of the Phase 3 Feeder studies (PS0008, PS0009, or PS0013)	Number of sites not provided; Australia, Belgium, Canada, Germany, Hungary, Italy, Japan, Poland, Republic of Korea, Russian Federation, Taiwan, UK,

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
								and US
PS0010	0290 5006	Phase 2, randomized, double-blind, placebo-controlled, dose-ranging	BKZ 64mg, 160mg, 320mg, or 480mg SC Q4W, or 320mg LD then 160mg Q4W, or PBO Q4W/	Primary efficacy: PASI90 response	12 weeks	250	Moderate to severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for systemic PSO therapy and/or phototherapy	40; Canada, Czech Republic, Hungary, Japan, Poland, and US
PS0011	0301 0527	Phase 2, double-blind, placebo-controlled extension study to PS0010	BKZ 64mg, 160mg, 320mg SC Q4W, treatment assigned based on PASI90 response in Trial PS0010	Primary (safety): Incidence of TEAEs adjusted by duration of subject exposure to treatment.	48 weeks	217	Subjects who completed Trial PS0010	36; Canada, Czech Republic, Hungary, Japan, Poland, and US
PS0016	0302 5542	Phase 2, Randomized, Subject-blind, Investigator-blind	BKZ 320mg SC at BL,vW4, and PBO SC at W16, BKZ 320mg SC at BL, W4, W16	Primary efficacy: Change from Baseline in PASI at Week 28	28 weeks	49	Moderate to Severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for systemic PSO therapy	7; Australia, Canada, Republic of Moldova, and US

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							and/or phototherapy	
PS0018	0323 0292	Open-Label Extension to Phase 2 Trial PS0016	BKZ 160mg SC Q4W; option to increase to 320mg SC Q4W if Inadequately controlled	Primary (safety): Incidence of TEAEs adjusted by duration of subject exposure to treatment.	48 weeks	43	Subjects who completed PS0016	9; Australia, Canada, Republic of Moldova, and US
		Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)						
UP0033	0370 7717	Randomized, Open-Label, parallel-group, 3-arm, single-dose, Bioequivalence	BKZ: BKZ 320mg/ BKZ-(b) (4) (b) (4) reference), BKZ-SS-1mL (b) (4) or BKZ-AI-1mL (b) (4) sc injection	Primary endpoint: PK parameters for BKZ	Single dose	189	Healthy Volunteers	2; Germany and US
UP0042	N/A	Randomized, Double-Blind, PBO-controlled, single-dose, parallel-group	BKZ: 80mg, 160mg, or 320mg or PBO sc injection	Primary endpoint: Plasma concentration of BKZ in Japanese subjects	Single dose	48	Healthy male Japanese and Caucasian volunteers	1; Japan
UP0008	0252 9956	Randomized, Subject-blind, Investigator-blind, PBO-controlled, single-dose, dose-escalating	BKZ: 8mg, 40mg, 160mg, 480mg, or 640mg or PBO iv infusion	Primary endpoint: Safety parameters, including AEs, vital signs, ECG data, clinical chemistry, hematology, urinalysis, coagulation/hemostasis tests, and fecal occult blood	Single dose	39	Mild to moderate plaque PSO (BSA≥5% with a minimum of 2 Pso lesions with 1 plaque in	1; UK

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
							location suitable for biopsy)	
UP0034	0389 5385	Randomized, Open-Label, parallel-group, single-dose	BKZ 320mg SC or No treatment (vaccination only) Influenza vaccine	Primary endpoint: Proportion of subjects with seroconversion response, defined as either a pre-vaccination hemagglutination inhibition (HI) titer $\leq$1/10 and a 4-week post-vaccination HI titer $\geq$1/40, or a pre-vaccination HI titer >1/10 and a $\geq$4-fold increase in HI titer 4 weeks after vaccination in at least 2 out of 4 serotypes	Single dose	56	Healthy Volunteers	1; US
DV0002	0376 6685	Open-Label, 2-arm (BKZ-AI-1mL; BKZ-SS-1mL), randomized, noncomparator (substudy of PS0014)(ongoing)	Depending on subject's treatment regimen in the feeder study: BKZ 320mg SC Q4W or Q8W using BKZ-AI-1mL or BKZ-SS-1mL	Primary endpoint: Percentage of study subjects able to self-administer safe and effective injections using the investigational device presentations 8 weeks after training in self-injection technique.	16 weeks	134	Moderate to severe plaque PSO (PASI≥12, IGA≥3, and BSA≥10%) who were candidates for systemic PSO therapy and/or phototherapy	35; Canada and US
DV0006	N/A	Open-Label, 2-arm (BKZ-AI-1mL; BKZ-SS-1mL),	Depending on subject's treatment regimen in the feeder study:	Primary endpoint: Percentage of study subjects able to	16 weeks (Europe) 9 weeks	88	Moderate to severe plaque PSO	24; Germany, Hungary, Poland, and

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		randomized, noncomparator (substudy of PS0014) (ongoing)	BKZ 320mg SC Q4W or Q8W using BKZ-AI-1mL or BKZ-SS-1mL	self-administer safe and effective injections using the investigational device presentations 8 weeks after training in self-injection technique.	(Japan)		(PASI≥12, IGA≥3, and BSA≥10%) who were candidates for systemic PSO therapy and/or phototherapy	Japan

ADA- Adalimumab, AEs- adverse events, AI- autoinjector, BL- baseline, BKZ- Bimekizumab, BSA-body surface area, IGA- Investigator's Global Assessment Score, LD- Loading dose, PASI- Psoriasis Area and Severity Index Score, PBO-placebo, PFS- pre-filled syringe, PK- pharmacokinetic, PSO-Psoriasis, SS- safety syringe, TEAE- treatment-emergent adverse event, (b) (4) PFS

7.2. Review Strategy

The sources of data used for the evaluation of the efficacy and safety of bimekizumab for the proposed indication included clinical study reports submitted by the Applicant, datasets [Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM)] and literature references. This application was submitted in eCTD format and entirely electronic. The electronic submission including protocols, statistical analysis plans (SAPs), clinical study reports, SAS transport datasets in legacy, Study Data Tabulation Modal (SDTM), and Analysis Data Model (ADaM) format were in the following network path:

- Original submission: \\CDSESUB1\evsprod\BLA761151\0001\m5

The Applicant submitted the required certification and disclosure information for participating investigators (Form 3454). Refer to Section 19.2 Financial Disclosure of this review for additional information.

8 Statistical and Clinical and Evaluation

8.1. Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design

The Applicant conducted three pivotal phase 3 trials, PS0008, PS0009 and PS0013. Trial PS0008 is a multicenter, randomized, double-blind, active comparator-controlled, parallel-group, Phase 3 trial with adalimumab as a comparator. Trial PS0009 is a multicenter, randomized, double-blind, placebo- and active comparator-controlled, parallel-group, phase 3 trial with ustekinumab as a comparator. Trial PS0013 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial with a randomized-withdrawal period.

The three phase 3 trials evaluated the efficacy, safety, PK of bimekizumab administered subcutaneously (SC) in adult subjects with moderate to severe chronic plaque psoriasis. All three trials are ongoing at the time of this review. It is noted that the submitted interim clinical study reports (CSRs) are a complete analysis of the first 56 weeks (52 for Trial PS0009) of the trials (including the initial treatment period and maintenance treatment period) based on clinical cutoff dates (October 28, 2019 for Trial PS0008, September 4, 2019 for Trial PS0009 and of October 18, 2019 for Trial PS0013).

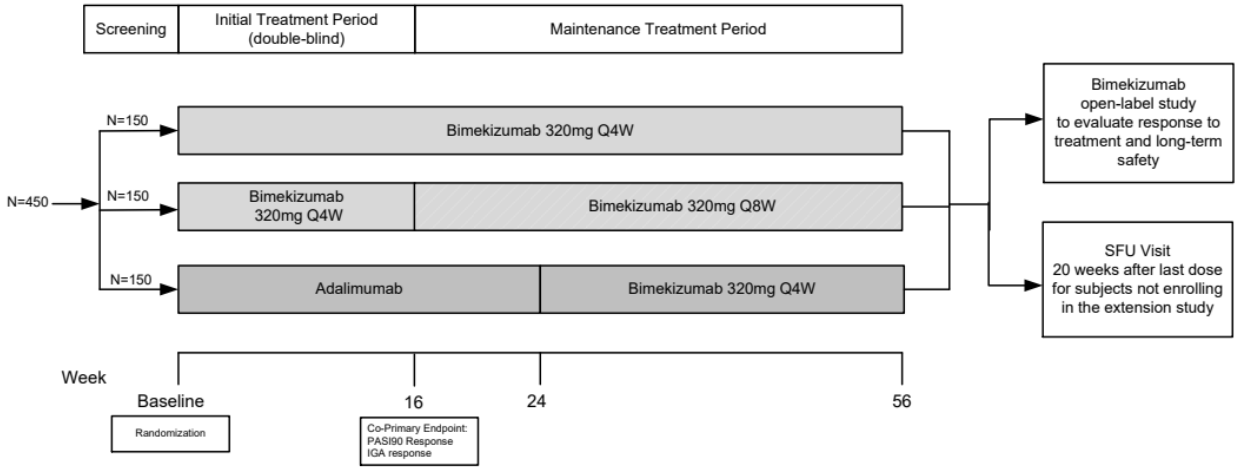
The following were the key inclusion criteria for the three pivotal trials:

- Male or female at least 18 years of age
- Chronic plaque psoriasis for at least 6 months prior to screening
- Investigator Global Assessment (IGA) score ≥3; see Table 86 in Appendix 19.5 for the IGA scale
- Psoriasis Area and Severity Index (PASI) ≥12; see Figure 28 in Appendix 19.5 for the PASI scale
- Body surface area (BSA) of involvement ≥10%
- Trial participant was a candidate for systemic psoriasis therapy and/or phototherapy

8.1.1.1. Trial PS0008 (NCT03412747)

The trial consists of a screening period (2-5 weeks), a double-blind, active comparator-controlled initial treatment period (16 weeks), a maintenance treatment period (40 weeks) and a safety follow-up period (20 weeks). The trial design schematic diagram for PS0008 is presented in Figure 11.

Figure 11: Trial Design Schematic Diagram for Trial PS0008



IGA=Investigator's Global Assessment; IMP=investigational medicinal product; N=number; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks; SFU=Safety Follow-Up
Note: At Week 36 and all following visits, trial participants on continuous treatment with the same IMP for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period were defined as nonresponders and should have discontinued IMP.
Source: Applicant's Clinical Study Report (CSR) for Trial PS0008; page 51

According to the protocol, approximately 450 subjects from approximately 100 centers in North America, Western Europe, Central/Eastern Europe, and Asia/Australia were planned to be enrolled and randomized in a 1:1:1 ratio to the following treatment arms:

- Bimekizumab 320mg every 4 weeks (Q4W) administered throughout the trial
- Bimekizumab 320mg administered Q4W until Week 16
- Adalimumab 80mg administered as an initial dose, followed by 40mg every 2 weeks (Q2W) starting 1 week after the initial dose ("i.e., adalimumab administered according to the labeling recommendations") until Week 24

To maintain double-blinding due to the differences in the dosing schedule between bimekizumab and adalimumab, subjects received placebo injections at certain visits.

Randomization was stratified by region (North America, Western Europe, Central/Eastern Europe and Asia/Australia) and prior biologic exposure (yes/no). Table 8 shows the geographic regions with corresponding countries.

Table 8: Geographic Regions and Corresponding Countries – Trial PS0008

Region	**Country**
North America	Canada, United States
Western Europe	Germany
Central/Eastern Europe	Czech Republic, Hungary, Poland, Russian Federation
Asia/Australia	Australia, Republic of Korea, Taiwan

Source: Applicant's Clinical Study Report (CSR) for Trial PS0008; page 76

After the 16-week initial treatment period, subjects entered the 40-week maintenance treatment period. Treatment during the maintenance treatment period started at Week 16 and

subjects returned to the clinic Q4W through Week 56. Treatment during the maintenance treatment period was based on initial treatment per the following:

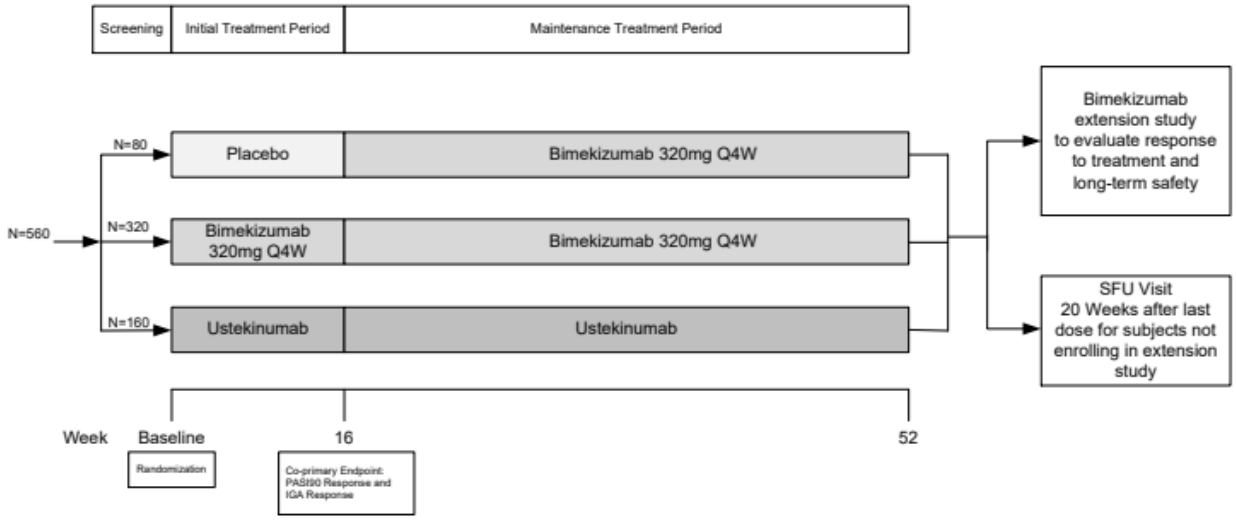
- Subjects in the bimekizumab 320mg Q4W treatment arm continued to receive bimekizumab 320mg Q4W
- Subjects in the bimekizumab 320mg Q4W/Q8W treatment arm received bimekizumab Q8W from Week 16 through Week 52
- Subjects in the adalimumab treatment arm received bimekizumab 320mg Q4W from Week 24 through Week 52

After completion of the maintenance treatment period, eligible subjects were allowed to enroll in the open-label trial PS0014. Subjects enrolling into PS0014 underwent the Week 56 assessments and then received their first dose of bimekizumab in PS0014. Subjects not enrolling in PS0014 had the Week 56 assessments and entered the safety follow-up period.

8.1.1.2. Trial PS0009 (NCT03370133)

The trial consists of a screening period (2-5 weeks), a double-blind, active comparator-controlled initial treatment period (16 weeks), a maintenance treatment period (36 weeks) and a safety follow-up period (20 weeks). The trial design schematic diagram for PS0009 is presented in Figure 12.

Figure 12: Trial Design Schematic Diagram for Trial PS0009



IGA=Investigator's Global Assessment; IMP=investigational medicinal product; N=number; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up
Note: At Week 24 and all following visits, trial participants on continuous treatment with the same IMP for at least 12 weeks with a persistent IGA score ≥3 over at least a 4-week period were defined as nonresponders and should have discontinued IMP.
Source: Applicant's Clinical Study Report (CSR) for Trial PS0009; page 53

According to the protocol, approximately 560 subjects from approximately 100 centers in North America, Western Europe, Central/Eastern Europe, and Asia/Australia were planned to be enrolled and randomized in a 4:2:1 ratio to the following treatment arms:

- Bimekizumab 320 mg administered Q4W
- Ustekinumab (160 subjects)
    - For subjects ≤ 100 kg (220 lbs), 45 mg SC at baseline and 4 weeks later
    - For subjects > 100 kg (220 lbs), 90 mg SC at baseline and 4 weeks later
- Placebo administered Q4W

Because of differences in the dosing schedule between bimekizumab and ustekinumab, all subjects were planned to receive two injections SC Q4W based on the following dosing scheme during the initial treatment period:

- Bimekizumab 320 mg Q4W receive 2 Bimekizumab 160 mg injections
- Ustekinumab at baseline and Week 4: Because ustekinumab is approved for weight-based dosing,
    - subjects ≤100 kg (220 lbs) receive ustekinumab 45 mg injection and one placebo injection at baseline and Week 4
    - subjects > 100 kg (220 lbs) receive ustekinumab 90 mg injection (2 ustekinumab 45 mg injections) at baseline and at Week 4
    - subjects receive placebo at Weeks 8 and 12
- Placebo Q4W

Randomization was stratified by region (North America, Western Europe, Central/Eastern Europe and Asia/Australia) and prior biologic exposure (yes/no). The corresponding countries for the geographic regions are the same as those for Trial PS0008; see Table 8.

After the 16-week initial treatment period, subjects entered the 36-week maintenance treatment period. Treatment during the maintenance treatment period started at Week 16 and subjects returned to the clinic Q4W through Week 52. Treatment during the maintenance treatment period was based on initial treatment per the following:

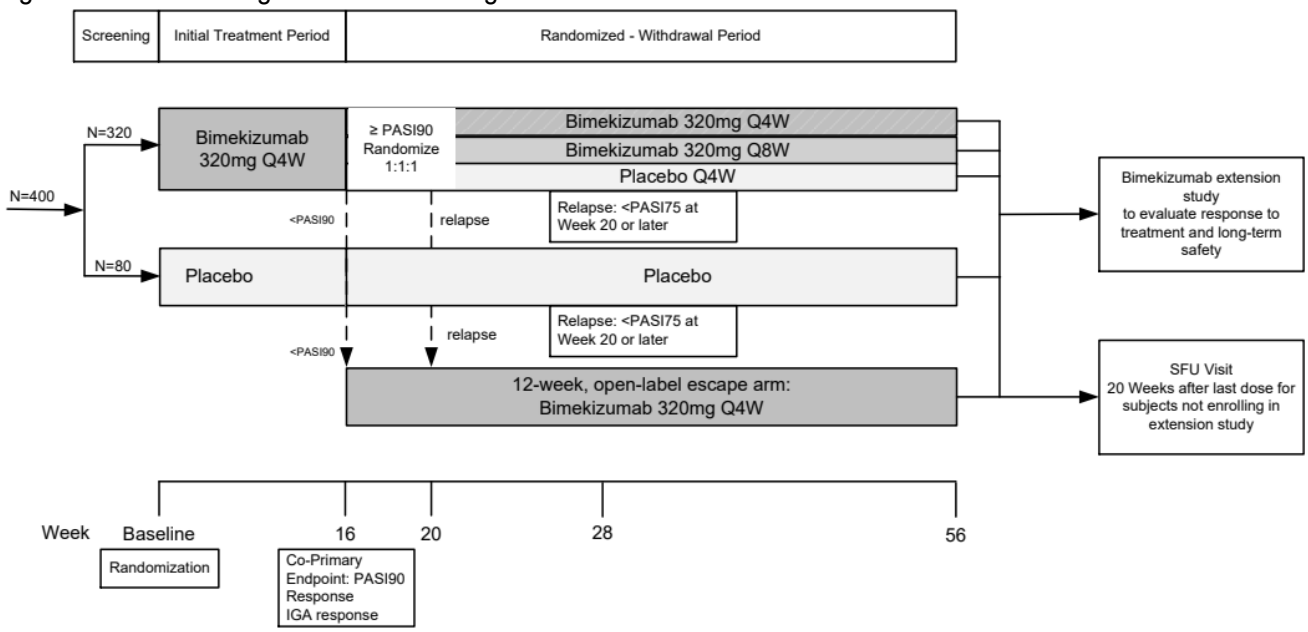
- Subjects in the bimekizumab 320mg treatment arm continued to receive bimekizumab 320mg Q4W
- Subjects in the ustekinumab treatment arm continued on ustekinumab (subjects weighing ≤100kg [220lbs] at baseline received 45mg every 12 weeks; subjects weighing >100kg [220lbs] at baseline received 90mg every 12 weeks)
- Subjects in the placebo arm received bimekizumab 320mg Q4W starting at Week 16

After completion of the maintenance treatment period, eligible subjects were allowed to enroll in the open-label trial PS0014. Subjects enrolling into PS0014 underwent the Week 52 assessments and then received their first dose of bimekizumab in PS0014. Subjects not enrolling in PS0014 had the Week 52 assessments and entered the safety follow-up period.

8.1.1.3. Trial PS0013 (NCT03410992)

The trial consists of a screening period (2-5 weeks), a double-blind, placebo-controlled initial treatment period (16 weeks), a randomized-withdrawal period (40 weeks) and a safety follow-up period (20 weeks). The trial design schematic diagram for PS0013 is presented in Figure 13.

Figure 13: Trial Design Schematic Diagram for Trial PS0013



Source: Applicant's Clinical Study Report (CSR) for Trial PS0013; page 54

According to the protocol, approximately 400 subjects from approximately 100 centers in North America, Western Europe, Central/Eastern Europe, and Asia/Australia were planned to be enrolled and randomized in a 4:1 ratio to the following treatment arms:

- Bimekizumab 320 mg administered Q4W
- Placebo administered Q4W

Subjects received placebo injections at certain visits in order to blind the IMP.

Randomization was stratified by region (North America, Western Europe, Central/Eastern Europe and Asia/Australia) and prior biologic exposure (yes/no). Table 9 shows the geographic regions with corresponding countries.

Table 9: Geographic Regions and Corresponding Countries – Trial PS0013

Region	**Country**
North America	Canada, United States
Western Europe	Germany, United Kingdom
Central/Eastern Europe	Hungary, Poland, Russian Federation
Asia/Australia	Australia, Republic of Korea

Source: Applicant's Clinical Study Report (CSR) for Trial PS0013; page 79

At the Week 16 study visit, subjects who achieved a PASI90 response entered into a double-blind, placebo-controlled randomized-withdrawal period lasting 40 weeks. Subjects who did not

achieve a PASI90 response at the Week 16 visit were allocated to the escape arm (open-label bimekizumab 320 mg). During the randomized-withdrawal period, dosing was based on treatment arm assignment at initial randomization as follows:

- Subjects initially randomized to bimekizumab 320mg Q4W who achieve a PASI 90 were re-randomized 1:1:1 to either bimekizumab 320mg Q4W or bimekizumab 320mg Q8W or placebo (i.e., treatment withdrawal)
- All subjects initially randomized to placebo who achieve a PASI 90 response at Week 16 continued to receive placebo (Q4W)

All subjects 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.

At the end of the randomized-withdrawal period, eligible subjects were allowed to enroll in the open-label study PS0014. Subjects enrolling into PS0014 underwent the Week 56 assessments and then received their first dose of bimekizumab in PS0014.

8.1.2. Endpoints

The protocol-specified co-primary efficacy endpoints in all three pivotal trials are:

1. PASI 90: Proportion of subjects achieving ≥90% improvement in PASI from baseline to Week 16
2. IGA 0/1: Proportion of subjects achieving IGA score of 0 (clear) or 1 (almost clear) with at least a 2-grade of improvement from baseline to Week 16

The protocols listed secondary endpoints as summarized in Table 10. Refer to Appendix 19.5 for the scales used to evaluate efficacy.

Table 10: Secondary Endpoints for Trials PS0008, PS0009 and PS0013

Trial PS0008	Trial PS0009	Trial PS0013
• PASI100 at Week 16 • PASI75 at Week 4 • PASI100 at Week 24 • PASI90 at Week 24 • IGA 0/1 at Week 24 • PASI90 at Week 56 (not adjusted for multiplicity) • IGA 0/1 at Week 56 (not adjusted for multiplicity)	• PASI100 at Week 16 • IGA 0 (defined as Clear [0] with at least a 2-grade improvement from baseline) at Week 16 [added in the SAP] • PASI90 at Week 12 • IGA 0/1 at Week 12 • PASI75 at Week 4 • PSD responses for pain, itch, and scaling at Week 16 • Scalp IGA 0/1 (defined as Clear [0] or Almost Clear [1]) with at least a 2-grade improvement from baseline) at Week 16 for subjects with scalp psoriasis at baseline • PASI90 at Week 52 • IGA 0/1 at Week 52	• PASI100 at Week 16 • IGA 0[added in the SAP] • PASI75 at Week 4 • PSD responses for pain, itch, and scaling at Week 16 • Scalp IGA 0/1 at Week 16 for subjects with scalp PSO at baseline • PASI90 at Week 56 among Week 16 PASI90 responders

Abbreviations: PASI = Psoriasis Area and Severity Index; PSD = Patient Symptom Diary; IGA = Investigator Global Assessment

The protocols specified many "other" efficacy endpoints, including endpoints for palmoplantar psoriasis and nail psoriasis; however, such endpoints were not included in the multiplicity testing procedure (MTP). In addition, the secondary endpoints of PASI90 and IGA 0/1 at Week 56 in Trial PS0008 were also not included in the MTP. Therefore, the results of these endpoints are considered exploratory and are not included in this review.

Patient Symptom Diary (PSD):
PSD is a Patient Reported Outcome measure used to assess key symptoms relevant to subjects with moderate to severe chronic plaque psoriasis. The PSD was used to collect data as a daily diary about the patients experience of the severity of the sign, symptom or impact, at its worst during the past 24 hours, on an 11-point numeric rating scale (NRS). The PSD was collected up to Week 16/Week 24 visit in Trials PS0009 and PS0013.

The PSD response was computed based on the responder definition on each item. Each of the 3 PSD responses (pain, itch, and scaling) were characterized in terms of the cumulative percent of subjects demonstrating a pre-specified point improvement at Week 16. The thresholds for the PSD response rates based on changes in pain, itch, and scaling item scores were 1.98, 2.39, and 2.86, respectively. The responder analysis was limited to subjects with a baseline PSD score at or above the applicable threshold score (i.e., at least 1.98, 2.39, and 2.86 for pain, itch, and scaling, respectively).

8.1.3. Statistical Methodologies

Analysis Sets:
The protocols/SAPs defined the following analysis sets for the three pivotal trials:

- Randomized Set (RS): all randomized subjects
- Full Analysis Set (FAS): all randomized subjects that received at least 1 dose of IMP, and had a valid measurement for each of the co-primary efficacy endpoints at baseline
- Per Protocol Set (PPS): all subjects in RS who had no important protocol violations affecting the primary efficacy endpoint.
- Maintenance Set (MS): all subjects who received at least 1 dose of active IMP (bimekizumab or adalimumab or ustekinumab) in the maintenance treatment period (Trials PS0008 and PS0009 only).
- The Escape Subject Set (ESS): 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 (Trial PS0013 only).
- Week 16 Responder Set (WKL16ResS): all subjects who achieve a PASI90 response at Week 16 and receive at least 1 dose of the IMP during the Randomized-Withdrawal Period at Week 16 or later (Trial PS0013 only).
- Active Medication Set (AMS): subjects who 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 (Trial PS0013 only).

- Safety Set (SS): all subjects who received at least 1 dose of IMP

The Applicant stated that the criteria for identifying important protocol deviations were defined within the appropriate protocol-specific document at trial start. The Applicant also stated that "Important protocol deviations were reviewed as part of the ongoing data cleaning process. Important protocol deviations including those that lead to exclusion from the analysis sets were identified and documented prior to unblinding."

Efficacy analyses were conducted using the randomized set. The primary analysis of the co-primary endpoints was repeated using the FAS and the PPS.

Analysis methods for the co-primary endpoints:
For the analysis of the co-primary endpoints (IGA 0/1 and PASI90 at Week 16), the protocols/SAPs specified pooling the two bimekizumab arms and using the Cochran-Mantel-Haenszel (CMH) test stratified by region and prior biologic exposure (yes/no). To calculate the stratified Mantel-Haenszel risk difference, the SAPs specified using the method of Greenland and Robins (Greenland S, Robins JM. *Estimation of common effect parameter from sparse follow up data*. Biometrics 1985;41:55-68).

As a sensitivity analysis for the co-primary efficacy endpoints, the protocols/SAPs specified using the logistic regression model, with factors of treatment group, region, and prior biologic exposure (yes/no). If the algorithm for fitting the logistic regression model did not converge, the protocols/SAPs specified that prior biologic exposure could be dropped from the model to facilitate convergence, and if the algorithm for fitting the model still did not converge, then region could have been removed as well. In addition, if the algorithm for fitting the logistic regression model did not converge, then Fisher's exact test was used for inferential comparisons.

For Trials PS0008 and PS0009, the SAPs specified testing of non-inferiority (NI) against adalimumab/ustekinumab at a 1-sided alpha level of 0.025 and based on a 1-sided 97.5% confidence interval (CI) for the stratified Mantel-Haenszel risk difference between bimekizumab and adalimumab/ustekinumab, using a NI margin of 10%. The SAPs specified using the Wald method to calculate the confidence interval. The evaluation of superiority to adalimumab/ustekinumab used pairwise treatment comparisons based on the CMH test. If one of the treatment arms had 0 or very low response where CMH could no longer be used, the logit method was to be applied instead.

Analysis methods for the secondary endpoints:
For the analysis of binary secondary endpoints, the protocols/SAPs specified using the stratified CMH test similar to the primary analysis.

For the analysis of the PASI90 response at Week 56 among Week 16 PASI90 responders in Trial PS0013, the protocol/SAP specified pooling both dose regimens (Q4W and Q8W) for comparison with placebo.

In order to differentiate between subjects remaining on Q4W dosing from those switching to Q8W dosing at Week 16 of Trial PS0008, the protocol/SAP specified performing the treatment comparisons at Week 24 for PASI100, PASI90 and IGA response in two different ways using the following randomized treatment arms:

- Bimekizumab Q4W and bimekizumab Q4W/Q8W combined vs adalimumab (testing H_7, H_8, and H_9)
- Bimekizumab Q4W only vs adalimumab (testing H_{10}, H_{11}, and H_{12})

According to the CSR, a third comparison was performed as described below:

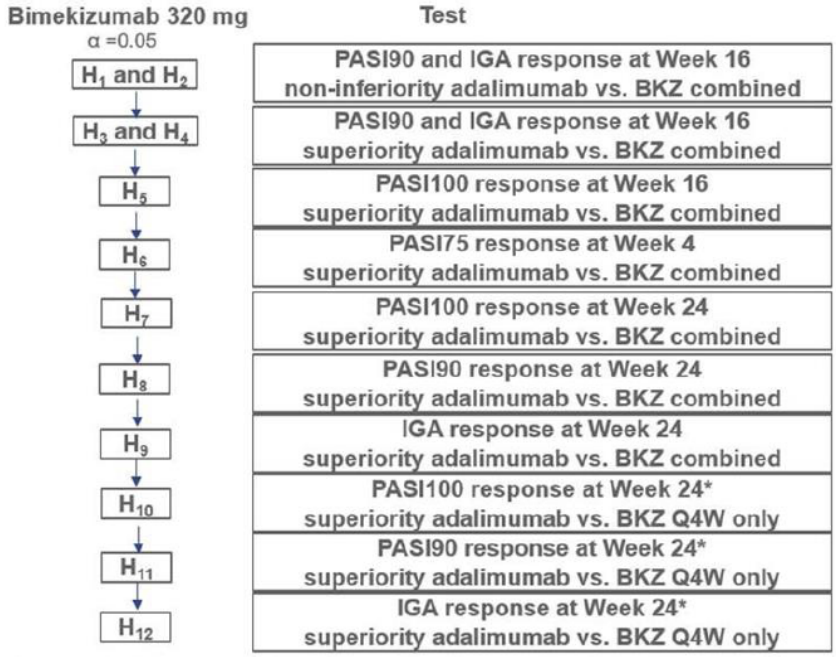
- Bimekizumab Q4W/Q8W vs adalimumab (not part of the hierarchical testing sequence; these analyses were exploratory, and the p-values produced were nominal)

Because all adalimumab subjects switched to bimekizumab treatment starting at Week 24, inferential comparisons against adalimumab after Week 24 were not performed. The PASI90 and IGA 0/1 responses at Week 56 were summarized using descriptive statistics only.

Multiplicity Testing Procedure (MTP):
The protocols/SAPs specified controlling the familywise Type I error rate at a 2-sided alpha level of 0.05 by using a fixed-sequence testing procedure, accounting for the co-primary efficacy endpoints and selected secondary efficacy endpoints. The testing hierarchy for Trials PS0008, PS0009 and PS0013 are outlined in Figure 14, Figure 15 and Figure 16, respectively.

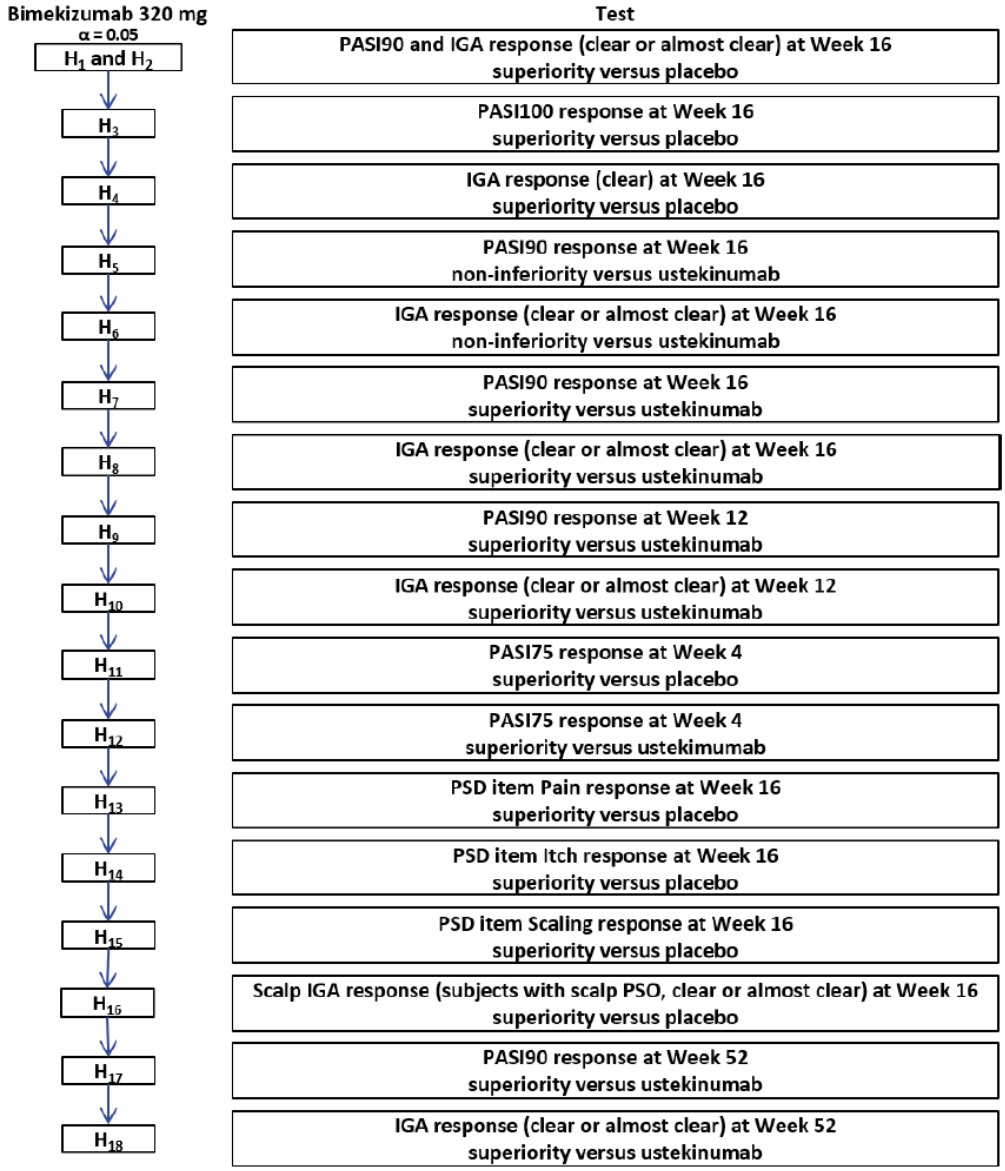
In the SAP for Trial PS0013, it is stated that "while not part of the fixed sequence testing procedure, it was a secondary objective to assess the maintenance of efficacy of bimekizumab dosing Q4W versus Q8W at Week 56". For this objective, the Applicant assessed the endpoint of PASI90 response at Week 56 among Week 16 PASI90 responders for each dosing regimen (Q4W and Q8W not combined).

Figure 14: Testing Hierarchy for Trial PS0008



BKZ=bimekizumab; H=hypothesis; IGA=Investigator's Global Assessment; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks
Note: Calculations for H_1 through H_9 were based on the combined bimekizumab arms with the sample size of 300.
* indicates that in H_{10} through H_{12}, calculations were based on the bimekizumab Q4W/Q4W arm only, with a sample size of 150.
Source: Applicant's Clinical Study Report (CSR) for Trial PS0008; page 82

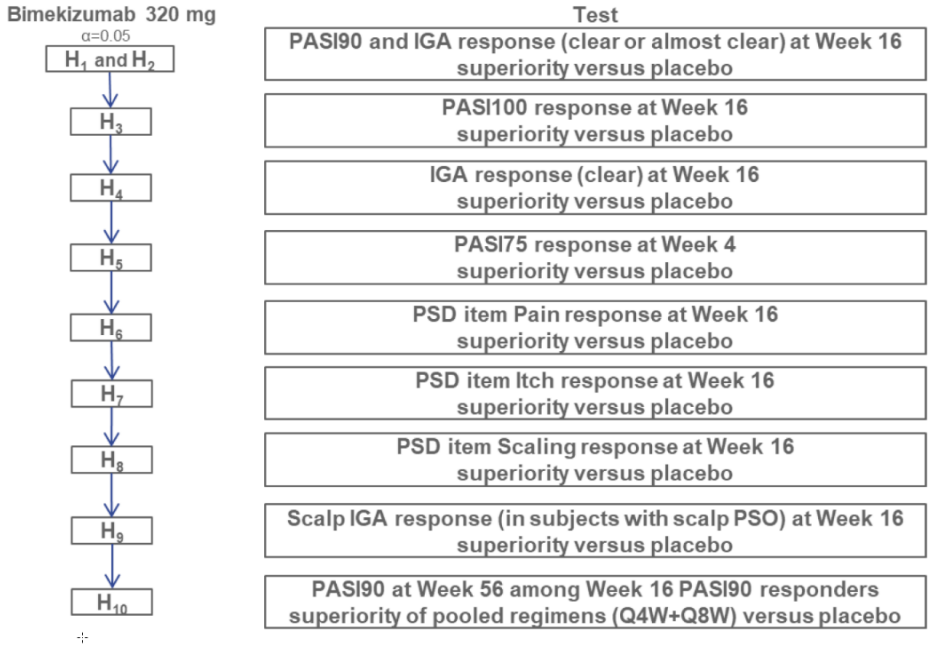
Figure 15: Testing Hierarchy for Trial PS0009



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

Source: Applicant's Clinical Study Report (CSR) for Trial PS009; page 86

Figure 16: Testing Hierarchy for Trial PS0013



H=hypothesis; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index, PSD=Patient Symptom Diary; PSO=psoriasis; Q4W=every 4 weeks; Q8W=every 8 weeks.

Source: Applicant's Clinical Study Report (CSR) for Trial PS008; page 86

Center-by-treatment interaction:

The protocols/SAPs specified testing the center-by-treatment interaction by replacing region with center in the logistic regression model described as a sensitivity analysis for the co-primary endpoints above, and by adding a center-by-treatment interaction term. In the model, center was based on the original centers prior to pooling. However, if the algorithm for fitting the did not converge due to a low number of subjects at a given center, pooling was to be implemented in order to allow the model to converge.

The following center pooling algorithm was used for each geographic region for centers that had fewer than 15 subjects for Trials PS0008 and PS0013. The same pooling algorithm was specified for centers that had fewer than 21 subjects in Trial PS0009.

- If a center had 15 or more subjects, then no pooling was done for that center.
- Centers with fewer than 15 subjects were ordered from largest to smallest with pooling proceeding in the following manner:
    - Two or more centers were combined until the cumulative subject total was at least 15.
    - Once a pooled center had at least 15 subjects, the process continued in an iterative fashion for the subsequent centers in the ordered list, where a new pooled center began each time at least 15 subjects were reached in the previous pool.
    - If this iterative process reached the end of the ordered list of centers where the final pooled center had fewer than 15 subjects, then the subjects from the centers in that pool were combined with the pooled center formed in the previous iteration.

This procedure was only to be performed within a geographic region; there was no pooling of centers across regions. In the event that the percentage of randomized subjects was less than 10% in either of the Asia/Australia or Western Europe regions, the 2 regions were combined as a geographic region stratum for efficacy modeling, so that there were no modeling convergence issues across efficacy variables.

If the center-by-treatment interaction was not found to be significant (alpha=0.1) then no further analyses were performed. On the other hand, if the interaction was significant, then further analyses were conducted to determine which center or centers were the source of the interaction. This was specified to be done by performing the logistic regression model (including the interaction term) where each center was systematically removed from the model. The impact of a given center was based on the change in the interaction p-value when that center was removed. The center or centers that appeared to be impacting the significant interaction effect were then removed from the model to verify that conclusions remained the same with or without the influential center(s).

Methods for handling the missing data:
The protocols/SAPs specified the non-responder imputation method for the handling of 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 and secondary endpoints at Week 16 time was considered as a non-responder.

For sensitivity analyses, the protocols/SAPs specified the following methods for the co-primary endpoints:

- Multiple imputation (MI) – Markov Chain Monte Carlo (MCMC) / Monotone Regression: Using MI methodology, intermittent missing data were imputed based on the MCMC method, and monotone missing data were imputed using monotone regression.
- Multiple Imputation – MCMC / Reference-based imputation method, where intermittent missing data were imputed based on the MCMC method, and monotone missing data were imputed using an imputation model based on placebo (reference) data (Trials PS0009 and PS0013 only).
- Observed case (OC)
- Last observation carried forward (LOCF)

For the secondary binary efficacy endpoints, the protocols/SAPs specified imputing missing data using NRI as primary method. MI-MCMC/monotone regression and OC methods were specified as sensitivity analysis. Table 11 through Table 13 depict which missing data handling approaches were used based on endpoint priority (primary, secondary, other) and endpoint type (responder, continuous, ordinal) for the three pivotal trials.

Table 11: Missing Data Handling Approach by Endpoint Priority and Type – Trial PS0008

Variable Priority	Variable Type	NRI	MI (MCMC/ Monotone Regression)	LOCF	OC
Primary	Responder	P	S [a]	S	S
Secondary	Responder	P	S [a]		S
	Continuous		P	B	S
Other	Responder	P			S [b, c]
	Continuous [d]		P	B	
	Ordinal				P [e]

B=Backup method; IGA= Investigator's Global Assessment; LOCF=Last observation carried forward; MCMC=Markov Chain Monte Carlo; MI=Multiple imputation; NRI=Nonresponder imputation; OC=Observed Case; P=Primary method; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area and Severity Index; S=Sensitivity method

Note: Backup method was only applicable when the primary method was unable to converge due to challenges with the imputation model.

[a] Imputation method was applied on continuous data, and responder variable was derived from the continuous variable based on complete data set.

[b] Only applied to by-visit summaries of variables that were in the multiplicity-controlled testing procedure.

[c] Included IGA 0/1 and IGA 0 response, PASI75, PASI90 and PASI100.

[d] For PASE, OC was the primary analysis method.

[e] Included Patient Global Assessment of PSO, IGA score and EQ-5D-3L responses.

Source: Applicant's Clinical Study Report (CSR) for Trial PS0008; page 82

Table 12: Missing Data Handling Approach by Endpoint Priority and Type – Trial PS0009

Variable Priority	Variable Type	NRI	MI (MCMC/ Monotone Regression)	MI (MCMC/ Reference-based)	LOCF	OC
Primary	Responder	P	S[a]	S[a]	S	S
Secondary	Responder	P	S[a]	-	-	S
	Continuous	-	P	-	B	S
Other	Responder	P	-	-	-	S[b, c]
	Continuous[e]	-	P	-	B	S[b, d]
	Ordinal	-	-	-	-	P[d]

B=Backup method; EQ-5D-3L= Euro-Quality of Life 5-Dimensions, 3 levels; IGA=Investigator's Global Assessment; LOCF=last observation carried forward; MI=multiple imputation; MCMC=Markov Chain Monte Carlo; NRI=Nonresponder imputation; OC=observed case; P=primary method; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area and Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis; S=sensitivity method

Note: Backup method was only applicable when the primary method was unable to converge due to challenges with the imputation model.

[a] Imputation method was applied to continuous data, and responder variable was derived from the continuous variable based on the complete data set.

[b] Only applied to by visit summaries of variables that were in the multiplicity-controlled testing procedure.

[c] Includes PASI75, PASI90, PASI100, Scalp IGA, IGA response, and PSD responder variables

[d] Includes Patient Global Assessment of PSO, IGA score, and EQ-5D-3L responses

[e] For PASE, OC was the primary analysis method.

Source: Applicant's Clinical Study Report (CSR) for Trial PS0009; page 82

Table 13: Missing Data Handling Approach by Endpoint Priority and Type – Trial PS0013

Variable Priority	Variable Type	NRI	MI (MCMC/ Monotone Regression)	MI (MCMC/ Reference-based)	LOCF	OC
Primary	Responder	P	S[a]	S[a]	S	S
Secondary	Responder	P	S[a]			S
	Continuous		P		B	S
Other	Responder	P				S[b, c]
	Continuous[d]		P		B	
	Ordinal					P[e]

B=backup method; EQ-5D-3L=Euro-Quality of Life 5-Dimensions, 3 levels; IGA=Investigator's Global Assessment; LOCF=Last observation carried forward; MCMC=Markov-Chain Monte Carlo; MI=multiple imputation; NRI=nonresponder imputation; OC=observed case; P=primary method; PASE=Psoriatic Arthritis Screening and Evaluation; PASI=Psoriasis Area and Severity Index; PSD=Patient Symptom Diary; PSO=psoriasis; S=sensitivity method

Note: Backup method was only applicable when the primary method was unable to converge due to challenges with the imputation model.

[a] Imputation method was applied on continuous data, and responder variable was derived from the continuous variable based on complete data set.

[b] Only applied to by-visit summaries of variables that were in the multiplicity-controlled testing procedure.

[c] Included IGA responses, scalp IGA, PASI75, PASI90, PASI100, and PSD of PSO for pain, itch, and scaling.

[d] For PASE and analysis of the Escape Period, OC was the primary analysis method.

[e] Included Patient Global Assessment of PSO, IGA score and EQ-5D-3L responses.

Source: Applicant's Clinical Study Report (CSR) for Trial PS0013; page 82

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial PS0008 enrolled and randomized a total of 478 subjects from 76 investigational sites. Trial PS0009 enrolled and randomized a total of 567 subjects from 98 investigational sites. Trial PS0013 enrolled and randomized a total of 435 subjects from 74 investigational sites.

Table 14 and Table 15 present the disposition of subjects during the first 16 weeks for the three pivotal trials. The discontinuation rate was slightly higher in the adalimumab and placebo arms compared to the bizekizumab arms in Trials PS0008 and PS0009. The discontinuation rates are comparable across the two treatment arms in Trial PS0013.

Table 16 and Table 17 present the demographics and baseline disease characteristics for the three pivotal trials. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were comparable across trials. Trial PS0009 had higher proportion of Asian subjects and lower proportion of White subjects compared to Trials PS0008 and PS0013. The majority of the subjects had IGA score of 3 (moderate) at baseline. Three subjects in Trial PS0009 (one in each treatment arm) had baseline IGA score of 2. The Applicant noted (page 122 of the PS0009 CSR) that these subjects had a pre-treatment IGA score of 3 at screening.

Table 14: Subject Disposition through Week 16 for Trial PS0008 (RS*)

	BKZ Q4W (N=158)	BKZ Q4W/Q8W (N=161)	BKZ Total (N=319)	ADA (N=159)
Completed	153 (97%)	154 (63%)	307 (96%)	150 (94%)
Discontinued	5 (3%)	7 (4%)	12 (4%)	9 (6%)
Reason for Discontinuation				
Adverse Event	2 (1%)	2 (1%)	4 (1%)	4 (2%)
Lack of Efficacy	0 (0%)	0 (0%)	0 (0%)	1 (1%)
Lost to Follow-up	2 (1%)	0 (0%)	2 (1%)	1 (1%)
Other	0 (0%)	1 (1%)	1 (<1%)	0 (0%)
Protocol Deviation	0 (0%)	0 (0%)	0 (0%)	2 (1%)
Withdrawal by Subject	1 (1%)	4 (2%)	5 (2%)	1 (1%)

Source: Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
Abbreviations: BKZ=bimekizumab; ADA=adalimumab; Q4W=every 4 weeks; Q8W=every 8 weeks
* Randomized Set (RS): all randomized subjects
Note: BKZ Total= BKZ Q4W + BKZ Q4W/Q8W

Table 15: Subject Disposition through Week 16 for Trials PS0009 and PS0013 (RS*)

	Trial PS0009			Trial PS0013	
	BKZ Q4W (N=321)	Uste (N=163)	PBO (N=83)	BKZ Q3W (N=349)	PBO (N=86)
Completed	306 (95%)	157 (96%)	74 (89%)	340 (97%)	82 (95%)
Discontinued	15 (5%)	6 (4%)	9 (11%)	9 (3%)	4 (5%)
Reason for Discontinuation					
Adverse Event	6 (2%)	3 (2%)	6 (7%)	5 (1%)	0 (0%)
Lack of Efficacy	1 (<1%)	0 (0%)	2 (2%)	1 (<1%)	2 (2%)
Lost to Follow-up	3 (1%)	0 (0%)	0 (0%)	3 (1%)	1 (1%)
Other	3 (1%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Protocol Deviation	0 (0%)	2 (1%)	0 (0%)	0 (0%)	0 (0%)
Withdrawal by Subject	2 (1%)	1 (1%)	1 (1%)	0 (0%)	1 (1%)

Source: Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
Abbreviations: BKZ=bimekizumab; Uste=ustekinumab; PBO=placebo; Q4W=every 4 weeks
* Randomized Set (RS): all randomized subjects

Table 16: Demographics and Baseline Disease Characteristics for Trial PS0008 (RS*)

	BKZ Q4W/Q4W (N=158)	BKZ Q4W/Q8W (N=161)	BKZ Total (N=319)	ADA (N=159)
Age (years)				
Mean (SD)	45.3 (13.2)	44.0 (13.5)	44.6 (13.3)	45.5 (14.3)
Median	45.5	43.0	44.0	44.0
Range	19 – 76	18 – 83	18 – 83	18 – 72
<65	147 (93%)	148 (92%)	295 (93%)	139 (87%)
≥65	11 (7%)	13 (8%)	24 (7%)	20 (13%)
Sex				
Male	102 (65%)	112 (70%)	214 (67%)	114 (72%)
Female	56 (35%)	49 (30%)	105 (33%)	45 (28%)
Race				
White	140 (89%)	140 (87%)	280 (88%)	141 (89%)
Black or African American	2 (1%)	2 (1%)	4 (1%)	2 (1%)
Native Hawaiian or Other Pacific Islander	1 (1%)	2 (1%)	3 (1%)	0 (0%)
Asian	10 (6%)	13 (8%)	23 (7%)	11 (7%)
Missing	5 (3%)	4 (2%)	9 (3%)	5 (3%)
Weight (Kg)				
Mean (SD)	89.6 (21.4)	93.1 (24.4)	91.4 (23.0)	30.5 (22.1)
Median	85.0	91.0	87.8	86.4
Range	47.6 – 152	45 – 237	45 – 237	45.6 – 181
<100Kg	112 (71%)	105 (65%)	217 (68%)	114 (72%)
≥100 Kg	46 (29%)	56 (35%)	102 (32%)	45 (28%)
Country				
US	48 (30%)	47 (29%)	95 (30%)	46 (29%)
Non-US	110 (70%)	114 (71%)	224 (70%)	113 (71%)
Prior Systemic Therapy				
Yes	116 (72%)	112 (71%)	228 (71%)	110 (69%)
No	45 (28%)	46 (29%)	91 (28%)	49 (31%)
Baseline IGA				
3 – Moderate	102 (65%)	111 (69%)	213 (67%)	114 (72%)
4 – Severe	56 (35%)	50 (31%)	106 (33%)	45 (28%)
PASI				
Mean (SD)	20.5 (6.9)	19.9 (6.1)	20.2 (6.5)	19.0 (5.9)
Median	18.1	19.0	18.5	17.4
Range	12 – 44.1	12 – 42.6	12 – 44.1	12 – 38
Percent BSA				
Mean (SD)	26.5 (15.9)	25.2 (12.4)	25.9 (14.2)	25.0 (14.4)
Median	20.0	22.0	20.0	20.0
Range	10 – 81	10 – 80	10 – 81	10 – 76
Baseline Scalp IGA				
0 – Clear	10 (6%)	5(3%)	15 (5%)	15 (10%)
1 – Almost Clear	6 (4%)	2 (1%)	8 (3%)	5 (3%)
2 – Mild	17 (11%)	37 (23%)	54 (17%)	33 (21%)
3 – Moderate	94 (59%)	93 (58%)	187 (69%)	83 (52%)
4 – Severe	31 (20%)	24 (15%)	55 (17%)	22 (14%)
Missing	0 (0%)	0 (0%)	0 (0%)	1 (1%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
Abbreviations: BKZ=bimekizumab; ADA=adalimumab; Q4W=every 4 weeks; Q8W=every 8 weeks
* Randomized Set (RS): all randomized subjects
Note: BKZ Total= BKZ Q4W + BKZ Q4W/Q8W

Table 17: Demographics and Baseline Disease Characteristics for Trials PS0009 and PS0013 (RS*)

		Trial PS0009			Trial PS0013	
		BKZ Q4W (N=321)	**USTE (N=163)**	**PBO (N=83)**	**BKZ Q4W (N=349)**	**PBO (N=86)**
Age (years)	Mean (SD)	45.2 (14.0)	46.0 (13.6)	49.7 (13.6)	44.5 (12.9)	43.5 (13.1)
	Median	43.0	47.0	50.0	45.0	42.0
	Range	18 – 81	18 – 79	19 – 78	18 – 81	18 – 77
	<65	287 (89%)	145 (89%)	73 (88%)	328 (94%)	82 (95%)
	≥65	34 (11%)	18 (11%)	10 (12%)	21 (6%)	4 (5%)
Sex	Male	229 (71%)	117 (72%)	60 (72%)	255 (73%)	58 (67%)
	Female	92 (29%)	46 (28%)	23 (28%)	94 (27%)	28 (33%)
Race	White	237 (74%)	120 (74%)	63 (76%)	324 (93%)	79 (92%)
	Black or African American	9 (3%)	3 (2%)	0 (0%)	6 (2%)	0 (0%)
	Native Hawaiian or Other Pacific Islander	1 (<1%)	1 (1%)	0 (0%)	2 (1%)	0 (0%)
	Asian	71 (22%)	36 (22%)	20 (24%)	13 (4%)	5 (6%)
	Missing	3 (1%)	3 (2%)	0 (0%)	4 (1%)	2 (2%)
Weight (Kg)	Mean (SD)	88.7 (23.1)	87.2 (21.1)	89.1 (26.4)	88.7 (20.6)	91.7 (22.2)
	Median	87.3	86.3	83.4	86.0	89.3
	Range	42.9 – 217.9	42.1 – 142.4	44.5 – 179.6	40.1 – 157.9	57 – 154
	<100 Kg	225 (70%)	120 (74%)	60 (72%)	255 (73%)	57 (66%)
	≥100 Kg	96 (30%)	43 (26%)	23 (28%)	94 (27%)	29 (34%)
Country	US	67 (21%)	34 (21%)	15 (18%)	72 (21%)	13 (15%)
	Non-US	254 (79%)	129 (79%)	68 (82%)	277 (79%)	73 (85%)
Prior Systemic Therapy	Yes	267 (83%)	132 (81%)	64 (77%)	276 (79%)	71 (83%)
	No	54 (17%)	31 (19%)	19 (12%)	73 (21%)	15 (17%)
Baseline IGA	2 – Mild	1 (<1%)	1 (1%)	1 (1%)	0 (0%)	0 (0%)
	3 – Moderate	201 (63%)	96 (59%)	54 (65%)	242 (69%)	62 (72%)
	4 – Severe	119 (37%)	66 (40%)	28 (34%)	107 (31%)	24 (28%)
PASI	Mean (SD)	22.0 (8.6)	21.3 (8.3)	20.0 (6.8)	20.4 (7.6)	20.1 (7.5)
	Median	19.4	18.5	17.6	18.0	17.8
	Range	11.7 – 52.8	12 – 51.4	12 – 39.2	12 – 49.5	12.1 – 44.8
Percent BSA	Mean (SD)	27.3 (16.7)	29.0 (17.1)	27.0 (16.3)	24.6 (15.2)	24.4 (16.0)
	Median	22.0	23.0	21.0	18.0	20.0
	Range	10 – 97	10 – 88	11 – 84	10 – 86	10 – 80
Baseline Scalp IGA	0 – Clear	17 (5%)	7 (4%)	10 (12%)	29 (8%)	8 (9%)
	1 – Almost Clear	17 (5%)	9 (5%)	1 (1%)	9 (3%)	4 (5%)
	2 – Mild	50 (16%)	32 (20%)	10 (12%)	59 (17%)	17 (20%)
	3 – Moderate	173 (54%)	84 (51%)	46 (55%)	202 (58%)	50 (58%)
	4 – Severe	62 (19%)	30 (18%)	16 (19%)	49 (14%)	7 (8%)
	Missing	2 (1%)	1 (1%)	0 (0%)	1 (1%)	0 (0%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
Abbreviations: BKZ=bimekizumab; Uste=ustekinumab; PBO=placebo; Q4W=every 4 weeks
* Randomized Set (RS): all randomized subjects

8.1.5. Results for the Co-Primary Efficacy Endpoints against Placebo

Table 18 presents the results for the co-primary efficacy endpoints at Week 16 for Trials PS0009 and PS0013. Bimekizumab was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials. A slightly higher treatment effect (by about 10%) is observed in Trial PS0013 compared to Trial PS0009 for both co-primary efficacy endpoints. The results for the PP and FAS populations were very similar (results for PP and FAS not presented herein).

Table 18: Results for the Co-Primary Endpoints at Week 16 – Trials PS0009 and PS0013 (RS; NRI[1])

	Trial PS0009		Trial PS0013	
	BKZ Q4W (N=321)	**PBO (N=83)**	**BKZ Q4W (N=349)**	**PBO (N=86)**
IGA 0/1	270 (84%)	4 (5%)	323 (93%)	1 (1%)
Difference from PBO (95% CI)[2]	79% (73%, 85%)		91% (88%, 95%)	
P-Value[2]	<0.001		<0.001	
PASI-90	273 (85%)	4 (5%)	317 (91%)	1 (1%)
Difference from PBO (95% CI)[2]	80% (74%, 86%)		90% (86%, 93%)	
P-Value[2]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; CI = Confidence Interval
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region and prior biologic use
Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.

Table 19 presents the number of subjects with missing data for the co-primary efficacy endpoints by week, treatment arm, and trial. The amount of missing data is relatively small. In Trial PS0009, the amount of missing data at Week 16 was higher in the placebo arm compared to the bimekizumab arm and compared to the placebo arm in Trial PS0013.

Table 19: Missing Data for the Co-Primary Endpoints by Week During the Initial Treatment Period - Trials PS00098, PS0009 and PS0013 (RS[1])

	Trial PS0009		Trial PS0013	
	BKZ Q4W (N=321)	**PBO (N=83)**	**BKZ Q4W (N=349)**	**PBO (N=86)**
Week 1	3 (1%)	5 (6%)	1 (1%)	0 (0%)
Week 2	3 (1%)	1 (1%)	7 (2%)	2 (2%)
Week 4	3 (1%)	3 (4%)	1 (<1%)	1 (1%)
Week 8	4 (1%)	4 (5%)	2 (1%)	3 (3%)
Week 12	7 (2%)	5 (6%)	10 (3%)	3 (3%)
Week 16	14 (4%)	7 (8%)	9 (3%)	3 (3%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO = Placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects

The primary method of handling missing data specified in the protocol was non-responder imputation (NRI). The protocol specified the following three sensitivity analyses for the handling

of missing data: (i) MI-MCMC/Monotone Regression, (ii) MI-MCMC/Reference-based, (iii)observed cases (missing data is not imputed) and (iv) impute missing data using LOCF. This reviewer conducted an additional sensitivity analysis under the worst case scenario (i.e., missing data for bimekizumab is imputed as non-responders and missing data for placebo is imputed as responders).

Table 20 and Table 21 present the results for the co-primary efficacy endpoints by the various imputation methods in Trials PS0009 and PS0013, respectively. For both trials, the results were very similar across the various methods. In the extreme case (i.e., worst case scenario), bimekizumab remained statistically significant to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials.

Table 20: Results for the Co-Primary Endpoints at Week 16 with Different Approaches of Handling the Missing Data at Week 16 – Trial PS0009 (RS[1])

	BKZ Q4W (N=321)	PBO (N=83)	Difference (P-value)[2]
IGA 0/1			
NRI (Primary)	84%	5%	79% (<0.001)
MI-MCMC/ Monotone Regression	87%	5%	82% (<0.001)
MI-MCMC/ Reference-based	85%	5%	80% (<0.001)
Observed Cases	88%	5%	83% (<0.001)
LOCF	87%	5%	82% (<0.001)
Worst Case Scenario	84%	13%	71% (<0.001)
PASI-90			
NRI (Primary)	85%	5%	80% (<0.001)
MI-MCMC/ Monotone Regression	88%	5%	82% (<0.001)
MI-MCMC/ Reference-based	85%	5%	80% (<0.001)
Observed Cases	89%	5%	84% (<0.001)
LOCF	87%	5%	83% (<0.001)
Worst Case Scenario	85%	13%	72% (<0.001)

Source: Statistical Reviewer's Analysis (NRI, MI, Observed Cases and LOCF same as Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO = Placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects
[2] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region and prior biologic use
Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.
Note: One subject in the placebo arm had baseline PASI score 30.3

Table 21: Results for the Co-Primary Endpoints at Week 16 with Different Approaches of Handling the Missing Data at Week 16 – Trial PS0013 (RS[1])

	BKZ Q4W (N=349)	PBO (N=86)	Difference (P-value)[2]
IGA 0/1			
NRI (Primary)	93%	1%	91% (<0.001)
MI-MCMC/ Monotone Regression	94%	1%	93% (<0.001)
MI-MCMC/ Reference-based	94%	1%	93% (<0.001)
Observed Cases	95%	1%	94% (<0.001)
LOCF	94%	1%	93% (<0.001)
Worst Case Scenario	93%	5%	91% (<0.001)
PASI-90			
NRI (Primary)	91%	1%	90% (<0.001)
MI-MCMC/ Monotone Regression	92%	1%	91% (<0.001)
MI-MCMC/ Reference-based	91%	1%	90% (<0.001)
Observed Cases	93%	1%	92% (<0.001)
LOCF	92%	1%	91% (<0.001)
Worst Case Scenario	90%	5%	86% (<0.001)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO = Placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects
[2] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region and prior biologic use
Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.

8.1.6. Results for the Secondary Efficacy Endpoints During the Initial Treatment Period against Placebo

This section summarizes the results for the investigator-reported major secondary efficacy endpoints during the initial treatment period in comparison to placebo. Section 8.1.7 summarizes the results for the major secondary efficacy endpoints based on patient reported outcomes (PROs). For comparisons against active comparators, refer to Section 8.1.9.

Table 22 presents the results for the investigator reported major secondary efficacy endpoints against placebo for Trials PS0009 and PS0013. In both trials, bimekizumab was statistically superior to placebo (p-values < 0.001) for all of the major secondary efficacy endpoints presented in Table 22.

To evaluate the impact of treatment with bimekizumab on psoriasis located on the scalp, the applicant included a secondary efficacy endpoint based on the Scalp Investigator's Global Assessment (Scalp IGA) scale, see Table 87 in Appendix 19.5. Specifically, the applicant evaluated the proportion of subjects with Scalp IGA score of 0 or 1 with at least a 2-grade improvement from baseline at Week 16 for bimekizumab compared to placebo. This analysis was pre-specified to include only subjects with a baseline Scalp IGA score of at least 2 (mild) and the results are presented in Table 22. Approximately 91% and 92% of subjects had Scalp IGA score≥2 at baseline and were included in the analysis for Trials PS0009 and PS0013, respectively. In both trials, bimekizumab was statistically superior to placebo (p-values < 0.001) for this endpoint at Week 16.

Table 22: Results for the Investigator Reported Secondary Endpoints During the Initial Treatment Period Against Placebo – Trials PS0009 and PS0013 (RS; NRI[1])

	Trial PS0009		Trial PS0013	
Endpoint	**BKZ Q4W (N=321)**	**PBO (N=83)**	**BKZ Q4W (N=349)**	**PBO (N=86)**
PASI-100 at Week 16	188 (59%)	0 (0%)	238 (68%)	1 (1%)
Difference (95% CI)[2]	59% (53%, 64%)		67% (62%, 72%)	
P-Value[2]	<0.001		<0.001	
IGA 0 at Week 16	188 (59%)	0 (0%)	243 (70%)	1 (1%)
Difference (95% CI)[2]	59% (53%, 64%)		69% (64%, 74%)	
P-Value[2]	<0.001		<0.001	
PASI-75 at Week 4	247 (77%)	2 (2%)	265 (76%)	1 (1%)
Difference (95% CI)[2]	74% (69%, 80%)		75% (70%, 80%)	
P-Value[2]	<0.001		<0.001	
Scalp IGA 0/1 at Week 16[3]	240/285 (84%)	11/72 (15%)	286/310 (92%)	5/74 (7%)
Difference (95% CI)[2]	62% (52%, 71%)		77% (70%, 83%)	
P-Value[2]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADIGA.xpt, ADPASI.xpt, ADSIGA.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; CI=Confidence Interval
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region and prior biologic use
[3] Scalp IGA 0/1 response was defined as Clear (0) or Almost clear (1) with at least a 2-grade improvement from baseline. Only subjects with a baseline score of at least 2 were included.
Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.

8.1.7. Patient Reported Outcomes (PROs)

In Trials PS0009 and PS0013, the protocols specified secondary endpoints based on the Patient Symptom Diary (PSD) responses for pain, itch, and scaling at Week 16. PSD is a Patient Reported Outcome measure used to assess key symptoms relevant to subjects with moderate to severe chronic plaque psoriasis. The PSD was used to collect data as a daily diary about the patient's experience of the severity of the sign, symptom or impact, at its worst during the past 24 hours, on an 11-point numeric rating scale (NRS). The PSD was collected up to Week 16/Week 24 visit in Trials PS0009 and PS0013.

The secondary endpoints were defined based on a responder definition on each PSD item (pain, itch, and scaling) as listed below:

- Proportion of subjects achieving PSD Item 1 (skin itching) score ≥ 2.39 at Week 16.
- Proportion of subjects achieving PSD Item 3 (skin pain) score ≥1.98 at Week 16.
- Proportion of subjects achieving PSD Item 5 (skin scaling) score >2.86 at Week 16.

Table 23 presents the results for these endpoints. In both trials, bimekizumab was statistically superior to placebo (p-values < 0.001) for these endpoints.

The full PRO Evidence Dossier, which was submitted to support the development of the PSD, was reviewed by the Clinical Outcome Assessment (COA) review team. Dr. Mira Patel, concluded that the three PSD items are appropriate for measurement of skin pain, skin itching, and skin

scaling due to plaque psoriasis; and validly and reliably measure these clinically relevant and important atopic dermatitis symptoms. However, the COA reviewer noted that "it is unknown whether the patients observed clinically meaningful within-patient score changes in each of the items due to deficiencies of the external anchors". In addition, the COA reviewer noted that: 1) these deficiencies limit the utility for anchor-based analyses as it does not fully address the question of clinical meaningfulness of the target COA endpoint, and 2) change from baseline in each of the three PSD item scores showed a pronounced separation between the treatment and placebo arm across a range that likely includes a clinically meaningful change threshold for all two trials.

The statistical reviewer repeated the responder analyses using a 4-point threshold; see Table 24. Furthermore, the statistical reviewer conducted additional analyses evaluating the proportion of patients achieving a score of 0 in all three symptoms (pain, itch, scaling). In Trial PS0009, 33% (75/225) of the subjects randomized to bimekizumab had a zero score in all three PSD symptoms compared to 0% of the subjects in the placebo arm. Similarly, in Trial PS0013, 33% (95/286) of the subjects randomized to bimekizumab had a zero score in all three PSD symptoms compared to 0% of the subjects in the placebo arm.

Table 23: Responder Analysis for PSD Symptoms – Trials PS0009 and PS0013 (RS; NRI[1])

PSD Symptom	Trial PS0009		Trial PS0013	
	BKZ Q4W (N=321)	PBO (N=83)	BKZ Q4W (N=349)	PBO (N=86)
Pain				
N[2]	229	54	255	67
≥1.98-point reduction	177 (77%)	9 (17%)	201 (79%)	6 (9%)
Difference from PBO (95% CI)[3]	61% (49%, 72%)		70% (61%, 78%)	
P-Value[3]	<0.001		<0.001	
Itch				
N[2]	244	61	278	72
≥2.39-point reduction	187 (77%)	8 (13%)	210 (75%)	4 (6%)
Difference from PBO (95% CI)[3]	64% (54%, 74%)		70% (62%, 77%)	
P-Value[3]	<0.001		<0.001	
Scaling				
N[2]	247	64	291	70
≥2.66-point reduction	198 (80%)	10 (16%)	230 (79%)	5 (7%)
Difference from PBO (95% CI)[3]	65% (55%, 75%)		72% (64%, 80%)	
P-Value[3]	<0.001		<0.001	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADPSD.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; CI=Confidence Interval
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] N is the number of subjects with a baseline item score of at least 1.98, 2.39, and 2.66 for pain, itch and scaling respectively.
[3] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region and prior biologic use
Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.

Table 24: Four-point Responder Analysis for PSD Symptoms – Trials PS0009 and PS0013 (RS; NRI[1])

PSD Symptom	Trial PS0009		Trial PS0013	
	BKZ Q4W (N=321)	PBO (N=83)	BKZ Q4W (N=349)	PBO (N=86)
Pain				
N[2]	190	48	209	49
≥4-point reduction	140 (74%)	5 (10%)	148 (71%)	0 (0%)
Difference from PBO (95% CI)[3]	62% (52%, 73%)		71% (64%, 77%)	
Nominal P-Value[3]	<0.001		<0.001	
Itch				
N[2]	222	53	244	60
≥4-point reduction	151 (68%)	6 (11%)	161 (66%)	0 (0%)
Difference from PBO (95% CI)[3]	57% (46%, 67%)		65% (59%, 71%)	
Nominal P-Value[3]	<0.001		<0.001	
Scaling				
N[2]	225	56	262	65
≥4-point reduction	171 (76%)	6 (11%)	198 (76%)	1 (1%)
Difference from PBO (95% CI)[3]	66% (55%, 76%)		74% (68%, 80%)	
Nominal P-Value[3]	<0.001		<0.001	

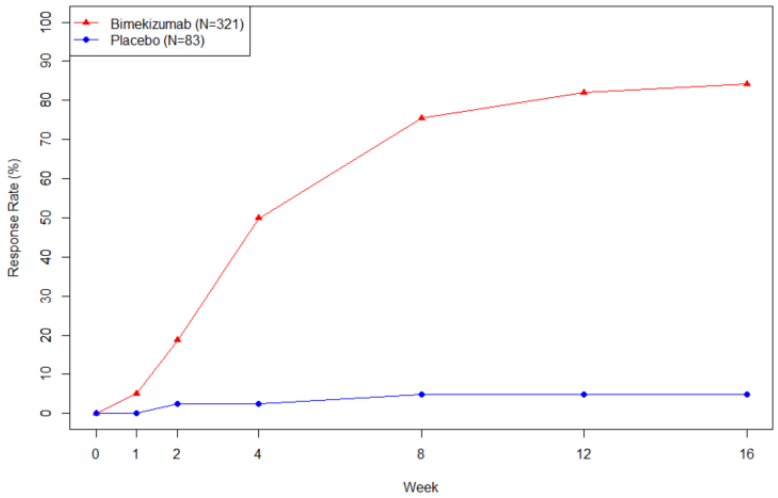
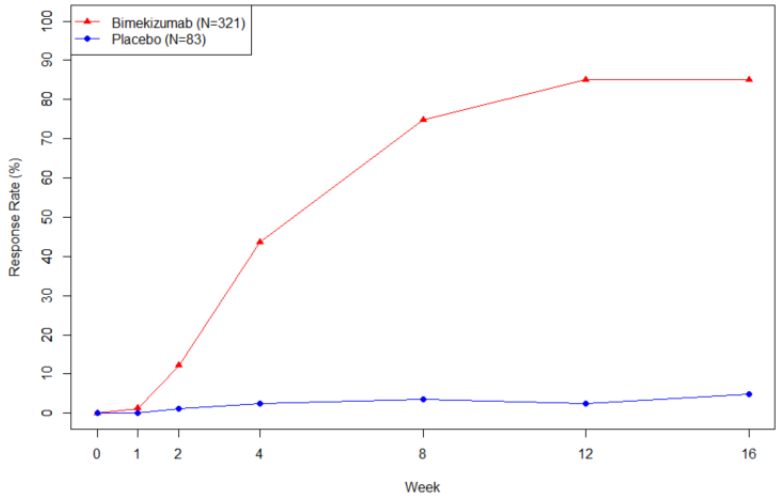
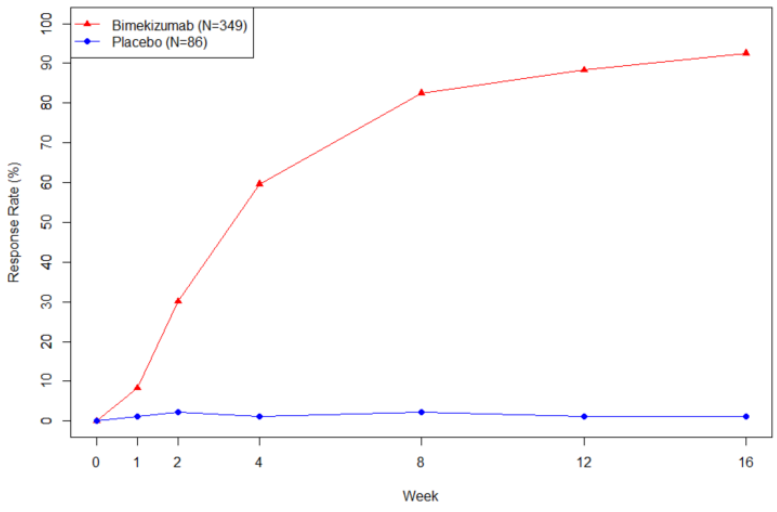
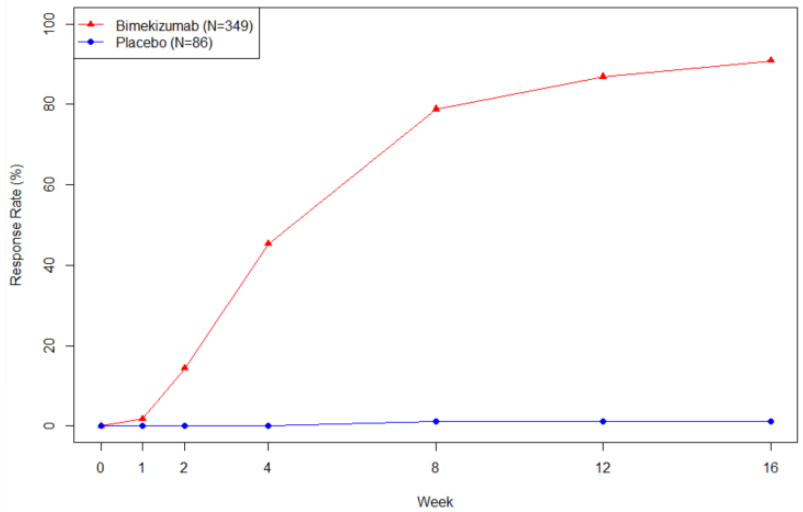
Source: Reviewer's Analysis (similar to Applicant's Analysis); ADPSD.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; CI=Confidence Interval
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] N is the number of subjects with a baseline item score of at least 4.
[3] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region and prior biologic use
Note: For Trial PS0013, Asia/Australia and Western Europe regions are pooled since at least one had less than 10% of the overall enrollment.

8.1.8. Efficacy Over Time

8.1.8.1. Initial Treatment Period

Figure 17 presents the results for IGA score of 0 or 1 and PASI 90 through Week 16 for Trials PS0009 and PS0013, respectively.

Figure 17: Results for IGA Score of 0 or 1 and PASI 90 Through Week 16 - Trials PS0009 and PS0013 (RS;NRI[1])

IGA 0/1	PASI-90
Trial PS0009 	
Trial PS0013 	

Source: Statistical Reviewer's Analysis; ADIGA.xpt, ADPASI.xpt
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

8.1.8.2. Maintenance Period or Randomized Withdrawal Period

Trial PS0008:

After the 16-week initial treatment period in Trial PS0008, subjects entered the 40-week maintenance treatment period. During the maintenance period, subjects originally randomized to bimekizumab 320mg Q4W continued the same treatment, subjects originally randomized to bimekizumab 320mg Q4W/Q8W received bimekizumab Q8W from Week 16 through Week 56, and subjects originally randomized to adalimumab received bimekizumab 320mg Q4W from Week 24 through Week 56. A total of 456 subjects were included in the Maintenance Set (MS), defined as all subjects who received at least 1 dose of active IMP in the maintenance treatment period. For the disposition of subjects during the maintenance period see Table 25.

Table 25: Disposition of Subjects during the Maintenance Period – Trial PS0008 (MS*)

	BKZ Q4W (N=153)	**BKZ Q4W/Q8W (N=154)**	**ADA (N=149)**
Completed Week 24	152 (99%)	149 (97%)	149 (100%)
Completed Week 56	143 (93%)	143 (93%)	133 (89%)
Discontinued between Week 16 and Week 24	1 (1%)	5 (3%)	0 (0%)
Discontinued between Week 24 and Week 56	9 (6%)	6 (4%)	16 (11%)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
Abbreviations: BKZ=bimekizumab; ADA=adalimumab; Q4W=every 4 weeks; Q8W=every 8 weeks
* Maintenance Set (MS): all subjects who received at least 1 dose of active IMP in the maintenance treatment period.

Table 26 presents PASI90 and IGA 0/1 response rates at Week 56. Results were similar between the bimekizumab Q4W and bimekizumab Q8W maintenance arms.

Table 26: PASI90 and IGA 0/1 Response Rates at Week 56 – Trial PS0008 (RS; NRI[1])

	BKZ Q4W/Q4W (N=158)	**BKZ Q4W/Q8W (N=161)**
PASI 90	134 (85%)	133 (83%)
IGA 0/1	130 (82%)	134 (83%)

Source: Statistical Reviewer's Analysis (same to Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; Q4W=every 4 weeks; Q8W=every 8 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

Trial PS0013:

At Week 16, subjects who achieved a PASI90 response entered into a 40-week, double-blind, placebo-controlled randomized-withdrawal period. Subjects who did not achieve a PASI90 response at the Week 16 visit were allocated to the escape arm (open-label bimekizumab 320 mg). During the randomized-withdrawal period, subjects initially randomized to bimekizumab 320mg Q4W who achieved a PASI 90 were re-randomized 1:1:1 to either bimekizumab 320mg Q4W or bimekizumab 320mg Q8W or placebo. All subjects initially randomized to placebo who achieved a PASI 90 response at Week 16 continued to receive placebo (Q4W). All subjects who relapsed at Week 20 or later during the randomized-withdrawal period (up to Week 56) were allocated to the escape arm (open-label bimekizumab 320 mg Q4W). Relapse was defined as not achieving a PASI75 response at Week 20 or later during the Randomized-Withdrawal Period.

A total of 312 subjects were PASI90 responders at Week 16 and received at least 1 dose of the IMP during the randomized-withdrawal period. Among these subjects, 1 subject was randomized to the placebo group in the initial treatment period; this subject started and completed the randomized-withdrawal period in the placebo/placebo arm. In addition, the Applicant noted that 6 subjects who entered the randomized-withdrawal period were moved to the escape arm without meeting the escape criteria; these subjects were excluded from both the Week 16 Responder Set (WKL16ResS). The Applicant noted in the CSR for Trial PS0013 that incorrect escape was due to site error, and the occurrence was distributed across multiple sites. For the disposition of subjects during the randomized-withdrawal period among subjects originally receiving bimekizumab see Table 27. It should be noted that one subject was re-randomized despite having a missing PASI score at Week 16.

Table 27: Disposition of Subjects during the Randomized-Withdrawal Period – Trial PS0013 (WK16ResS*)

	BKZ Q4W/Q4W (N=106)	**BKZ Q4W/Q8W (N=100)**	**BKZ Q4W/PBO (N=105)**
Completed Randomized-Withdrawal Period	33 (31%)	93 (93%)	94 (89%)
Received Escape Treatment	7 (7%)	4 (4%)	67 (64%)
Discontinued Trial	5 (5%)	3 (3%)	6 (6%)

Source: Statistical Reviewer's Analysis (same to Applicant's Analysis); ADSL.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks
* Week 16 Responder Set (WKL16ResS): all subjects who achieve a PASI90 response at Week 16 and receive at least 1 dose of the IMP during the randomized-withdrawal period

Table 28 presents the proportion of Week 16 responders (PASI-90, IGA 0/1 and PASI-100) who maintained their response at Week 56. The proportion of subjects that maintained their response at Week 56 was similar between the bimekizumab Q4W and bimekizumab Q8W maintenance arms. The proportion of subjects that maintained their response at Week 48 was higher in the bimekizumab arms compared to placebo. Figure 18 presents IGA 0/1 and PASI-90 response rates during the randomized-withdrawal period.

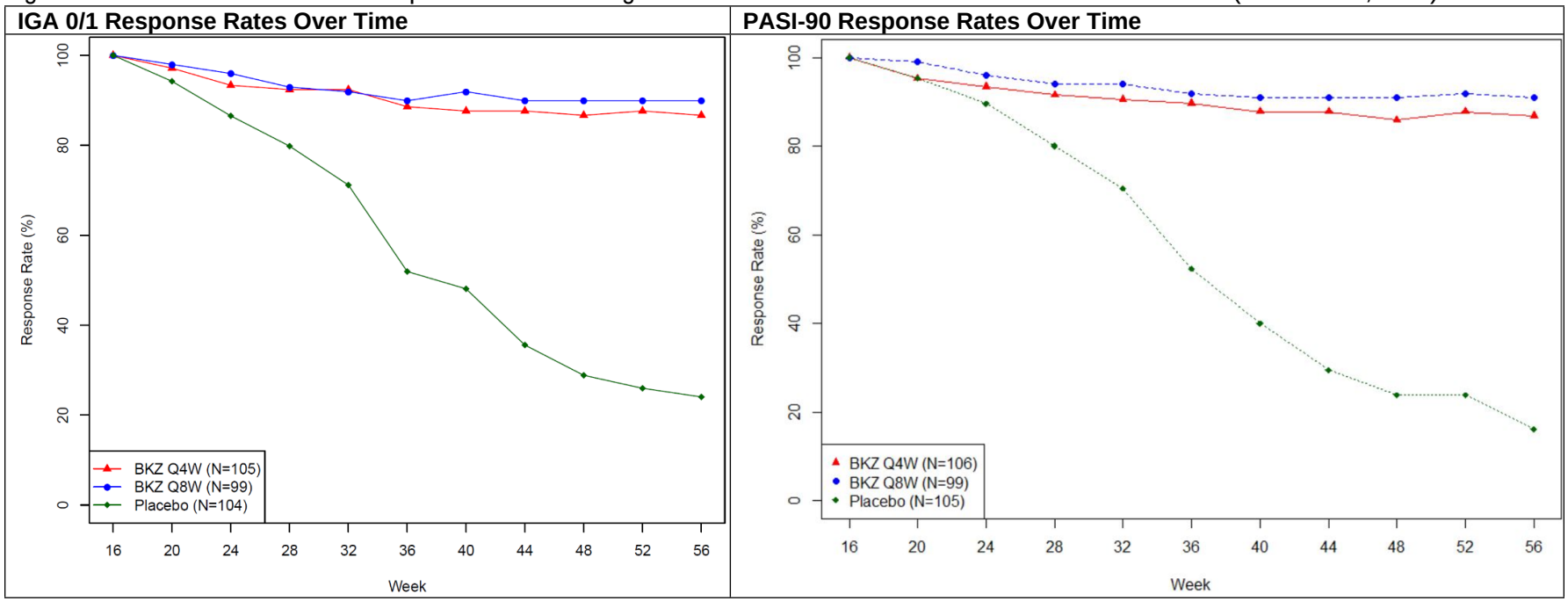
Table 28: Maintenance of Response at Week 56 – Trial PS0013 (WK16ResS; NRI[1])

Endpoint	**BKZ Q4W/Q4W (N=106)**	**BKZ Q4W/Q8W (N=100)**	**BKZ Q4W/PBO (N=105)**
PASI-90 among Week 16 PASI-90 responders	92/106 (87%)	91/99[2] (91%)	17/105 (16%)
IGA 0/1 among Week 16 IGA 0/1 responders	91/105 (87%)	89/99 (90%)	25/104 (24%)
PASI-100 among Week 16 PASI-100 responders	63/73 (86%)	71/82 (87%)	9/78 (11%)

Source: Statistical Reviewer's Analysis (same to Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks; Q8W=every 8 weeks
[1] Week 16 Responder Set (WKL16ResS): all subjects who achieve a PASI90 response at Week 16 and receive at least 1 dose of the IMP during the randomized-withdrawal period; missing data are imputed using non-responder imputation (NRI)
[2] one subject was re-randomized despite having a missing PASI score at Week 16.

For PASI-90 responders at Week 16 who were re-randomized to treatment withdrawal, the median time to loss of PASI-90 was approximately 24 weeks. In addition, for IGA 0/1 responders at Week 16 who were re-randomized to treatment withdrawal, the median time to loss of IGA 0/1 response was also approximately 24 weeks.

Figure 18: IGA 0/1 and PASI-90 Response Rates During the Randomized-Withdrawal Period - Trial PS0013 (WK16ResS; NRI[1])



Source: Statistical Reviewer's Analysis; ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; Q4W=every 4 weeks; Q8W=every 8 weeks
[1] Week 16 Responder Set (WKL16ResS): all subjects who achieve a PASI90 response at Week 16 and receive at least 1 dose of the IMP during the randomized-withdrawal period; missing data are imputed using non-responder imputation (NRI)

8.1.9. Comparison to Active Control

Trial PS0008 included adalimumab as an active comparator and Trial PS0009 included ustekinumab as an active comparator. In Trial PS0008, all subjects randomized to adalimumab in the North American sites (i.e., U.S. and Canada) received US-sourced adalimumab. Subjects randomized to adalimumab at all other sites received EU-approved adalimumab. In Trial PS0009, US-sourced ustekinumab was used in all sites in the US; all other sites received EU-approved ustekinumab. As the Applicant did not provide an adequate scientific bridge between U.S. licensed adalumimab/ustekinumab and EU-approved adalimumab/ustekinumab, these products are considered distinct products for the purpose of this review.

Table 29 and Table 30 present the efficacy results at Week 16 for the overall population and by country for Trials PS0008 and PS0009, respectively. In both trials, bimekizumab was statistically superior (p-values < 0.001) to the active control in both the overall population and the US-sourced subgroup for all efficacy endpoints.

Table 29: Results for the Co-Primary Endpoints and Secondary Endpoints During the Initial Treatment Period Against Adalimumab – Trial PS0008 (RS; NRI[1])

Endpoint	BKZ Q4W (N=319)	ADA (N=159)	Difference (95% CI)[2]	P-Value[2]
IGA 0/1 at Week 16 (Co-Primary)	272 (85%)	91 (57%)	28% (20%, 37%)	<0.001
North America[3]	122 (83%)	38 (53%)	29% (16%, 43%)	<0.001
All Other[4]	150 (87%)	53 (60%)	27% (16%, 38%)	<0.001
PASI-90 at Week 16 (Co-Primary)	275 (86%)	75 (47%)	39% (31%, 48%)	<0.001
North America[3]	117 (80%)	30 (42%)	37% (24%, 51%)	<0.001
All Other[4]	158 (92%)	45 (51%)	41% (29%, 52%)	<0.001
PASI-100 at Week 16 (Secondary)	194 (61%)	38 (24%)	37% (29%, 45%)	<0.001
North America[3]	82 (56%)	18 (25%)	31% (18%, 43%)	<0.001
All Other[4]	112 (65%)	20 (23%)	43% (31%, 54%)	<0.001
PASI-75 at Week 4 (Secondary)	244 (76%)	50 (31%)	45% (36%, 53%)	<0.001
North America[3]	118 (80%)	25 (35%)	45% (32%, 58%)	<0.001
All Other[4]	126 (73%)	25 (28%)	45% (33%, 56%)	<0.001

Source: Statistical Reviewer's Analysis (similar to Applicant's Analysis); ADIGA.xpt, ADPASI;xpt
Abbreviations: BKZ=bimekizumab; ADA=adalimumab; Q4W=every 4 weeks; CI=Confidence Interval
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region (only for the overall population) and prior biologic use
[3] US and Canada. Sample sizes = (NB, NA) = (147,71)
[4] Germany, Czech Republic, Hungary, Poland, Russian Federation, Australia, Republic of Korea, Taiwan. Sample sizes = (NB, NA) = (172, 88).

Table 30: Results for the Secondary Endpoints During the Initial Treatment Period Against Ustekinumab – Trial PS0009 (RS; NRI[1])

Endpoint	BKZ Q4W (N=321)	USTE (N=163)	Difference (95% CI)[2]	P-Value[2]
IGA 0/1 at Week 16	270 (84%)	87 (53%)	30% (22%, 39%)	<0.001
USA[3]	52 (78%)	14 (41%)	36% (16%, 56%)	<0.001
All Other[4]	218 (86%)	73 (57%)	29% (20%, 39%)	<0.001
PASI-90 at Week 16	273 (85%)	82 (50%)	35% (27%, 43%)	<0.001
USA[3]	52 (78%)	11 (32%)	45% (26%, 65%)	<0.001
All Other[4]	221 (87%)	70 (54%)	33% (23%, 42%)	<0.001
IGA 0/1 at Week 12	263 (82%)	85 (52%)	30% (21%, 38%)	<0.001
USA[3]	55 (82%)	13 (38%)	43% (24%, 62%)	<0.001
All Other[4]	208 (82%)	72 (56%)	26% (17%, 36%)	<0.001
PASI-90 at Week 12	273 (85%)	71 (44%)	41% (33%, 49%)	<0.001
USA[3]	55 (82%)	12 (35%)	47% (28%, 65%)	<0.001
All Other[4]	218 (86%)	59 (46%)	40% (30%, 50%)	<0.001
PASI-75 at Week 4	247 (77%)	25 (15%)	61% (54%, 69%)	<0.001
USA[3]	49 (73%)	4 (12%)	61% (46%, 76%)	<0.001
All Other[4]	198 (78%)	21 (16%)	62% (53%, 70%)	<0.001

Source: Reviewer's Analysis (similar to Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; USTE=ustekinumab; Q4W=every 4 weeks; CI=Confidence Interval
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Estimate, 95% CI and p-value for the difference are based on CMH test stratified for region (only for the overall population) and prior biologic use
[3] Sample sizes = (NB, NU) = (67,34)
[4] Germany, Czech Republic, Hungary, Poland, Russian Federation, Australia, Republic of Korea, Taiwan. Sample sizes = (NB, NU) = (254, 129).

The protocol for Trial PS0008 specified comparison of the secondary endpoints of PASI-100, PASI-90 and IGA 0/1 at Week 24 against adalumimab. The results for the endpoints at Week 24 are presented in Table 31 without combining the two bimekizumab arms and are considered exploratory.

Post-hoc sensitivity analysis for secondary endpoints in Trial PS0008:
On July 15, 2019, the Applicant notified the Agency that during the conduct of the Trial PS0008 24 subjects in the bimekizumab 320mg Q4W/Q8W arm received incorrect treatment at Week 20 due to an Interactive Response Technology (IRT) system programming issue. All subsequent treatments were administered per the protocol. In the clinical study report (page 114), the Applicant noted that at the time of Week 20 dosing, the IRT programming had not been updated to reflect the treatment reallocation which occurred based on changes in Protocol Amendment 1 (dated October 15, 2017). Therefore, instead of receiving placebo treatment at Week 20 to switch from bimekizumab 320mg Q4W to Q8W dosing, 24 subjects in the bimekizumab 320mg Q4W/Q8W arm received bimekizumab 320mg treatment at Week 20.

The main analyses of the endpoints at Week 24 included all subjects in the RS; however, the potential impact of this on the Week 24 secondary endpoints (PASI90, PASI100, and IGA 0/1 response) was assessed through sensitivity analyses excluding these subjects from the analysis population. The results excluding these subjects are presented in Table 31.

Table 31: Results for the Secondary Endpoints at Week 24 – Trial PS0008 (RS; NRI[1])

	Including All Subjects			Excluding Subjects with Dosing Error at Week 20		
Endpoint	**BKZ Q4W/Q4W (N=158)**	**BKZ Q4W/Q8W (N=161)**	**ADA (N=159)**	**BKZ Q4W/Q4W (N=158)**	**BKZ Q4W/Q8W (N=137)**	**ADA (N=159)**
PASI-100	107 (68%)	106 (66%)	47 (30%)	107 (68%)	93 (68%)	47 (30%)
North America[2]	44 (60%)	48 (65%)	22 (31%)	44 (60%)	48 (65%)	22 (31%)
All Other[3]	63 (74%)	58 (67%)	25 (28%)	63 (74%)	58 (67%)	25 (28%)
PASI-90	136 (86%)	137 (85%)	82 (52%)	136 (86%)	117 (85%)	82 (52%)
North America[2]	55 (73%)	61 (82%)	35 (49%)	55 (75%)	61 (82%)	35 (49%)
All Other[3]	81 (95%)	76 (87%)	47 (53%)	81 (95%)	76 (87%)	47 (53%)
IGA 0/1	136 (86%)	140 (87%)	92 (58%)	136 (86%)	118 (86%)	92 (58%)
North America[2]	56 (77%)	64 (86%)	38 (53%)	56 (77%)	64 (86%)	38 (53%)
All Other[3]	80 (94%)	76 (87%)	54 (61%)	80 (94%)	76 (87%)	54 (61%)

Source: Reviewer's Analysis (similar to Applicant's Analysis); ADIGA.xpt, ADPASI.xpt
Abbreviations: BKZ=bimekizumab; ADA=adalimumab; Q4W=every 4 weeks; Q8W=every 8 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] US and Canada. Sample sizes including all subjects= (NBQ4, NBQ8, NA) = (73, 74, 71)
[3] Germany, Czech Republic, Hungary, Poland, Russian Federation, Australia, Republic of Korea, Taiwan. Sample sizes including all subjects= (NBQ4, NBQ8, NA) = (85, 87, 88)

Maintenance Period:

After the 16-week initial treatment period in Trial PS0009, subjects entered the 36-week maintenance treatment period. Subjects in the bimekizumab arm continued to receive bimekizumab 320mg Q4W, subjects in the ustekinumab treatment arm continued on ustekinumab and subjects in the placebo arm received bimekizumab 320mg Q4W starting at Week 16. A total of 537 subjects were included in the Maintenance Set (MS), defined as all subjects who received at least 1 dose of active IMP in the maintenance treatment period. For the disposition of subjects during the maintenance period see Table 32. The protocol for Trial PS0009 specified comparison of the secondary endpoints of PASI-90 and IGA 0/1 at Week 52 against ustekinumab. The results for such endpoints are presented in Table 33 without combining the two bimekizumab arms. These endpoints are considered exploratory.

Table 32: Disposition of Subjects during the Maintenance Period – Trial PS0009 (MS*)

	BKZ Q4W/Q4W (N=321)	**PBO/BKZ Q4W (N=83)**	**USTE (N=163)**
Completed Maintenance Period	283 (92%)	69 (93%)	141 (90%)
Discontinued Trial during Maintenance Period	23 (8%)	5 (7%)	16 (10%)

Source: Reviewer's Analysis (same as Applicant's Analysis)
Abbreviations: BKZ=bimekizumab; USTE=ustekinumab; PBO=placebo
* Maintenance Set (MS): all subjects who received at least 1 dose of active IMP in the maintenance treatment period.

Table 33: Results for the Secondary Endpoints at Week 52 – Trial PS0009 (RS; NRI[1])

	BKZ Q4W/Q4W (N=321)	**USTE (N=163)**
PASI 90	262 (82%)	91 (56%)
USA[2]	45 (67%)	14 (41%)
All Other[3]	217 (85%)	77 (60%)
IGA 0/1	250 (78%)	99 (61%)
USA[2]	45 (67%)	17 (50%)
All Other[3]	205 (81%)	82 (64%)

Source: Reviewer's Analysis (similar to Applicant's Analysis)
Abbreviations: BKZ=bimekizumab; USTE=ustekinumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Sample sizes = (NB, NU) = (67, 34)
[3] Germany, Czech Republic, Hungary, Poland, Russian Federation, Australia, Republic of Korea, Taiwan. Sample sizes = (NB, NU) = (254, 129).

8.1.10. Common Investigators/Sites

The enrollment periods for the pivotal trials PS0008, PS0009 and PS0013 overlapped. As a result, there were several common investigators/sites across the three pivotal trials. On 8/31/2020, the Agency requested that the sponsor clarify how subjects were allocated to each of the pivotal trials, and the applicant responded on 09/02/2020 and stated that for instances where trials were enrolling concurrently at a site, the choice of which trial for a subject to enroll in was left to the investigators and the decision was documented at the screening visit. The Applicant added that no specific instructions regarding trial assignment of subjects were given to investigators and factors influencing an Investigator's decision could include the medical needs and preferences of the individual subject, use of placebo, use of comparators, and nuances in inclusion/exclusion criteria. Furthermore, the Applicant stated that randomization numbers were randomly generated and were unique for subjects across the trials. A list of the common sites/Investigators across more than one trial is provided in Appendix 19.5. However, the impact of common sites/Investigators was minimal as even after excluding the largest common sites (sites #365, #370, #657 and #929) bimekizumab remained superior to placebo ($p<0.0001$).

8.1.11. Findings in Special/Subgroup Populations

8.1.11.1. Sex, Race, Age, Weight, Baseline Disease Severity and Prior Use of Systemic Therapy

Table 34 and Table 35 present, respectively, the results for the co-primary efficacy endpoints (i.e., IGA score of 0 or 1 at Week 16 and PASI 90 at Week 16) by age (18-64 and ≥65 years), sex, race (White, Non-White), weight (<100 kg, ≥100 kg), baseline IGA score and prior use of systemic therapy for Trial PS0009. The same results for Trial PS0013 are presented in Table 36 and Table 37.

Approximately 89% and 94% of subjects were 18 to 64 years of age in Trials PS0009 and PS0013, respectively; therefore, it would be difficult to detect any differences in efficacy between this subgroup and its complement (i.e., ≥65 years). For sex, the treatment effect was slightly larger in females compared to males for IGA 0/1 in Trial PS0013; however, the treatment effect was larger in males in Trial PS0009. For PASI 90, treatment effect was generally consistent across these subgroups in Trial PS0013; however, the treatment effect was larger in females in Trial PS009. For race, the treatment effect was slightly higher in White

subjects compared to non-White subjects for both co-primary endpoints in Trial PS0013, while treatment effect was generally consistent in Trial PS0009. However, it should be noted that in both trials the sample size for the non-White subgroup was relatively small. For weight, the treatment effect was larger in those that weighed <100 kg compared to ≥100 kg for both co-primary endpoints in both trials. For baseline disease severity, the treatment effect tended to be larger for subjects with more disease severity (i.e., IGA score of 4[severe]) in Trial PS0009; however, there was more variability in treatment effect across these subgroups in Trial PS0013. The treatment effect was larger for subjects who had prior use of systemic therapy use compared to subjects who didn't in both trials.

Table 34: IGA 0/1 at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy - Trial PS0009 (RS; NRI[1])

Subgroups (n[BKZ], n[P])	BKZ Q4W (N=321)	PBO (N=83)	Difference	95% CI
Age (years)				
18-64 (287, 73)	86%	5%	80%	(74%, 87%)
≥65 (34, 10)	71%	0%	71%	(55%, 86%)
Sex				
Male (229, 60)	85%	5%	80%	(73%, 87%)
Female (92, 23)	81%	4%	77%	(66%, 89%)
Race				
White (237, 63)	84%	6%	78%	(70%, 86%)
Non-White (84, 20)	83%	0%	83%	(75%, 91%)
Baseline Weight				
<100 kg (225, 60)	86%	5%	81%	(74%, 88%)
≥100 kg (96, 23)	80%	4%	76%	(64%, 87%)
Baseline IGA[2]				
Moderate (201, 54)	85%	7%	78%	(69%, 86%)
Severe (119, 28)	82%	0%	82%	(75%, 89%)
Prior Systemic Therapy				
Yes (267, 64)	85%	2%	82%	(77%, 88%)
No (54, 19)	85%	16%	69%	(50%, 88%)
Overall	**84%**	**5%**	**79%**	**(73%, 85%)**

Source: Statistical Reviewer's Analysis; ADIGA.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Two subjects (1 in each arm) had baseline IGA score of mild

Table 35: PASI-90 Response at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy - Trial PS0009 (RS; NRI[1])

Subgroups (n[BKZ], n[P])	BKZ Q4W (N=321)	PBO (N=83)	Difference	95% CI
Age (years)				
18-64 (287, 73)	86%	5%	81%	(74%, 87%)
≥65 (34, 10)	73%	0%	73%	(59%, 88%)
Sex				
Male (229, 60)	85%	7%	78%	(71%, 86%)
Female (92, 23)	85%	0%	85%	(77%, 92%)
Race				
White (237, 63)	85%	5%	80%	(73%, 87%)
Non-White (84, 20)	86%	5%	81%	(69%, 93%)
Baseline Weight				
<100 kg (225, 60)	86%	5%	81%	(74%, 88%)
≥100 kg (96, 23)	83%	4%	79%	(68%, 90%)
Baseline IGA				
Moderate (201, 54)	86%	7%	78%	(70%, 87%)
Severe (119, 28)	84%	0%	84%	(77%, 91%)
Prior Systemic Therapy				
Yes (267, 64)	85%	3%	82%	(76%, 88%)
No (54, 19)	83%	10%	73%	(56%, 90%)
Overall	**85%**	**5%**	**80%**	**(74%, 86%)**

Source: Statistical Reviewer's Analysis; ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)
[2] Two subjects (1 in each arm) had baseline IGA score of mild

Table 36: IGA 0/1 at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy - Trial PS0013 (RS; NRI[1])

Subgroups (n[BKZ], n[P])	BKZ Q4W (N=349)	PBO (N=86)	Difference	95% CI
Age (years)				
18-64 (328, 82)	93%	1%	91%	(88%, 95%)
≥65 (21, 4)	90%	0%	90%	(78%, 100%)
Sex				
Male (255, 58)	81%	2%	90%	(86%, 95%)
Female (94, 28)	94%	0%	94%	(89%, 99%)
Race				
White (324, 79)	93%	1%	92%	(89%,96%)
Non-White (25, 7)	80%	0%	80%	(64%, 96%)
Baseline Weight				
<100 kg (255, 57)	94%	2%	92%	(88%, 97%)
≥100 kg (94, 29)	88%	0%	88%	(82%, 95%)
Baseline IGA				
Moderate (242, 62)	95%	2%	93%	(89%, 97%)
Severe (107, 24)	88%	0%	88%	(82%, 94%)
Prior Systemic Therapy				
Yes (276, 71)	92%	0%	92%	(89%, 95%)
No (73, 15)	93%	7%	86%	(73%, 100%)
Overall	**93%**	**1%**	**91%**	**(88%, 95%)**

Source: Statistical Reviewer's Analysis; ADIGA.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

Table 37: PASI-90 Response at Week 16 by Age, Sex, Race, Weight, Baseline IGA Score and Prior Use of Systemic Therapy - Trial PS0013 (RS; NRI[1])

Subgroups (n[BKZ], n[P])	BKZ Q4W (N=349)	PBO (N=86)	Difference	95% CI
Age (years)				
18-64 (328, 82)	91%	1%	90%	(86%, 94%)
≥65 (21, 4)	86%	0%	86%	(71%, 100%)
Sex				
Male (255, 58)	91%	2%	89%	(85%, 94%)
Female (94, 28)	91%	0%	91%	(86%, 97%)
Race				
White (324, 79)	92%	1%	90%	(87%, 94%)
Non-White (25, 7)	80%	0%	80%	(64%, 96%)
Baseline Weight				
<100 kg (255, 57)	93%	2%	92%	(87%, 96%)
≥100 kg (94, 29)	84%	0%	84%	(77%, 91%)
Baseline IGA				
Moderate (242, 62)	91%	2%	89%	(84%, 94%)
Severe (107, 24)	91%	0%	91%	(85%, 96%)
Prior Systemic Therapy				
Yes (276, 71)	91%	0%	91%	(88%, 94%)
No (73, 15)	90%	7%	84%	(69%, 98%)
Overall	**91%**	**1%**	**80%**	**(86%, 93%)**

Source: Statistical Reviewer's Analysis; ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

8.1.11.2. Geographic Location (Country)

Trial PS0009 was conducted in 11 countries (i.e., Australia, Canada, Belgium, Germany, Hungary, Italy, Poland, United Kingdom, Japan, Russian Federation, and United States). and Trial PS0013 was conducted in 9 countries (i.e., Australia, Canada, Germany, Hungary, Poland, United Kingdom, Korea, Russian Federation, and United States).

Table 38 and Table 39 present, respectively, the results for the co-primary efficacy endpoints (i.e., IGA score of 0 or 1 at Week 16 and PASI 90 at Week 16) by country for Trial PS0009. The same results for Trial PS0013 are presented in Table 40 and Table 41. In both trials, there was some variability in treatment effect across the countries; however, this may be due to the relatively small sample sizes in several of the countries.

Table 38: IGA 0/1 at Week 16 by Country - Trial PS0009 (RS; NRI[1])

Country	BKZ Q4W (N=321)	PBO (N=83)	Difference	95% CI
Poland (83, 18)	94%	6%	88%	(77%, 100%)
United States (67, 15)	78%	7%	71%	(55%, 87%)
Japan (79, 62)	82%	0%	82%	(73%, 92%)
Germany (39, 7)	79%	0%	79%	(67%, 92%)
Canada (33, 11)	88%	9%	79%	(58%, 99%)
Hungary (18, 5)	72%	20%	52%	(12%, 93%)
Russian Federation (7, 4)	100%	0%	100%	-
Australia (7, 1)	86%	0%	86%	(60%,100%)
United Kingdom (3, 1)	67%	0%	67%	(13%, 100%)
Belgium (2, 1)	50%	0%	50%	(-19%, 100%)
Italy (0, 3)	-	0%	-	-
Overall	**84%**	**5%**	**79%**	**(73%, 85%)**

Source: Statistical Reviewer's Analysis; ADIGA.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

Table 39: PASI-90 Response at Week 16 by Country - Trial PS0009 (RS; NRI[1])

Country	BKZ Q4W (N=321)	PBO (N=83)	Difference	95% CI
Poland (83, 18)	94%	0%	94%	(89%, 99%)
United States (67, 15)	78%	7%	71%	(55%, 87%)
Japan (79, 62)	85%	6%	80%	(65%, 94%)
Germany (39, 7)	79%	0%	79%	(67%, 92%)
Canada (33, 11)	88%	9%	79%	(58%, 99%)
Hungary (18, 5)	78%	20%	58%	(18%, 98%)
Russian Federation (7, 4)	100%	0%	100%	-
Australia (7, 1)	89%	0%	89%	(60%, 100%)
United Kingdom (3, 1)	67%	0%	67%	(13%, 100%)
Belgium (2, 1)	50%	0%	50%	(-19%, 100%)
Italy (0, 3)	-	0%	-	-
Overall	**85%**	**5%**	**80%**	**(74%, 86%)**

Source: Statistical Reviewer's Analysis; ADPASI.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

Table 40: IGA 0/1 at Week 16 by Country - Trial PS0013 (RS; NRI[1])

	BKZ Q4W (N=349)	PBO (N=86)	Difference	95% CI
Poland (121, 29)	98%	0%	98%	(96%, 100%)
Canada (68, 21)	91%	0%	91%	(84%, 98%)
United States (72, 13)	83%	8%	76%	(59%, 92%)
Germany (30, 8)	93%	0%	93%	(84%, 100%)
Hungary (24, 7)	96%	0%	96%	(88%, 100%)
Russian Federation (15, 4)	100%	0%	100%	-
Australia (8, 2)	88%	0%	88%	(65%, 100%)
Korea (6, 1)	100%	0%	100%	-
United Kingdom (5, 1)	60%	0%	60%	(17%, 100%)
Overall	**93%**	**1%**	**91%**	**(88%, 95%)**

Source: Statistical Reviewer's Analysis; ADIGA.xpt
Abbreviations: BKZ=bimekizumab; PBO=placebo; Q4W=every 4 weeks
[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

Table 41: PASI-90 Response at Week 16 by Country - Trial PS0013 (RS; NRI[1])

	BKZ Q4W (N=349)	PBO (N=86)	Difference	95% CI
Poland (121, 29)	98%	0%	98%	(96%, 100%)
Canada (68, 21)	88%	0%	88%	(81%, 96%)
United States (72, 13)	81%	8%	73%	(56%, 90%)
Germany (30, 8)	90%	0%	90%	(96%, 100%)
Hungary (24, 7)	96%	0%	96%	(88%, 100%)
Russian Federation (15, 4)	100%	0%	100%	-
Australia (8, 2)	75%	0%	75%	(45%, 100%)
Korea (6, 1)	100%	0%	100%	-
United Kingdom (5, 1)	60%	0%	60%	%, 100%(1)
Overall	**91%**	**1%**	**80%**	**(86%, 93%)**

Source: Statistical Reviewer's Analysis; ADIGA.xpt

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

[1] Randomized Set (RS): all randomized subjects; missing data are imputed using non-responder imputation (NRI)

8.2. Review of Safety

8.2.1. Safety Review Approach

The primary review of safety of bimekizumab for the treatment of moderate to severe plaque psoriasis focused on pooled data from phase 3 trials PS0008, PS0009, and PS0013. Long-term safety data were provided by phase 3, open-label, long term extension Trial PS0014. The phase 3 trials were conducted in adult subjects with moderate to severe plaque psoriasis, defined as Psoriasis Area and Severity score (PASI) ≥12, Investigator Global Assessment score (IGA) ≥3 ("moderate"), and involved body surface area (BSA) ≥10% who were candidates for systemic therapy of phototherapy.

Phase 2 trials PS0010, PS0011, PS0016, and PS0018 provided supportive safety data. The ability of subjects to perform self-injection using the to-be-marketed safety syringe (SS) and autoinjector (AI) devices was evaluated in two clinical-use trials (DV0002 and DV0006). The effect of a single dose of bimekizumab 320 mg on the response to influenza vaccine in healthy volunteers was evaluated in Trial UP0034.

Trial PS0008 was a randomized, double-blind, active-controlled, parallel-group trial. Subjects were randomized 1:1:1 to 1 of 3 treatment arms: bimekizumab 320 mg SC every 4 weeks (Q4W), bimekizumab 320 mg Q4W Week 0-16 followed by bimekizumab 320 mg Q8W, or adalimumab 80 mg SC loading dose, then 40 mg SC Q2W until Week 24, then bimekizumab 320 mg SC Q4W through Week 52. The trial consisted of an Initial Treatment Period from Week 0-16 followed by a Maintenance Treatment Period from Week 16-56.

Trial PS0009 was a randomized, double-blind, placebo- and active comparator-controlled, parallel-group trial. Subjects were randomized 4:2:1 to 1 of 3 treatment arms: bimekizumab 320 mg SC Q4W, ustekinumab 45 mg or 90 mg (based on weight) SC Week 0 and 4, then Q12W, or placebo SC Q4W Week 0-16, then bimekizumab 320 mg SC Q4W through Week 48. The trial consisted of an Initial Treatment Period from Week 0-16 followed by a Maintenance Treatment Period from Week 16-52.

Trial PS0013 was a randomized, double-blind, placebo-controlled trial. Subjects were randomized 4:1 to 1 of 2 treatment arms: bimekizumab 320 mg SC Q4W or placebo SC Q4W. The trial consisted of an Initial Treatment Period from Week 0-16 followed by a Randomized Withdrawal Period from Week 16-56. Subjects in the bimekizumab 320 mg SC Q4W arm who achieved a PASI90 response at Week 16 were re-randomized 1:1:1 to 1 of 3 arms: bimekizumab 320mg Q4W, bimekizumab 320mg Q8W, or placebo (i.e., treatment withdrawal). Subjects in either treatment arm during Week 0-16 who did not achieve PASI90, as well as subjects who relapsed at Week 20 or later during the Randomized-Withdrawal Period (up to Week 56) were allocated to the escape arm. The escape arm consisted of bimekizumab 320 mg Q4W for 12 weeks. Subjects who achieved a PASI50 response at Week 12 of the open-label escape arm could enroll in the open-label extension trial (PS0014).

Trial PS0014 is an ongoing, phase 3, multicenter, open-label study to assess the long-term safety, tolerability, and efficacy of bimekizumab in adult subjects with moderate to severe plaque psoriasis who completed 1 of the Phase 3 feeder trials (PS0008, PS0009, or PS0013). Subjects received bimekizumab 320mg Q4W or 320mg Q8W based on their treatment regimen and PASI response in the feeder trial. Subjects must have achieved a PASI50 response by the designated time in the feeder trial to be eligible for PS0014.

The analysis of the safety of bimekizumab was performed using the following pools of safety data:

- Pool S1: The primary analysis dataset for the review of safety included pooled data from the Initial Treatment Period (Week 0-16) of the placebo-controlled Phase 3 Trials PS0009 and PS0013.
- Pool S2B: This consisted of data from the Maintenance and Randomized Withdrawal Periods of Trials PS0009 and PS0013, respectively and supported the analysis of safety through Week 56, in comparison to Pool S1.
- Pool S2C: This consisted of data from the Maintenance and Randomized Withdrawal Periods of Trials PS0008 and PS0013, respectively and supported the analysis of the comparative safety of the Q4W and Q8W dosing regimens.

Active comparators were included in phase 3 Trials PS0008 and PS0009. In Trial PS0008, US-licensed adalimumab was used in all sites in the US and Canada; all other sites used EU-approved adalimumab. In Trial PS0009, US-licensed ustekinumab was used in all sites in the US; all other sites used EU-approved ustekinumab. The Applicant did not establish a scientific bridge between US-licensed and EU-approved products. The US-licensed and EU approved comparators will be considered distinct products for the purpose of this review. Although an evaluation of comparative safety against the active comparators will be included in this review, this information will not be included in product labeling. The review team evaluated the comparative safety of bimekizumab with the active comparators by reviewing safety data from the individual trials rather than by analysis of pooled safety data.

The review team analyzed the following types of pooled data: exposure, demographics and baseline characteristics, treatment emergent adverse events (TEAEs), serious AEs (SAEs), and AEs leading to discontinuation. In addition, the safety evaluation included the following adverse events of special interest (AESI): infections, malignancies, major adverse cardiovascular events (MACE), neutropenia, suicidal ideation/behavior (SI/B), inflammatory bowel disease (IBD), anaphylactic, hypersensitivity, and injection site reactions, and elevated liver enzymes and hepatic events.

8.2.2. Review of the Safety Database

Overall Exposure

As described in the previous section, the primary analysis dataset (Pool S1) for the review of safety of bimekizumab included pooled data from the Initial Treatment Period (Week 0-16) of the placebo-controlled phase 3 Trials PS0009 and PS0013. The safety population for Pool S1 includes 670 subjects treated with bimekizumab 320 mg Q4W and 169 subjects treated with placebo. Pool S2B consisted of data from the Maintenance and Randomized Withdrawal Periods of Trials PS0009 and PS0013, respectively and was used to evaluate Safety through Week 56, in comparison to Pool S1. The safety population for Pool S2B includes 488 subjects treated with bimekizumab 320 mg Q4W and 103 subjects treated with bimekizumab 320 mg Q8W. Pool S2C consisted of data from the Maintenance and Randomized Withdrawal Periods of Trials PS0008 and PS0013, respectively. This was used to evaluate the comparative safety of the Q4W and Q8W dosing regimens. The safety population for Pool S2C includes 261 subjects treated with bimekizumab 320 mg Q4W and 257 subjects treated with bimekizumab 320 mg Q8W. Safety data from these populations were analyzed according to the treatment that subjects received.

The Applicant provided an overall summary of exposure in the 120-day Safety Update. During the Phase 2/3 trials, a total of 1789 subjects were exposed to bimekizumab, including 1591 subjects for ≥8 months and 1371 for ≥12 months. The overall exposure in the phase 2/3 trials was 2424.7 subject-years.

Relevant characteristics of the safety population:
The demographics of the phase 2/3 safety population are summarized as follows. The majority of subjects were white (82.1%) and male (70.0%). The mean age was 45 years and a total of 153 (8.6%) subjects were 65 years of age and older. The demographic characteristics were comparable across treatment groups. Refer to Section 8.1.4 for a demographic summary of the study population.

The medical histories of the phase 3 population were remarkable for hypertension (31.1%), obesity (10.3%), hyperlipidemia (8.7%), type 2 diabetes mellitus (8.2%), and depression (7.1%).

Adequacy of the safety database:

The total subject exposure to bimekizumab, 320 mg Q4W or Q8W for the treatment of moderate to severe plaque psoriasis provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. The total exposures for up to 1 year are sufficient to characterize the safety of the product over longer treatment periods.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of bimekizumab. We evaluated data quality and fitness in conjunction with the JumpStart Team. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

The Applicant defined an adverse event as "any untoward medical occurrence in a patient or clinical investigation study participant administered a pharmaceutical product, that does not necessarily have a causal relationship with this treatment." The Applicant defined a treatment-emergent adverse event (TEAE) as "those AEs that had a start date on or following the first dose of study treatment through the final dose of study treatment + 140 days (covering the 20-week SFU period)." TEAEs form the primary basis for the review of safety. The Applicant classified TEAEs based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

AEs were collected by subject reports or observation by the investigator and recorded in the electronic Case Report form (eCRF). Investigators were instructed to report any AE that was experienced by a subject during all phases of study participation and to follow the AE until it had resolved, had stable sequelae, the Investigator determined that it was no longer clinically significant, or the subject was lost to follow up. Investigators also recorded their assessment of relationship of the AE to study drug. The severity of AEs was characterized by investigators using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.

The Applicant defined a serious AE (SAE) as any AE that results in any of the following outcomes:

- Death
- Life threatening
  (Life threatening did not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may have jeopardized the patient or study participant and may have required medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious AE (Important medical events may have included, but have not been limited to, potential Hy's Law, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

If an SAE was reported, the investigator was required to inform the Applicant within 24 hours of receipt of this information by the site.

If an Investigator was notified that a subject had become pregnant after the first intake of any IMP, the Investigator immediately notified the Applicant by providing the completed Pregnancy Report and Outcome form. The subject was withdrawn from the study as soon as pregnancy was known (by positive pregnancy test), and the following were completed:

- The subject returned for an early discontinuation visit.
- The subject immediately stopped the intake of the IMP.
- A safety follow-up (SFU) Visit was scheduled 20 weeks after the subject has discontinued her IMP.

Investigators followed the progression of the pregnancy and the eventual outcome, including following the health of the infant (if applicable) for up to 30 days.
The Applicant also designated adverse events of special interest (AESI), which are listed in Section 8.2.1 of this review and discussed in more detail in Section 8.2.5 of this review.

Routine Clinical Tests

The Applicant's safety assessments included clinical evaluation of AEs, SAEs, vital signs, physical examinations, clinical laboratory evaluation (chemistry, hematology, and urinalysis), and ECGs. Safety assessments also included pregnancy testing at Screening and periodically throughout the trials. Investigators assessed for suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) in all trials, the Hospital Anxiety and Depression Scale (HADS) during the phase 2 trials, and the Patients' Health Questionnaire 9 (PHQ-9) during the phase 3 trials. Subjects were tested at Screening for tuberculosis (TB) and were reassessed periodically using a TB risk assessment questionnaire. The schedules of safety assessments were similar among the trials.

8.2.4. Safety Results

Deaths

The Applicant reported 5 deaths in the initial BLA submission and one additional death in the 120-day safety update in subjects treated with bimekizumab. The Applicant considered none of the deaths to be related to treatment with bimekizumab. Brief narratives for these subjects are provided below:

- A 67 y/o male (Subject PS0011-(b) (6)) enrolled in phase 2 trial PS0011 and treated with bimekizumab 320 mg Q4W experienced fatal dyspnea, respiratory failure, and circulatory collapse. The fatal event occurred on Day 262, and 94 days since his most recent dose of bimekizumab. He had multiple comorbidities including type 2 diabetes, asthma, HTN, and prior acute MI. Per the Applicant, cardiac causes for the fatal event were excluded.

- A 50 y/o male (Subject PS0010-(b) (6)) enrolled in phase 2 trial PS0011 and treated with bimekizumab 320 mg Q4W experienced fatal hypovolemic shock on Day 320, 31 days after his most recent dose of bimekizumab. This was secondary to an upper GI hemorrhage which occurred after a 2-week alcohol binge episode.
- A 63 y/o female (Subject PS0009-(b) (6)) enrolled in phase 3 Trial PS0009 and treated with bimekizumab 320 mg Q4W experienced a fatal sudden cardiac arrest on Day 31. The event occurred 28 days after her first dose and 3 days after her most recent dose of bimekizumab. The fatal event occurred "a few days after a non-STEMI which was treated and considered resolved". Cardiovascular risk factors included hypertension, mixed hyperlipidemia, BMI>30kg/m^2, smoker, mitral valve incompetence, and aortic valve stenosis.
- A 50 y/o male (Subject PS0009-(b) (6)) enrolled in phase 3 Trial PS0009 and treated with bimekizumab 320 mg Q4W died of an unknown cause on Day 208, 95 days after the most recent dose of bimekizumab. He was withdrawn from the trial at Week 24 for noncompliance and refusal of treatment for a nonserious AE of cellulitis. He was lost to follow-up and the death was reported 3 months after withdrawal.
- A 49 y/o male (Subject PS0013-(b) (6)) enrolled in phase 3 open-label extension Trial PS0014 and treated with bimekizumab 320 mg Q4W experienced fatal acute cardiorespiratory failure 101 days after his first and 15 days after his most recent dose of bimekizumab. He experienced a cardiorespiratory arrest during left hip replacement and was resuscitated. Post-procedure, he experienced left femoral artery embolism requiring emergent surgery. The fatal cardiorespiratory failure event occurred post-operatively in the ICU. Cardiovascular risk factors included hypertension, diabetes mellitus, BMI>30 kg/m^2, and tobacco smoker.
- A 65 y/o male (Subject PS0013-(b) (6)) enrolled in phase 3 open-label extension Trial PS0014 and treated with bimekizumab 320 mg Q8W experienced a fatal MI 437 days after the first and 36 days after his most recent dose of bimekizumab. Cardiac risk factors included obesity, HTN, history of CVA 10 years prior, and alcohol use.

Serious Adverse Events

Serious adverse events (SAEs) will be discussed using the following data pools:

- Pool S1: Includes the placebo-controlled periods of Trials PS0009 and PS0013
- Pool S2C: Includes data from the Maintenance Period of Trial PS0008 and the Randomized Withdrawal Period of Trial PS0013 and allows comparison of Q4W and Q8W regimens
- Initial treatment period of Trial PS0008: comparison of bimekizumab and adalimumab
- Maintenance treatment Period of Trial PS0009: comparison of bimekizumab and ustekinumab
- Pool S2B: Includes the Maintenance Period of Trial PS0009 and the Randomized Withdrawal Period of Trial PS0013; allows comparison of exposure adjusted incidence rates (EAIR) between short-term (Pool S1) and long-term exposure to bimekizumab 320 mg Q4W

In all of the above pools, most SAEs were experienced by single subjects in a treatment group.

During the placebo-controlled period of Trials PS0009 and PS0013 (Pool S1), SAEs were reported by 11/670 (1.6%, EAIR 5.3/100 subject-years) of subjects treated with bimekizumab and 4/169 (2.4%, EAIR 7.8/100 subject-years) treated with placebo. The most common system-organ classes (SOCs) in which SAEs were reported in the bimekizumab group was GI disorders (3 subjects), followed by Infections and Infestations and Musculoskeletal and Connective Tissue Disorders (2 subjects each). SAEs reported in Pool S1 are presented in the table below:

Table 42: SAEs by SOC and Preferred Term, Pool S1

System Organ Class/Preferred Term	BKZ 320mg Q4W n=670	Placebo n=169
Gastrointestinal disorders	3 (0.4%)	0 (0.0%)
Diverticular perforation	1 (0.1%)	0 (0.0%)
Colitis ulcerative	1 (0.1%)	0 (0.0%)
Enteritis	1 (0.1%)	0 (0.0%)
Infections and infestations	2 (0.3%)	0 (0.0%)
Enterovirus infection	1 (0.1%)	0 (0.0%)
Pneumonia	1 (0.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	2 (0.3%)	0 (0.0%)
Osteochondrosis	1 (0.1%)	0 (0.0%)
Facet joint syndrome	1 (0.1%)	0 (0.0%)
Cardiac disorders	1 (0.1%)	2 (1.2%)
Cardiac arrest	1 (0.1%)	0 (0.0%)
Acute myocardial infarction	1 (0.1%)	0 (0.0%)
Myocardial infarction	0 (0.0%)	1 (0.6%)
Mitral valve prolapse	0 (0.0%)	1 (0.6%)
Injury, poisoning and procedural complications	1 (0.1%)	2 (1.2%)
Humerus fracture	1 (0.1%)	0 (0.0%)
Tendon injury	0 (0.0%)	1 (0.6%)
Toxicity to various agents	0 (0.0%)	1 (0.6%)
Eye disorders	1 (0.1%)	0 (0.0%)
Retinal detachment	1 (0.1%)	0 (0.0%)
Hepatobiliary disorders	1 (0.1%)	0 (0.0%)
Cholelithiasis	1 (0.1%)	0 (0.0%)
Nervous system disorders	1 (0.1%)	0 (0.0%)
Intracranial aneurysm	1 (0.1%)	0 (0.0%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (0.6%)
Oesophageal adenocarcinoma	0 (0.0%)	1 (0.6%)
Total	11 (1.6%)	4 (2.4%)

Source: Reviewer's Table

Narrative summaries for SAEs in subjects treated with bimekizumab in Pool S1 are presented below:

SAEs considered by the investigator as related to treatment:

- A 32 y/o Asian male (Subject PS0009-(b) (6)) with no reported history of inflammatory bowel disease experienced an SAE of colitis ulcerative on Day 100. The SAE was considered moderate in intensity and the outcome was not resolved. He discontinued treatment with bimekizumab, and the investigator considered the event related to treatment with bimekizumab.
- A 23 y/o white female (Subject PS0013-(b) (6)) experienced SAEs of colitis and gastrointestinal inflammation on Day 111, for which she was hospitalized. She was seen by a gastroenterologist and the workup included a colonoscopy. The gastroenterologist considered the events consistent with "a very early stage of Crohn's disease or drug-induced colitis". Both events were considered moderate in intensity and the outcome for both was resolved. Treatment with bimekizumab was interrupted during the event but resumed after resolution. She completed the trial and enrolled in the open-label extension Trial PS0014. The investigator considered both events to be related to treatment with bimekizumab.
- A 77 y/o white female (Subject PS0013-(b) (6)) experienced an SAE of pneumonia on Day 27 for which she was hospitalized. She was treated with oxygen and antibiotics. The event was considered moderate in intensity and the outcome was resolved after treatment. Treatment with bimekizumab was interrupted during the event but resumed after resolution. The investigator considered the event as related to treatment with bimekizumab.

SAEs considered not related to treatment by the investigator:

- A 71 y/o white male (Subject PS0009-(b) (6)) with a history of spinal stenosis at L4/L5 treated surgically (b) (6) experienced an SAE of facet joint syndrome of lumbar discs 4 and 5 on Day 102. The event was considered severe in intensity and the outcome was resolved with sequelae. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 32 y/o white female (Subject PS0009-(b) (6)) with a history of traumatic ligament rupture of the right ankle (b) (6) experienced an SAE of osteochondrosis dissecans of the right ankle on Day 23. The event was considered moderate in severity and the outcome was not resolved. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 63 y/o white female (Subject PS0009-(b) (6)) experienced an SAE of acute myocardial infarction on Day 28 and died on Day 32. The narrative for this subject is presented above in the subsection regarding deaths.
- A 44 y/o Japanese male (Subject PS0009-(b) (6)) with a history of hypertension experienced an SAE of intracranial aneurysm on Day 100. The aneurysm was treated with coil embolization. The SAE was considered moderate in intensity and the outcome

was resolving. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.

- A 48 y/o white male (Subject PS0013-(b) (6)) with a history of corneal transplants in (b) (6), and a history of recurrent retinal detachment of the left eye experienced two SAEs of retinal detachment of the left eye on Day 48 and 196. The first event was considered mild in intensity and occurred while the subject was treated with bimekizumab. The second event was considered moderate in intensity and occurred after he was rerandomized to placebo prior to the randomized withdrawal period of the trial. The action taken with study drug was dose not changed, and the outcome for both events was resolved. The investigator considered the events not related to treatment with bimekizumab.
- A 25 y/o white female (Subject PS0013-(b) (6)) with a history of gastric bypass surgery (b) (6) experienced an SAE of cholelithiasis on Day 109 and was treated with laparoscopic cholecystectomy. The SAE was considered moderate in intensity and the outcome was resolved. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 57 y/o white female (Subject PS0013-(b) (6)) experienced an SAE of diverticular perforation with pericolonic abscess on Day 11. She was treated with IV antibiotics and percutaneous drainage. The event was considered severe in intensity and the outcome was resolved after treatment. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab. She experienced a second SAE of humerus fracture (right comminuted proximal humerus fracture, 2-part fracture/dislocation) resulting from a fall on Day 47. She underwent surgical repair of the fracture. The event was considered severe in intensity and the outcome was resolved after treatment. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 66 y/o black male (Subject PS0013-(b) (6) experienced an SAE of enterovirus infection presenting as viral pneumonia on Day 5. He was hospitalized and treatment included supplemental oxygen and bilevel positive airway pressure (BiPAP) therapy. The event was considered severe in intensity and the outcome was resolved after treatment. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.

Comparison of SAEs Between Short-term and Long-term Exposure

In Pool S2B, SAEs were reported in 23/488 (4.7%, EAIR 7.0/100 subject-years) subjects treated with bimekizumab Q4W. The SOCs and PTs for the SAEs for these subjects are included below in the tables for Pool S2C and PS0009. Narratives for subjects in Pool S2B who were treated with bimekizumab are also provided below under Pool S2C and PS0009.

Comparison of SAEs between Q4W and Q8W dosing regimens (Pool S2C)

Pooled data from the Maintenance Period of Trial PS0008 and the Randomized Withdrawal Period of Trial PS0013 (Pool S2C) allow for direct comparison of safety between the bimekizumab 320 mg Q4W and 320 mg Q8W regimens. In Pool S2C, SAEs were reported by 8/261 (3.1%, EAIR 4.2/100 subject-years) of subjects treated with the Q4W regimen and 11/257 (4.3%, EAIR 5.8/100 subject-years) of subjects treated with the Q8W regimen. The most common SOC in which SAEs were reported in the Q4W group was Infections and Infestations (2/261, 0.8%, EAIR 1.0/100 subject-years) subjects. The most common SOCs in which SAEs were reported in the Q8W group were GI disorders (4/257, 1.6%, EAIR 2.1/100 subject-years) subjects and Infections and Infestations (2/257, 0.8%, EAIR 1.0/100 subject-years) subjects. SAEs reported in Pool S2C are presented in the table below:

Table 43: SAEs by SOC and Preferred Term, Pool S2C

System Organ Class/Preferred Term	BKZ 320mg Q4W n=261	BKZ 320mg Q8W n=257	Totals n=518
Gastrointestinal disorders	1 (0.4%)	4 (1.6%)	5 (1.0%)
Diarrhea	0 (0.0%)	2 (0.8%)	2 (0.4%)
Duodenal ulcer hemorrhage	0 (0.0%)	1 (0.4%)	1 (0.2%)
Umbilical hernia	0 (0.0%)	1 (0.4%)	1 (0.2%)
Pancreatitis	1 (0.4%)	0 (0.0%)	1 (0.2%)
Infections and infestations	2 (0.8%)	2 (0.8%)	4 (0.8%)
Subcutaneous abscess	1 (0.4%)	0 (0.0%)	1 (0.2%)
Otitis media chronic	1 (0.4%)	0 (0.0%)	1 (0.2%)
Appendicitis	0 (0.0%)	1 (0.4%)	1 (0.2%)
Erysipelas	0 (0.0%)	1 (0.4%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4%)	1 (0.4%)	2 (0.4%)
Ovarian adenoma	1 (0.4%)	0 (0.0%)	1 (0.2%)
Colon cancer	0 (0.0%)	1 (0.4%)	1 (0.2%)
Cardiac disorders	0 (0.0%)	1 (0.4%)	1 (0.2%)
Acute myocardial infarction	0 (0.0%)	1 (0.4%)	1 (0.2%)
Musculoskeletal and connective tissue disorders	1 (0.4%)	0 (0.0%)	1 (0.2%)
Psoriatic arthropathy	1 (0.4%)	0 (0.0%)	1 (0.2%)
Metabolism and nutrition disorders	1 (0.4%)	0 (0.0%)	1 (0.2%)
Diabetes mellitus inadequate control	1 (0.4%)	0 (0.0%)	1 (0.2%)
Injury, poisoning and procedural complications	1 (0.4%)	0 (0.0%)	1 (0.2%)
Injury	1 (0.4%)	0 (0.0%)	1 (0.2%)
General disorders and administration site conditions	0 (0.0%)	1 (0.4%)	1 (0.2%)
Non-cardiac chest pain	0 (0.0%)	1 (0.4%)	1 (0.2%)
Hepatobiliary disorders	1 (0.4%)	0 (0.0%)	1 (0.2%)
Cholecystitis	1 (0.4%)	0 (0.0%)	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	1 (0.4%)	0 (0.0%)	1 (0.2%)
Abortion spontaneous	1 (0.4%)	0 (0.0%)	1 (0.2%)

System Organ Class/Preferred Term	BKZ 320mg Q4W n=261	BKZ 320mg Q8W n=257	Totals n=518
Blood and lymphatic system disorders	0 (0.0%)	1 (0.4%)	1 (0.2%)
Hemorrhagic anemia	0 (0.0%)	1 (0.4%)	1 (0.2%)
Investigations	0 (0.0%)	1 (0.4%)	1 (0.2%)
Hepatic enzyme increased	0 (0.0%)	1 (0.4%)	1 (0.2%)
Eye disorders	1 (0.4%)	0 (0.0%)	1 (0.2%)
Cataract	1 (0.4%)	0 (0.0%)	1 (0.2%)
Vascular disorders	0 (0.0%)	1 (0.4%)	1 (0.2%)
Hypertension	0 (0.0%)	1 (0.4%)	1 (0.2%)
TOTAL	8 (3.1%)	11 (4.3%)	19 (3.7%)

Source: Reviewer's Table

Narrative summaries for SAEs in subjects in Pool S2C are presented below:

Subjects treated with bimekizumab 320 mg Q4W

SAEs considered by the investigator as related to treatment:

- A 54 y/o white female (Subject PS0008-(b) (6)) with a history of Type 2 diabetes experienced an SAE of left axillary abscess on Day 344. The abscess was treated with drainage and packing. The SAE was considered severe in intensity and the outcome was resolved after treatment. She continued treatment with bimekizumab, and the investigator considered the event of left axillary abscess as related to treatment with bimekizumab. On Day 347, she experienced an SAE of uncontrolled diabetes mellitus type 2 which was treated with medications, including insulin. The SAE was considered severe in intensity and the outcome was resolved after treatment. She continued treatment with bimekizumab, and the investigator considered the event of uncontrolled type 2 diabetes mellitus as not related to treatment with bimekizumab.

SAEs considered not related to treatment by the investigator:

- A 34 y/o white female (Subject PS0008-(b) (6)) experienced an SAE of pregnancy with contraceptive device (verbatim term: condom failure pregnancy) on Day 138. Treatment with bimekizumab was discontinued. On Day 161, she experienced an SAE of abortion spontaneous. Both SAEs were considered severe in intensity. The outcomes of the SAEs were resolved with sequelae and resolved, respectively. The investigator considered both SAEs as not related to treatment with bimekizumab.
- A 35 y/o white female (Subject PS0008-(b) (6)) with a history of obesity experienced SAEs of gallstone pancreatitis on Day 421 and cholecystitis on Day 422, treated with cholecystectomy. She had completed treatment with bimekizumab, and the final dose was given 73 days prior to the first SAE. Both SAEs were considered severe in intensity, and the outcome of each was resolved. The investigator considered both SAEs as not related to treatment with bimekizumab.

- A 64 y/o white female (Subject PS0013-(b) (6)) experienced an SAE of cataract (right eye) on Day 160. She had previously experienced nonserious AEs of cataracts in both eyes. The SAE was the second event of cataract in the right eye and she was hospitalized for surgery. She continued treatment with bimekizumab. The event was considered moderate in intensity, and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 53 y/o white male (Subject PS0013-(b) (6)) experienced an SAE of psoriatic arthropathy on Day 290. He had no previous history of psoriatic arthropathy. He was hospitalized and treated with methotrexate, ultracet, folic acid, methylprednisone, and meloxicam. He continued treatment with bimekizumab. The event was considered severe in intensity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 25 y/o white female (Subject PS0013-(b) (6)) with a history of polycystic ovaries experienced an SAE of ovarian adenoma (verbatim term: benign cystadenoma serosum of the right ovary) on Day 120. She was hospitalized and underwent laparoscopic surgical excision of the adenoma. She continued treatment with bimekizumab. The event was considered moderate in intensity, and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 41 y/o white male (Subject PS0013-(b) (6) experienced an SAE of injury (traumatic skin and soft tissue injury to left calf while playing soccer) on Day 264. He was hospitalized and underwent surgical repair of the wound. He continued treatment with bimekizumab. The event was considered moderate in intensity, and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 69 y/o white male (Subject PS0013-(b) (6)) experienced an SAE of otitis media chronic on Day 191. He was hospitalized and treated with IV antibiotics. He continued treatment with bimekizumab. The event was considered moderate in intensity, and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.

<u>Subjects treated with bimekizumab 320 mg Q8W (All SAEs in this subgroup were considered not related to treatment by the investigator.)</u>

- A 56 y/o white male (Subject PS0008-(b) (6)) experienced an SAE of umbilical hernia on Day 332. He was treated with a transabdominal umbilical patch plasty. Treatment with bimekizumab was temporarily discontinued due to the SAE, and he completed the trial. The event was considered severe in intensity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 62 y/o white male (Subject PS0008-(b) (6)) with a history of hypertension and type 2 diabetes experienced an SAE of non-cardiac chest pain on Day 375 and was hospitalized. He had completed treatment with bimekizumab, and the final dose was given 38 days prior to the SAE. The event was considered moderate in intensity and the

outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.

- A 21 y/o white female (Subject PS0008-(b) (6)) with a history of autoimmune thyroiditis experienced an SAE of hepatic enzyme increased on Day 190. She was initially as screen failure because of elevated hepatic enzymes. However, on rescreening her laboratory values had normalized. She was hospitalized, and treatment with bimekizumab was discontinued because of the SAE. Concomitant medications at the time of the SAE included ciprofloxacin and metronidazole. The event was considered severe in intensity and the outcome was resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab. This subject is discussed in more detail in Section 8.2.5.3 of this review, which discusses hepatotoxicity.
- A 43 y/o white male (Subject PS0008-(b) (6)) with a history of obesity and tobacco use (0.75 packs per day, 27 years) experienced an SAE of hypertension on Day 185. He was hospitalized and treated with nitrendipine, ramipril, and indapamide. The event was considered severe in intensity and the outcome was resolved at the time of the report. He continued treatment with bimekizumab. The investigator considered the event not related to treatment with bimekizumab.
- A 50 y/o white male (Subject PS0008-(b) (6)) experienced an SAE of erysipelas on Day 188. He was treated with antibiotics and treatment with bimekizumab was interrupted. The event was considered severe in intensity. The outcome was resolved with sequelae and he resumed treatment with bimekizumab. The investigator considered the event not related to treatment with bimekizumab.
- A 32 y/o white male (Subject PS0008-(b) (6)) experienced an SAE of appendicitis on Day 239. He underwent an appendectomy. The event was considered moderate in intensity, the outcome was resolved, and he continued treatment with bimekizumab. The investigator considered the event not related to treatment with bimekizumab.
- A 47 y/o white female (Subject PS0008-(b) (6)) experienced SAEs of duodenal ulcer hemorrhage and hemorrhagic anemia on Day 348 and was hospitalized for treatment. The events were considered severe in intensity, the outcome was resolved, and she continued treatment with bimekizumab. The investigator considered the events not related to treatment with bimekizumab.
- A 48 y/o white male (Subject PS0008-(b) (6)) experienced an SAE of colon cancer (Stage IV) on Day 266 and discontinued treatment with bimekizumab. Per the investigator, he did not have risk factors for colon cancer, including smoking, high alcohol consumption, physical inactivity, or excess body weight. The event was considered severe in intensity and the outcome was not resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab.
- A 53 y/o white male (Subject PS0013-(b) (6)) with a history of obesity, dyslipidemia, hypertension, type 2 diabetes, and tobacco use (2 packs/day, 38 years) experienced an SAE of acute myocardial infarction on Day 275. He was hospitalized and underwent coronary angiography with stent placement. He continued treatment with

bimekizumab. The event was considered severe in intensity and the outcome was reported as resolved. The investigator considered the event not related to treatment with bimekizumab.

- A 31 y/o white male (Subject PS0013-[redacted]) experienced an SAE of diarrhea on Day 309. He was hospitalized for evaluation. Colonoscopy revealed polyps but no evidence of inflammatory bowel disease. Treatment with bimekizumab was discontinued. The event was considered moderate in intensity and the outcome was reported as resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 64 y/o white female (Subject PS0013-[redacted]) with a history of irritable bowel syndrome and functional diarrhea experienced an SAE of diarrhea on Day 356. She was hospitalized for evaluation, but no definitive diagnosis was made. She continued treatment with bimekizumab. The event was considered moderate in intensity and the outcome was reported as resolved. The investigator considered the event not related to treatment with bimekizumab.

SAEs from Trials PS0008 (Initial Treatment Period) and PS0009 (Maintenance Treatment Period)

Pool S1 and Pool S2C did not include data from the initial treatment period of Trial PS0008 or the maintenance treatment period of trial PS0009. SAEs from these treatment periods are summarized below.

During the initial treatment period of Trial PS0008, SAEs were reported in 4/319 (1.3%, EAIR 4.1/100 subject-years) of subjects treated with bimekizumab, and 3/159 (1.9%, EAIR 6.2/100 subject-years) of subjects treated with adalimumab. SAEs from this period are presented in the table below.

Table 44: SAEs, Initial Treatment Period Trial PS0008

System Organ Class/Preferred Term	Bimekizumab N=319 n (%) [#] Incidence (95% CI) Event Rate	Adalimumab N=159 n (%) [#] Incidence (95% CI) Event Rate
Total	4 (1.3) [4] 4.10 (1.12, 10.50) 4.07	3 (1.9) [3] 6.21 (1.28, 18.15) 6.14
Eye Disorders	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	0
Retinal Detachment	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	0
Gastrointestinal disorders	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	1 (0.6) [1] 2.06 (0.05, 11.46) 2.05

System Organ Class/Preferred Term	Bimekizumab N=319 n (%) [#] Incidence (95% CI) Event Rate	Adalimumab N=159 n (%) [#] Incidence (95% CI) Event Rate
Irritable bowel syndrome	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0
Hemorrhoidal hemorrhage	0	1 (0.6) [1] 2.06 (0.05, 11.46) 2.05
Infections and infestations	1 (0.3) [1] 1.02 (0.03, 5.69) 1.02	0
Cellulitis	1 (0.3) [1] 1.02 (0.03, 5.69) 1.02	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	1 (0 .6) [1] 2.05 (0.05, 11.42) 2.05
Squamous cell carcinoma of the tongue	0	1 (0 .6) [1] 2.05 (0.05, 11.42) 2.05
Renal and urinary disorders	0	1 (0 .6) [1] 2.06 (0.05, 11.48) 2.05
Calculus urinary	0	1 (0 .6) [1] 2.06 (0.05, 11.48) 2.05
Reproductive system and breast disorders	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	0
Ovarian cyst ruptured	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	0

n- number of subjects reporting at least one SAE
[#]- number of individual occurrences of the SAE
Incidence- Incidence of new cases per 100 subject-years, and associated 95% CI
Event rate- event rate per 100 subject-years
Source: Applicant's Table 8.1.3.3, PS0008 Clinical Study Report

Narratives for subjects treated with bimekizumab are presented below:

SAEs considered by the investigator as related to treatment:

- A 57 y/o black or African American female (Subject PS0008-(b) (6) experienced an SAE of cellulitis on Day 12. She was hospitalized and treated with IV antibiotics. The event was considered severe in intensity and the outcome was resolved. Treatment with bimekizumab was interrupted during the event. She later resumed treatment and completed the trial. The investigator considered the event as related to treatment with

bimekizumab.

SAEs considered not related to treatment by the investigator:

- A 66 y/o white male (Subject PS0008-[redacted] (b) (6)) with no previous history of eye trauma, retinal detachment, or recent cataract surgery experienced an SAE of retinal detachment on Day 44 which was treated surgically. The event was considered severe in intensity and the outcome was resolved. Treatment with bimekizumab was interrupted during the event. He later resumed treatment and completed the trial. The investigator considered the event as not related to treatment with bimekizumab.
- A 67 y/o white female (Subject PS0008-[redacted] (b) (6)) with a history of upper abdominal pain experienced an SAE of irritable bowel syndrome on Day 97. She was hospitalized and underwent gastroscopy and colonoscopy. The gastroscopy revealed a hiatal hernia, and the colonoscopy was normal. The event was considered mild in intensity and the outcome was resolved with sequelae (sequelae were not specified). She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab. A 25 y/o white female (Subject PS0008-[redacted] (b) (6)) experienced an SAE of ovarian cyst ruptured on Day 58 which was treated surgically. The event was considered severe in intensity and the outcome was resolved. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.

During the maintenance period of Trial PS0009, SAEs were reported in 18/380 (4.7%, EAIR 7.1/100 subject-years) of subjects treated with bimekizumab and 7/157 (4.5%, EAIR 6.8/100 subject-years) of subjects treated with ustekinumab. The most common SOCs for SAEs in the bimekizumab group were Infections and Infestations with 5/380 (1.3%, EAIR 1.9/100 subject-years) and Cardiac Disorders with 3/380 (0.8%, EAIR 1.2/100 subject-years) subjects. SAEs from the Maintenance Period of Trial PS0009 are presented in the table below:

Table 45: SAEs, Maintenance Treatment Period Trial PS0009

System Organ Class/Preferred Term	Bimekizumab 320 mg Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Total	18 (4.7) [20] 7.09 (4.20, 11.21) 7.73	7 (4.5) [10] 6.76 (2.72, 13.93) 9.40
Cardiac Disorders	3 (0.8) [3] 1.17 (0.24, 3.41) 1.13	0
Myocardial Infarction	2 (0.5) [2] 0.78 (0.09, 2.80) 0.77	0

System Organ Class/Preferred Term	Bimekizumab 320 mg Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Acute myocardial infarction	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
General disorders and administration site Conditions	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Death	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Gastrointestinal disorders	0	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94
Hemorrhoids	0	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94
Infections and infestations	5 (1.3) [5] 1.94 (0.63, 4.53) 1.93	2 (1.3) [4] 1.89 (0.23, 6.84) 3.76
Gastroenteritis	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Esophageal candidiasis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Mastoiditis	0	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94
Otitis externa	0	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94
Otitis media acute	0	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94
Pneumonia	0	1 (0.6) [1] 0.94 (0.02, 5.25) 0.94
Infective tenosynovitis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Necrotizing fasciitis	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Subglottic laryngitis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0

System Organ Class/Preferred Term	Bimekizumab 320 mg Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Injury, poisoning and procedural complications	2 (0.5) [2] 0.77 (0.09, 2.80) 0.77	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Humerus fracture	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Tibia fracture	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Upper limb fracture	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Investigations	2 (0.5) [2] 0.77 (0.09, 2.80) 0.77	0
Liver function test increased	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Interferon gamma release assay positive	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Metabolism and nutrition Disorders	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Diabetes mellitus	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Musculoskeletal and connective tissue Disorders	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	1 (0.6) [1] 0.94 (0.02, 5.25) 0.94
Arthritis	0	1 (0.6) [1] 0.94 (0.02, 5.25) 0.94
Spinal column stenosis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94
Gastric cancer	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Thyroid adenoma	0	1 (0.6) [1] 0.95 (0.02, 5.27) 0.94

System Organ Class/Preferred Term	Bimekizumab 320 mg Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Nervous system disorders	2 (0.5) [2] 0.77 (0.09, 2.80) 0.77	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Cerebral infarction	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Hydrocephalus	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Vocal cord paresis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Psychiatric disorders	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Alcoholism	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Skin and subcutaneous tissue disorders	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Psoriasis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Surgical and medical procedures	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Metabolic surgery	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0

n- number of subjects reporting at least one SAE
[#]- number of individual occurrences of the SAE
Incidence- Incidence of new cases per 100 subject-years, and associated 95% CI
Event rate- event rate per 100 subject-years
Note: Bimekizumab 320 mg Q4W group also includes subjects that switched from placebo to bimekizumab (only events after switch are reported)
Source: Applicant's Table 8.1.3.2.1, PS0009 Clinical Study Report

Narratives for subjects treated with bimekizumab are presented below:

<u>SAEs considered by the investigator as related to treatment:</u>

- A 57 y/o Asian female (Subject PS0009-(b) (6) experienced an SAE of esophageal candidiasis on Day 138. She was hospitalized and treated with amphotericin and fluconazole. The event was considered severe in intensity and the outcome was

resolved. Treatment with bimekizumab was discontinued, and the investigator considered the event as related to treatment with bimekizumab.

- A 28 y/o white female (Subject PS0009-(b) (6) experienced SAEs of subglottic laryngitis and vocal cord paresis on Day 180. She was hospitalized and required ICU care for dyspnea. Both events were considered moderate in severity and the outcomes for both were resolved. Treatment with bimekizumab was discontinued, and the investigator considered the event as related to treatment with bimekizumab.

SAEs considered not related to treatment by the investigator:

- A 73 y/o white male (Subject PS0009-(b) (6) experienced an SAE of myocardial infarction on Day 166 and was hospitalized and treated with coronary angioplasty and stenting. During the hospitalization he also experienced a GI bleed (bleeding ulcer). Treatment with bimekizumab was discontinued but he remained in the trial. The event was considered severe in intensity and the outcome was resolved. On Day 253, he experienced an SAE of gastric cancer after which he discontinued from the trial. The event was considered moderate in intensity and the outcome was not resolved. The investigator considered both SAEs as not related to treatment with bimekizumab.
- A 42 y/o white male (Subject PS0009-(b) (6)) with a history of hypertension, hyperlipidemia, and obesity experienced an SAE of myocardial infarction on Day 172. He was hospitalized and treated with coronary angioplasty and stenting. The event was considered severe in intensity and the outcome was resolved with sequelae. Treatment with bimekizumab was interrupted during the event. He later resumed treatment and completed the trial. The investigator considered the event as not related to treatment with bimekizumab.
- A 47 y/o white male (Subject PS0009-(b) (6)) with a history of hyperlipidemia and previous tobacco use experienced an SAE of acute myocardial infarction on Day 147. He was hospitalized and treated with coronary angioplasty and stenting. The event was considered severe in intensity and the outcome was resolved. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 50 y/o male (Subject PS0009-(b) (6) who died of an unknown cause on Day 208 subject is presented above in the subsection regarding deaths.
- A 57 y/o white female (Subject PS0009-(b) (6)) experienced an SAE of gastroenteritis on Day 360 which include 2 weeks of diarrhea and bloody stools. She was hospitalized and underwent colonoscopy which revealed normal mucosa and a small hyperplastic rectal polyp. She was diagnosed with gastroenterocolitis. The event was considered moderate in intensity and the outcome was resolved. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 63 y/o white female (Subject PS0009-(b) (6)) with a history of psoriatic arthritis experienced an SAE of infective tenosynovitis of the right middle finger on Day 258. She was hospitalized and treated with IV antibiotics and incision and drainage. The event

was considered severe in intensity and the outcome was resolved. She continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.

- A 47 y/o white male (Subject PS0009-(b) (6)) experienced an SAE of necrotizing fasciitis of the scrotum and perineum on Day 298. He was hospitalized and treated with surgical debridement and IV antibiotics. The event was considered severe in intensity and the outcome was resolved. Treatment with bimekizumab was interrupted during the event, and the subject withdrew from the trial. The investigator considered the event as not related to treatment with bimekizumab.
- A 44 y/o Japanese male (Subject PS0009-(b) (6) experienced an SAE of humerus fracture on Day 281 after a fall from a motorcycle and was hospitalized. The event was considered moderate in intensity and the outcome was resolved. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 46 y/o white male (Subject PS0009-(b) (6) experienced an SAE of bilateral upper limb fracture on Day 308 after a bicycle accident. He was hospitalized and underwent open fixation. The event was considered moderate in intensity and the outcome was resolved. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 61 y/o white female (Subject PS0009-(b) (6)) with a history of cholelithiasis, cholecystectomy, bile duct perforation, and common bile duct repair experienced an SAE of liver function test increased on Day 141. The event was considered severe in intensity and the outcome was resolved. Treatment with bimekizumab was discontinued, and the investigator considered the event as not related to treatment with bimekizumab. This subject is also discussed in Section 8.2.5.3 of this review regarding hepatotoxicity.
- A 20 y/o white female (Subject PS0009-(b) (6)) experienced an SAE of interferon gamma release assay (IGRA) false positive on Day 350. She was hospitalized with productive cough when the positive IGRA test occurred. However, bronchoscopy, bronchoalveolar lavage, sputum culture, and TB polymerase chain reaction were negative for TB. Follow-up IGRA testing was negative. The event was considered moderate in intensity and the outcome was resolved. She had received her final dose of bimekizumab in the trial prior to the event. The investigator considered the event as not related to treatment with bimekizumab.
- A 59 y/o white male (Subject PS0009-(b) (6) with a history of intervertebral disc protrusion, L4 L5 herniated disk, and laminectomy experienced an SAE of spinal column stenosis on Day 204. He was hospitalized and underwent lumbar fusion. The event was considered moderate in intensity and the outcome was resolved. Treatment with bimekizumab was interrupted during the event. He resumed treatment after recovery and completed the trial. The investigator considered the event as not related to treatment with bimekizumab.
- A 60 y/o white male (Subject PS0009-(b) (6)) with a history of type 2 DM, obesity, hypertension, and previous tobacco use experienced an SAE of cerebral infarction on

Day 283. He was hospitalized and a magnetic resonance imaging scan of the brain revealed appearances of a subacute infarct within the left posterior cerebral artery territory. The event was considered moderate in intensity and the outcome was resolved. Treatment with bimekizumab was interrupted during the event. He resumed treatment after recovery and completed the trial. The investigator considered the event as not related to treatment with bimekizumab.

- A 76 y/o Japanese male (Subject PS0009-(b) (6)) experienced an SAE of alcoholism on Day 283 and was hospitalized where he attended an abstinence program. The event was considered mild in intensity and the outcome was resolving. He continued treatment with bimekizumab, and the investigator considered the event as not related to treatment with bimekizumab.
- A 35 y/o white female (Subject PS0009-(b) (6)) experienced an SAE of worsening psoriasis on Day 268 and was hospitalized. Treatment included brodalumab and corticosteroids. The event was considered moderate in intensity and the outcome was resolved. Treatment with bimekizumab was discontinued, and the investigator considered the event as not related to treatment with bimekizumab.
- A 33 y/o white female (Subject PS0009-(b) (6)) with a history of obesity experienced an SAE of metabolic surgery on Day 302 for which she was hospitalized. The event was considered mild in intensity and the outcome was resolved. Treatment with bimekizumab was interrupted during the event. She resumed treatment after recovery and completed the trial. The investigator considered the event as not related to treatment with bimekizumab.

Dropouts and/or Discontinuations Due to Adverse Effects

Data regarding discontinuations because of AEs will be presented using the same data pools as for SAEs.

In Pool S1, 11/670 (1.6%) subjects treated with bimekizumab and 7/169 (4.1%) subjects treated with placebo discontinued because of an adverse event. The most common SOCs for AEs leading to discontinuation in the bimekizumab group were Infections and Infestations (3/670, 0.4%), Skin and Subcutaneous Disorders (2/670, 0.3%), and Investigations (2/670, 0.3%). Two of the three AEs from the Infections and Infestations SOC involved mucocutaneous fungal infections, which are consistent with the immunosuppressive properties of bimekizumab. AE which led to discontinuation in Pool S1 are presented in the table below.

Table 46: AEs leading to Discontinuation, Pool S1

System-Organ Class/Preferred Term	BKZ 320mg Q4W n=670	Placebo n=169
Infections and infestations	3 (0.4%)	0 (0.0%)
Oropharyngeal candidiasis	1 (0.1%)	0 (0.0%)
Oropharyngitis fungal	1 (0.1%)	0 (0.0%)
Tooth abscess	1 (0.1%)	0 (0.0%)

System-Organ Class/Preferred Term	BKZ 320mg Q4W n=670	Placebo n=169
Skin and subcutaneous tissue disorders	2 (0.3%)	3 (1.8%)
Eczema	2 (0.3%)	0 (0.0%)
Psoriasis	0 (0.0%)	3 (1.8%)
Investigations	2 (0.3%)	0 (0.0%)
Blood pressure decreased	1 (0.1%)	0 (0.0%)
Hepatic enzyme increased	1 (0.1%)	0 (0.0%)
Cardiac disorders	1 (0.1%)	0 (0.0%)
Cardiac arrest	1 (0.1%)	0 (0.0%)
Psychiatric disorders	1 (0.1%)	0 (0.0%)
Bipolar disorder	1 (0.1%)	0 (0.0%)
Gastrointestinal disorders	1 (0.1%)	1 (0.6%)
Colitis ulcerative	1 (0.1%)	0 (0.0%)
Diarrhea	0 (0.0%)	1 (0.6%)
Immune system disorders	1 (0.1%)	0 (0.0%)
Hypersensitivity	1 (0.1%)	0 (0.0%)
Musculoskeletal and connective tissue disorders	0 (0.0%)	1 (0.6%)
Psoriatic arthropathy	0 (0.0%)	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (0.6%)
Esophageal adenocarcinoma	0 (0.0%)	1 (0.6%)
Blood and lymphatic system disorders	0 (0.0%)	1 (0.6%)
Lymphadenopathy	0 (0.0%)	1 (0.6%)
TOTAL	11 (1.6%)	7 (4.1%)

Source: Reviewer's Table

Narratives for subjects treated with bimekizumab in Pool S1 who discontinued because of an AE are presented below:

TEAEs leading to discontinuation considered related to treatment by the investigator:

- A 56 y/o white female (Subject PS0009-(b) (6) experienced oropharyngeal candidiasis (3rd event) on Day 110 and discontinued treatment with bimekizumab. She was treated with amphotericin B and nystatin. The event was considered moderate in severity and the outcome was not resolved at the time of discontinuation. The investigator considered the event related to treatment with bimekizumab.
- A 39 y/o white female (Subject PS0009-(b) (6)) experienced oropharyngitis fungal on Day 70 and discontinued treatment with bimekizumab. She was treated with omeprazole and amphotericin B. The event was considered moderate in intensity and the outcome was resolved. The investigator considered the event related to treatment with bimekizumab.
- A 35 y/o Japanese male (Subject PS0009-(b) (6) with a reported history of alcohol use (7 units/week) experienced an AE of elevated liver enzymes (PT: hepatic enzyme increased) on Day 57 and discontinued treatment with bimekizumab. The event was

considered moderate in intensity and the outcome was reported by the Applicant as resolved on Day 294. The investigator considered the event related to treatment with bimekizumab.

- 32 y/o Asian male (Subject PS0009-(b) (6)) discontinued because of an SAE of ulcerative colitis. The narrative for this subject is presented above in the subsection regarding SAEs.
- A 53 y/o white male (Subject PS0013-(b) (6)) experienced an AE of eczema on Day 41 and discontinued treatment with bimekizumab. The event was considered moderate in intensity and the outcome was not resolved at the time of the report. The investigator considered the event related to treatment with bimekizumab.
- A 44 y/o Hispanic or Latino male (Subject PS0013-(b) (6)) experienced an AE of hypersensitivity (verbatim term: dermal hypersensitivity upper trunk) on Day 9 and discontinued treatment with bimekizumab. He was treated with diphenhydramine and emollients. The event was considered moderate in intensity and the outcome was resolving at the time of the report. The investigator considered the event related to treatment with bimekizumab.

TEAEs leading to discontinuation considered not related to treatment by the investigator:

- A 63 y/o white female (Subject PS0009-(b) (6)) with fatal myocardial infarction is presented above under deaths.
- A 66 y/o white male (Subject PS0009-(b) (6)) experienced an AE of eczema on Day 3 and discontinued treatment with bimekizumab. The event was considered severe in intensity and the outcome was not resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab.
- A 51 y/o white female (Subject PS0013-(b) (6)) with a history of hypertension experienced an AE of blood pressure decreased on Day 66 and discontinued treatment with bimekizumab. No blood pressure readings were available at the time of the event, and her reported concomitant medications did not include antihypertensives. The event was considered moderate in intensity and the outcome was unknown at the time of the report. The investigator considered the event not related to treatment with bimekizumab.
- A 52 y/o white male (Subject PS0013-(b) (6)) with a history of bipolar disorder, anxiety, and depression experienced an AE of psychiatric evaluation abnormal (verbatim term: elevated PHQ-9) on Day 113 and discontinued treatment with bimekizumab. The event was considered moderate in intensity and the outcome was not resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab.
- A 75 y/o white female (Subject PS0013-(b) (6) experienced an AE of tooth abscess on Day 108 and discontinued treatment with bimekizumab. The event was considered mild in intensity and the outcome was resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab.

Comparison of AEs leading to discontinuation between Q4W and Q8W dosing regimens

In Pool S2C, 4/261 (1.5%) of subjects treated with the Q4W and 7/257 (2.7%) subjects treated with the Q8W dosing regimens had AEs which led to discontinuation. The only SOC in which more than one subject had an AE leading to discontinuation was Skin and Subcutaneous Disorders. A total of 2 subjects each from the Q4W and Q8W regimens discontinued because of AEs from this SOC. AEs leading to discontinuation in Pool S2C are presented in the table below:

Table 47: AEs leading to Discontinuation, Pool S2C

System-Organ Class/Preferred Term	BKZ 320mg Q4W n=261	BKZ 320mg Q8W n=257	Totals n=518
Investigations	0 (0.0%)	2 (0.8%)	2 (0.4%)
Hepatic enzyme increased	0 (0.0%)	2 (0.8%)	2 (0.4%)
Skin and subcutaneous tissue disorders	2 (0.8%)	2 (0.8%)	4 (0.8%)
Alopecia	1 (0.4%)	1 (0.4%)	2 (0.4%)
Dermatitis psoriasiform	0 (0.0%)	1 (0.4%)	1 (0.2%)
Dermatitis exfoliative	1 (0.4%)	0 (0.0%)	1 (0.2%)
Infections and infestations	0 (0.0%)	1 (0.4%)	1 (0.2%)
Viral upper respiratory tract infection	0 (0.0%)	1 (0.4%)	1 (0.2%)
Gastrointestinal disorders	0 (0.0%)	1 (0.4%)	1 (0.2%)
Diarrhea	0 (0.0%)	1 (0.4%)	1 (0.2%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0%)	1 (0.4%)	1 (0.2%)
Colon cancer	0 (0.0%)	1 (0.4%)	1 (0.2%)
Pregnancy, puerperium and perinatal conditions	1 (0.4%)	0 (0.0%)	1 (0.2%)
Pregnancy with contraceptive device	1 (0.4%)	0 (0.0%)	1 (0.2%)
Abortion spontaneous	1 (0.4%)	0 (0.0%)	1 (0.2%)
Congenital, familial and genetic disorders	1 (0.4%)	0 (0.0%)	1 (0.2%)
Porokeratosis	1 (0.4%)	0 (0.0%)	1 (0.2%)
TOTAL	4 (1.5%)	7 (2.7%)	11 (2.1%)

Source: Reviewer's Table

Narratives for subjects with AEs leading to discontinuation in Pool S2C are presented below:

Subjects treated with bimekizumab 320 mg Q4W

TEAEs leading to discontinuation considered related to treatment by the investigator:

- A 28 y/o white female (Subject PS0008-(b) (6) experienced an AE of porokeratosis on Day 260 and discontinued treatment with bimekizumab. The AE was considered mild in severity and the outcome was resolving. The investigator considered the event related to treatment with bimekizumab.

TEAEs leading to discontinuation considered not related to treatment by the investigator:

- A 64 y/o white male (Subject PS0008-(b) (6) experienced an AE of dermatitis exfoliative (verbatim term: erythroderma secondary to eczema) on Day 320 and discontinued treatment with bimekizumab. He was treated with cyclosporin for exfoliative dermatitis. The AE was considered moderate in severity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 34 y/o white female (Subject PS0008-(b) (6)) with pregnancy with contraceptive device and abortion spontaneous was presented under SAEs.
- A 57 y/o white male (Subject PS0008-(b) (6) experienced an AE of alopecia (verbatim term: hair loss-scalp) on Day 257 and discontinued treatment with bimekizumab. The AE was considered severe in severity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.

Subjects treated with bimekizumab 320 mg Q8W

TEAEs leading to discontinuation considered related to treatment by the investigator:

- A 61 y/o white female (Subject PS0008-(b) (6) experienced an AE of dermatitis psoriasiform (verbatim term: paradoxical psoriasiform dermatitis on feet and scalp) on Day 135 and discontinued treatment with bimekizumab. The AE was considered moderate in severity and the outcome was resolving at the time of the report. The investigator considered the event related to treatment with bimekizumab.

TEAEs leading to discontinuation considered not related to treatment by the investigator:

- A 21 y/o white female (Subject PS0008-(b) (6)) who discontinued due to an SAE of hepatic enzyme increased was presented under SAEs.
- A 36 y/o white male (Subject PS0008-(b) (6) with a history of gamma glutamyl transferase increased, non-alcoholic fatty liver, and alcohol use (4 units/week) experienced an AE of hepatic enzyme increased on Day 122 and discontinued treatment with bimekizumab. The AE was considered severe in severity and the outcome was not resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab. The probable cause was attributed to NAFLD and alcohol.
- A 37 y/o white male (Subject PS0008-(b) (6) experienced an AE of alopecia (verbatim term: hair thinning) on Day 155 and discontinued treatment with bimekizumab. The AE was considered mild in severity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 48 y/o white male (Subject PS0008-(b) (6)) who discontinued due to SAE of colon cancer was presented under SAEs.
- A 31 y/o white male (Subject PS0013-(b) (6) who discontinued due to an SAE of diarrhea was presented under SAEs.
- A 25 y/o white female (Subject PS0013-(b) (6) experienced an AE of viral upper respiratory tract infection on 230 and discontinued treatment with bimekizumab. The

AE was considered moderate in intensity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.

Discontinuations from Trials PS0008 (Initial Treatment Period) and PS0009 (Maintenance Treatment Period)

During the Initial Treatment Period of Trial PS0008, 5/319 (1.6%) of subjects treated with bimekizumab and 4/159 (2.5%) of subjects treated with adalimumab discontinued because of an AE. No SOC had more than a single subject with an AE leading to discontinuation. AEs leading to discontinuation are presented in the table below:

Table 48: AEs leading to Discontinuation, Trial PS0008 Initial Treatment Period

System Organ Class/Preferred Term	Bimekizumab N=319 n (%) [#] Incidence (95% CI) Event Rate	Adalimumab n=159 n (%) [#] Incidence (95% CI) Event Rate
Total	5 (1.6) [6] 5.11 (1.66, 11.92) 6.11	4 (2.5) [4] 8.29 (2.26, 21.23) 8.19
Gastrointestinal disorders	1 (0.3) [2] 1.02 (0.03, 5.67) 2.04	0
Diarrhea	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0
Nausea	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0
Hepatobiliary disorders	0	1 (0.6) [1] 2.06 (0.05, 11.48) 2.05
Hepatitis alcoholic	0	1 (0.6) [1] 2.06 (0.05, 11.48) 2.05
Injury, poisoning and procedural complications	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0
Arthropod bite	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0
Investigations	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	1 (0.6) [1] 2.06 (0.05, 11.47) 2.05
Hepatic enzyme increased	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	1 (0.6) [1] 2.06 (0.05, 11.47) 2.05

System Organ Class/Preferred Term	Bimekizumab N=319 n (%) [#] Incidence (95% CI) Event Rate	Adalimumab n=159 n (%) [#] Incidence (95% CI) Event Rate
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	1 (0.6) [1] 2.05 (0.05, 11.42) 2.05
Anal squamous cell carcinoma	1 (0.3) [1] 1.02 (0.03, 5.68) 1.02	0
Squamous cell carcinoma of the tongue	0	1 (0 .6) [1] 2.05 (0.05, 11.42) 2.05
Psychiatric disorders	0	1 (0.6) [1] 2.05 (0.05, 11.41) 2.05
Alcohol abuse	0	1 (0.6) [1] 2.05 (0.05, 11.41) 2.05
Skin and subcutaneous tissue disorders	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0
Psoriasis	1 (0.3) [1] 1.02 (0.03, 5.67) 1.02	0

n- number of subjects reporting at least one AE leading to discontinuation
[#]- number of individual occurrences of the AE leading to discontinuation
Incidence- Incidence of new cases per 100 subject-years, and associated 95% CI
Event rate- event rate per 100 subject-years
Source: Applicant's Table 8.1.4.3, PS0008 Clinical Study Report

Narratives for subjects in the bimekizumab group are presented below:

<u>TEAEs leading to discontinuation considered related to treatment by the investigator:</u>

- A 37 y/o white female (Subject PS0008-(b) (6)) with a history of ulcerative colitis experienced AEs of diarrhea and nausea on Day 17 and discontinued treatment with bimekizumab. The events were considered moderate in severity and the outcome of the events was unknown at the time of the report. The investigator considered the events related to treatment with bimekizumab.
- A 52 y/o Asian male (Subject PS0008-(b) (6) experienced an AE of psoriasis (verbatim term: worsening of psoriasis) on Day 110 and discontinued treatment with bimekizumab. The event was considered moderate in severity and the outcome was not resolved at the time of the report. The investigator considered the event related to treatment with bimekizumab.

TEAEs leading to discontinuation considered not related to treatment by the investigator:

- A 26 y/o Asian male (Subject PS0008-(b) (6) experienced an AE of arthropod bite (verbatim term: insect bite reaction) on Day 47 and discontinued treatment with bimekizumab. He was treated with prednisone. The event was considered moderate in severity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.
- A 36 y/o white male (Subject PS0008-(b) (6) with a history of alcohol use (56 units/week) experienced an AE of hepatic enzyme increased on Day 1 and discontinued treatment with bimekizumab. His transaminase levels were elevated at Baseline as well. The event was considered moderate in severity and the outcome was not resolved at the time of the report. The investigator considered the event not related to treatment with bimekizumab.
- A 51 y/o Native Hawaiian or other Pacific Islander male (Subject PS0008-(b) (6) experienced an AE of anal squamous cell carcinoma on Day 45 and discontinued treatment with bimekizumab. The event was considered mild in severity and the outcome was unknown at the time of the report. The investigator considered the event not related to treatment with bimekizumab.

During the Maintenance Period of Trial PS0009, 15/380 (3.9%) of subjects treated with bimekizumab and 4/157 (2.5%) of subjects treated with ustekinumab discontinued because of an AE. The most common SOC for AEs leading to discontinuation in the bimekizumab group was Infections and infestations with 8/380 (2.1%) subjects. Of these 8 subjects, 4 discontinued because of mucocutaneous fungal infections, which are consistentwith the immunosuppressive properties of bimekizumab. AEs leading to discontinuation are presented in the table below:

Table 49: AEs leading to Discontinuation, Trial PS0009 Maintenance Treatment Period

System Organ Class/Preferred Term	Bimekizumab Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Total	15 (3.9) [17] 5.89 (3.30, 9.72) 6.57	4 (2.5) [4] 3.80 (1.04, 9.74) 3.76
Hepatobiliary disorders	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Drug-induced liver injury	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Infections and infestations	8 (2.1) [9] 3.12 (1.35, 6.14) 3.48	0

System Organ Class/Preferred Term	Bimekizumab Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Cellulitis	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Oral candidiasis	3 (0.8) [3] 1.16 (0.24, 3.40) 1.16	0
Esophageal candidiasis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Conjunctivitis	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Impetigo	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Staphylococcal infection	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Peritonsillar abscess	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Investigations	2 (0.5) [2] 0.77 (0.09, 2.80) 0.77	0
Liver function test increased	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Columbia suicide severity rating scale abnormal	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Metabolism and nutrition disorders	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Diabetes mellitus	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Musculoskeletal and connective tissue disorders	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Psoriatic arthropathy	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0

System Organ Class/Preferred Term	Bimekizumab Q4W N=380 n (%) [#] Incidence (95% CI) Event Rate	Ustekinumab N=157 n (%) [#] Incidence (95% CI) Event Rate
Gastric cancer	1 (0.3) [1] 0.39 (0.01, 2.15) 0.39	0
Nervous system disorders	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Vocal cord paresis	1 (0.3) [1] 0.39 (0.01, 2.16) 0.39	0
Psychiatric disorders	0	2 (1.3) [2] 1.89 (0.23, 6.82) 1.88
Generalized anxiety disorder	0	1 (0.6) [1] 0.94 (0.02, 5.26) 0.94
Suicide attempt	0	1 (0.6) [1] 0.94 (0.02, 5.24) 0.94
Skin and subcutaneous tissue disorders	3 (0.8) [3] 1.16 (0.24, 3.40) 1.16	0
Psoriasis	3 (0.8) [3] 1.16 (0.24, 3.40) 1.16	0

n- number of subjects reporting at least one AE leading to discontinuation
[#]- number of individual occurrences of the AE leading to discontinuation
Incidence- Incidence of new cases per 100 subject-years, and associated 95% CI
Event rate- event rate per 100 subject-years
Note: Bimekizumab 320 mg Q4W group also includes subjects that switched from placebo to bimekizumab (only events after switch are reported)
Source: Applicant's Table 8.1.4.2.1, PS0008 Clinical Study Report

Narratives for subjects in the bimekizumab group are presented below:

<u>TEAEs leading to discontinuation considered related to treatment by the investigator:</u>

- A 44 y/o Japanese male (Subject PS0009-(b) (6) with a history of "liver disorder" and alcohol use (73 units/week) experienced an AE of drug induced liver injury on Day 141 and discontinued treatment with bimekizumab. The event was considered severe in intensity and the outcome was resolved. The investigator considered the event related to treatment with bimekizumab. This subject is also discussed in Section 8.2.5.3 of this review regarding hepatotoxicity.
- A 50 y/o white male (Subject PS0009-(b) (6) experienced an AE of cellulitis on Day 169 and discontinued treatment with bimekizumab. The event was considered

severe in intensity and the outcome was unknown at the time of the report. The investigator considered the event related to treatment with bimekizumab. The subject died of an unknown cause on Day 209 and is also discussed above in the subsection regarding deaths.

- A 69 y/o Japanese male (Subject PS0009-(b) (6) experienced an AE of oral candidiasis (second event) on Day 287 and discontinued treatment with bimekizumab. The event was considered mild in intensity and the outcome was resolved. The investigator considered the event related to treatment with bimekizumab.
- A 42 y/o Japanese male (Subject PS0009-(b) (6) experienced an AE of oral candidiasis on Day 337 (second event) and discontinued treatment with bimekizumab. The event was considered mild in intensity and the outcome was resolved. The investigator considered the event related to treatment with bimekizumab.
- A 56 y/o white female (Subject PS0009-(b) (6) experienced an AE of oral candidiasis and discontinued treatment with bimekizumab. The event was considered mild in intensity and the outcome was unknown at the time of the report. The investigator considered the event related to treatment with bimekizumab.
- A 57 y/o Asian female (Subject PS0009-(b) (6) discontinued because of an SAE of esophageal candidiasis. The narrative for this subject is presented above in the subsection regarding SAEs.
- A 31 y/o white female (Subject PS0009-(b) (6) experienced AEs of impetigo (third event) on Day 322 and conjunctivitis on Day 325 and discontinued treatment with bimekizumab. The AE of impetigo was considered moderate in intensity and the outcome was resolved. The AE of conjunctivitis was considered moderate in intensity and the outcome was not resolved at the time of the report. The investigator considered both events related to treatment with bimekizumab.
- A 45 y/o white male (Subject PS0009-(b) (6) experienced an AE of staphylococcal infection (verbatim term: MRSA lower extremities) and discontinued treatment with bimekizumab. The event was considered moderate in intensity and the outcome was not resolved at the time of the report. The investigator considered the event related to treatment with bimekizumab.
- A 31 y/o white female (Subject PS0009-(b) (6) experienced an AE of peritonsillar abscess on Day 247 and discontinued treatment with bimekizumab. The event was considered severe in intensity and the outcome was resolved. The investigator considered the event related to treatment with bimekizumab
- A 36 y/o Japanese male (Subject PS0009-(b) (6) experienced AEs of Columbia Suicide Severity Rating Scale abnormal and psoriasis (verbatim term: psoriasis aggravated [paradoxical reaction]) on Day 141 and discontinued treatment with bimekizumab. Both AEs were considered moderate in intensity. The outcome of the Columbia Suicide Severity Rating Scale abnormal was resolved. The outcome of the

psoriasis was not resolved at the time of the report. The investigator considered both events related to treatment with bimekizumab.

- A 54 y/o white male (Subject PS0009-(b) (6) experienced an AE of psoriasis (verbatim term: worsening psoriasis both hands and arms) on Day 124 and discontinued treatment with bimekizumab. The event was considered moderate in intensity and the outcome was not resolved at the time of the report. The investigator considered the event related to treatment with bimekizumab.
- A 28 y/o white female (Subject PS0009-(b) (6) discontinued because of an SAE of vocal cord paresis. The narrative for this subject is presented above in the subsection regarding SAEs.

TEAEs leading to discontinuation considered not related to treatment by the investigator:

- A 61 y/o white female (Subject PS0009-(b) (6) discontinued because of an SAE of liver function test increased. The narrative for this subject is presented above in the subsection regarding SAEs.
- A 73 y/o white male (Subject PS0009-(b) (6) discontinued because of an SAE of gastric cancer. The narrative for this subject is presented above in the subsection regarding SAEs.
- A 35 y/o white female (Subject PS0009-(b) (6)) experienced an AE of psoriasis (verbatim term: worsening plaque psoriasis) on Day 268 and discontinued treatment with bimekizumab. The event was considered moderate in intensity and the outcome was resolved. The investigator considered the event not related to treatment with bimekizumab.

Significant Adverse Events

Refer to Section 8.2.5 of this review for a discussion of the Adverse Events of Special Interest (AESI).

Treatment Emergent Adverse Events and Adverse Reactions

Adverse Reactions for Labeling

The primary analysis pool for treatment-emergent adverse events (TEAEs) and adverse reactions (ARs) for labeling is Pool S1, which consists of data from the placebo-controlled periods of Trials PS0009 and PS0013 (Week 0-16). In Pool S1, TEAEs occurred in 394/670 (58.8%) of subjects treated with bimekizumab 320 mg Q4W and 74/169 (43.8%) of subjects treated with placebo. In subjects treated with bimekizumab, the most common system-organ classes (SOCs) in which TEAEs were reported were Infections and Infestations (241/670, 36.0%), Skin and Subcutaneous Tissue Disorders (77/670, 11.5%), and Gastrointestinal Disorders (62/670, 9.3%). TEAEs by SOC in Pool S1 are presented in the table below:

Table 50: Treatment Emergent AEs by System-Organ Class, Pool S1

System-Organ Class	BKZ 320mg Q4W n=670	Placebo n=169
Infections and infestations	241 (36.0%)	38 (22.5%)
Skin and subcutaneous tissue disorders	77 (11.5%)	16 (9.5%)
Gastrointestinal disorders	62 (9.3%)	9 (5.3%)
Nervous system disorders	45 (6.7%)	2 (1.2%)
Musculoskeletal and connective tissue disorders	39 (5.8%)	21 (12.4%)
General disorders and administration site conditions	37 (5.5%)	4 (2.4%)
Investigations	32 (4.8%)	5 (3.0%)
Injury, poisoning and procedural complications	31 (4.6%)	5 (3.0%)
Respiratory, thoracic and mediastinal disorders	26 (3.9%)	6 (3.6%)
Vascular disorders	14 (2.1%)	3 (1.8%)
Eye disorders	12 (1.8%)	0 (0.0%)
Metabolism and nutrition disorders	12 (1.8%)	4 (2.4%)
Psychiatric disorders	12 (1.8%)	1 (0.6%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	9 (1.3%)	2 (1.2%)
Renal and urinary disorders	8 (1.2%)	1 (0.6%)
Ear and labyrinth disorders	7 (1.0%)	1 (0.6%)
Cardiac disorders	7 (1.0%)	3 (1.8%)
Immune system disorders	6 (0.9%)	0 (0.0%)
Blood and lymphatic system disorders	6 (0.9%)	1 (0.6%)
Reproductive system and breast disorders	4 (0.6%)	1 (0.6%)
Hepatobiliary disorders	3 (0.4%)	1 (0.6%)
Congenital, familial and genetic disorders	2 (0.3%)	0 (0.0%)
Surgical and medical procedures	1 (0.1%)	0 (0.0%)

Abbreviations: BKZ=bimekizumab, Q4W=every 4 weeks
Source: Reviewer's Table

To better evaluate the overall frequency of occurrence, the review team pooled preferred terms (PTs) for TEAEs for clinically similar events. The review team then identified imbalances in TEAEs occurring in ≥1% of subjects treated with bimekizumab and more frequently than placebo as potential ARs. These TEAEs are presented in the table below.

Table 51: TEAEs Reported in **≥1%** of Bimekizumab Group and more frequently than Placebo

	BKZ 320 mg Q4W N=670 n, %	Placebo N=169 n, %
Pooled URI[a]	102 (15.2)	24 (14.2)
Pooled Candida Infections[b]	66 (9.9)	1 (0.6)
Pooled Gastroenteritis[c]	29 (4.3)	6 (3.6)
Headache	22 (3.3)	0 (0.0)
Pooled Injection Site Reactions[d]	19 (2.8)	2 (1.2)
Pooled Tinea Infections[e]	18 (2.7)	1 (0.6)
Hypertension	11 (1.6)	2 (1.2)
Pooled Herpes Simplex Infections[f]	9 (1.3)	0 (0.0)

	BKZ 320 mg Q4W N=670 n, %	Placebo N=169 n, %
Acne	8 (1.2)	0 (0.0)
Folliculitis	8 (1.2)	0 (0.0)
Pooled Lower Respiratory Tract Infections[g]	8 (1.2)	1 (0.6)
Fatigue	7 (1.1)	0 (0.0)
Pooled Leukopenias[h]	7 (1.0)	1 (0.6)

Abbreviations: BKZ=bimekizumab, Q4W=every 4 weeks
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[d] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[e] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
[g] Lower Respiratory Tract Infections include bronchitis, lower respiratory tract infection, and pneumonia
[h] Leukopenias include neutrophil count decreased, white blood cell count decreased, lymphocyte count decreased, lymphopenia, and neutropenia; one subject in the placebo group experienced Grade 3 neutropenia which was not reported as an AE by the Applicant
Source: Reviewer's Table

For the TEAE of hypertension and the pooled TEAEs of lower respiratory infections and leukopenias, the imbalance was less than 1% between bimekizumab and placebo groups. We found no evidence that these imbalances represented clinically significant ARs, and these will not be reported in the table in Section 6 of product labeling.

During labeling negotiations, the Applicant proposed more narrow pooling for gastroenteritis and that oropharyngeal Candida and other Candida infections be pooled separately. Pooling for these ARs is presented in the tables below:

Table 52: Revised Pooled Gastroenteritis Pool S1

Preferred Term	BKZ 320mg Q4W N=670 100 subject yrs=2.08 n (%) [EAIR]	Placebo N=169 100 subject yrs=0.52 n (%) [EAIR]
Pooled Gastroenteritis	12 (1.8) [5.8]	0 (0) [0]
Enterovirus infect on	1 (0.1) [0.5]	0 (0) [0]
Gastroenteritis	8 (1.2) [3.9]	0 (0) [0]
Gastroenteritis bacterial	1 (0.1) [0.5]	0 (0) [0]
Gastroenteritis viral	2 (0.3) [1]	0 (0) [0]

Source: Statistical Reviewer's Table

Table 53: Revised Pooled Candida Infections

Preferred Term	BKZ 320mg Q4W N=670 100 subject yrs=2.08 n (%) [EAIR]	Placebo N=169 100 subject yrs=0.52 n (%) [EAIR]
Pooled Oral Candidiasis	61 (9.1) [30.6]	0 (0) [0]
Oral candidiasis	49 (7.3) [24.3]	0 (0) [0]
Oral fungal infection	2 (0.3) [1]	0 (0) [0]
Oropharyngeal candidiasis	8 (1.2) [3.9]	0 (0) [0]
Oropharyngitis fungal	2 (0.3) [1]	0 (0) [0]
Pooled Other Candida Infections	7 (1) [3.4]	1 (0.6) [1.9]
Genital candidiasis	1 (0.1) [0.5]	0 (0) [0]
Skin Candida	1 (0.1) [0.5]	0 (0) [0]
Vulvovaginal candidiasis	3 (0.4) [1.4]	0 (0) [0]
Vulvovaginal mycotic infection	3 (0.4) [1.4]	1 (0.6) [1.9]

Source: Statistical Reviewer's Table

This information will be included in the AR table in Section 6 of labeling.

The following table will be included in Section 6 of labeling:

Table 1. Adverse Reactions Occurring in **≥1%** of Subjects with Plaque Psoriasis in the BIMZELX Group and More Frequently Than in the Placebo Group in the Placebo-Controlled Trials

	BIMZELX N=670 n, %	Placebo N=169 n, %
URI[a]	102 (15)	24 (14)
Oral Candidiasis[b]	61 (9)	0 (0)
Headache	22 (3)	0 (0)
Injection Site Reactions[c]	19 (3)	2 (1)
Tinea Infections[d]	18 (3)	1 (1)
Gastroenteritis[e]	12 (2)	0 (0)
Herpes Simplex Infections[f]	9 (1)	0 (0)
Acne	8 (1)	0 (0)
Folliculitis	8 (1)	0 (0)
Other Candida Infections[g]	7 (1)	1 (1)
Fatigue	7 (1)	0 (0)

[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Oral Candidiasis includes oral candidiasis, oropharyngeal candidiasis, oral fungal infection, fungal pharyngitis, and oropharyngitis fungal
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes Enterovirus infection, gastroenteritis, gastroenteritis bacterial, and gastroenteritis viral
[f] Herpes Simplex Infections include herpes simplex and oral herpes
[g] Other Candida Infections include, vulvovaginal candidiasis, vulvovaginal mycotic infection, skin candida, and genital candidiasis.

Source: Reviewer's Table

Long Term Safety

To evaluate the long-term safety of bimekizumab, the review team compared exposure-adjusted incidence rates (EAIRs) of TEAEs and ARs from the bimekizumab 320 mg Q4W arms in Pool S1 to Pool S2B, which consisted of the Maintenance and Randomized Withdrawal Periods of Trials PS0009 (Week 16-52) and PS0013 (Weeks 16-56), respectively. Overall, EAIRs for TEAEs did not increase with extended exposure to bimekizumab. In Pool S1, TEAEs were reported in 58.8% of subjects treated with bimekizumab, with an EAIR of 305.8/100 subject-years. In the bimekizumab 320 mg Q4W arm in Pool S2B, TEAEs were reported in 74.2% of subjects. However, the EAIR for this group was 221.2/100 subject-years. EAIRs for two most commonly reported SOCs were 141.7 (Pool S1) and 124.1 (Pool S2B) for Infections and Infestations, and 40.0 (Pool S1) and 22.98 (Pool S2B) for Skin and Subcutaneous Disorders.

We also compared EAIRs from Pool S1 and Pool S2B for the ARs identified during the placebo-controlled period. The EAIRs for URIs (52.8 vs 59.2/100 subject-years) and folliculitis (3.9 vs 4.5/100 subject-years) were slightly higher in subjects with longer exposure. However, the EAIRs for the remaining ARs in Pool S2B were similar to or less than the EAIRs reported in Pool S1.

After review of the safety data from Pool S2B, the review team did not identify any new potential ARs emerging after a longer duration of exposure. Specifically, the EAIRs in Pool S2B for the pooled TEAEs of leukopenias and lower respiratory tract infections were all less that those reported for Pool S1.

Comparison of Safety in Q4W and Q8W Dosing Regimens

To evaluate the comparative safety of the bimekizumab 320 mg Q4W and 320 mg Q8W regimens, the review team compared EAIRs of TEAEs and ARs reported during the Maintenance and Randomized Withdrawal Periods (Weeks 16-56) of Trials PS0008 and PS0013 (Pool S2C), respectively. Overall, the EAIR for all TEAEs was higher in the bimekizumab 320 mg Q8W group (76.7%; EAIR: 227.6/100 subject-years) than the bimekizumab 320 mg Q4W group (73.9%; EAIR: 208.1/100 subject-years).

We also compared the EAIRs for the ARs identified during the placebo-controlled period. The EAIRs were adjusted for study size. These are presented in the table below.

Table 54: Adjusted EAIRs of ARs in BKZ 320 mg Q4W vs Q8W Regimen

	Phase 3 BKZ 320mg Q4W N=261 100 subject yrs=1.94 n (%) [adj. %] EAIR [adj. EAIR]	**Phase 3 BKZ 320mg Q8W N=257 100 subject yrs=1.92 n (%) [adj. %] EAIR [adj. EAIR]**
URI[a]	80 (30.7) [30.7] 52.9 [53.1]	94 (36.6) [36.6] 64.7 [64.7]
Candida Infections[b]	45 (17.2) [17.2] 26.0 [26.0]	32 (12.5) [12.4] 18.1 [18.1]
Headache	6 (2.3) [2.3] 3.1 [3.1]	4 (1.6) [1.6] 2.1 [2.1]
Injection Site Reactions[c]	3 (1.1) [1.1] 1.6 [1.6]	4 (1.6) [1.5] 2.1 [2.1]
Tinea Infections[d]	10 (3.8) [3.8] 5.3 [5.3]	11 (4.3) [4.3] 5.9 [5.9]
Gastroenteritis[e]	10 (3.8) [3.8] 5.29 [5.3]	19 (7.4) [7.4] 10.32 [10.33]
Herpes Simplex Infections[f]	4 (1.5) [1.5] 2.1 [2.1]	3 (1.2) [1.2] 1.6 [1.6]
Acne	1 (0.4) [0.4] 0.5 [0.5]	0 (0) [0] 0 [0]
Folliculitis	5 (1.9) [1.9] 2.6 [2.6]	5 (1.9) [1.9] 2.6 [2.6]
Fatigue	0 (0) [0] 0 [0]	2 (0.8) [0.8] 1.05 [1.05]

Abbreviations: adj. EAIR= exposure-adjusted incidence rate, adjusted for study size, BKZ=bimekizumab, EAIR=exposure-adjusted incidence rate, Q4W=every four weeks, Q8W=every 8 weeks, TEAE=treatment-emergent adverse event, yrs=years.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Clinical Reviewer's table

As seen in the table above, the adjusted EAIR for Candida infections was higher in the Q4W (25.99/100 subject-years) than the Q8W (18.11/100 subject-years) regimens. Otherwise, the adjusted EAIRs were similar between the regimens. We detected no dose-response effect for ARs identified during the placebo-controlled period.

Safety vs Active Comparators

In Trial PS0008, adalimumab was included as an active comparator. All subjects randomized to adalimumab in the North American sites (i.e., U.S. and Canada) received US-licensed adalimumab. Subjects randomized to adalimumab at all other sites received EU-approved adalimumab. In Trial PS0009, ustekinumab was included as an active comparator. US-licensed ustekinumab was used in all sites in the U.S.; all other sites received EU-approved ustekinumab Because the Applicant did not establish a scientific bridge between US-licensed and EU-approved comparator products, they will be considered as distinct products for the purpose of this review and safety analyses will be reported accordingly.

To assess the comparative safety of bimekizumab to the US-licensed and EU-approved active comparator products, the review team focused on comparison of the frequencies and EAIRs of the adverse reactions identified in Pool S1 which were proposed for inclusion in labeling. Results of these analyses will be presented below.

Trial PS0008

For the Initial Treatment Period (Week 0-16) of Trial PS0008, subjects were randomized to bimekizumab 320 mg Q4W (continuing through Week 56), bimekizumab 320 mg Q4W (changing at Week 16 to bimekizumab 320 mg Q8W), or adalimumab 80 mg, followed by 40 mg Q2W starting 1 week after the initial dose (switching to bimekizumab 320 mg Q4W at Week 24). To evaluate the comparative safety of bimekizumab to US-licensed and EU-approved adalimumab, this review will focus on the Initial Treatment Period.

During the Initial Treatment Period of Trial PS0008 (Week 0-16), TEAEs were reported in 199/319 (62.4%, EAIR 337.4/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 43/71 (60.6%, EAIR 239.0/100 subject-years) in subjects treated with US-licensed adalimumab, and 53/88 (60.2%, EAIR 329.0/100 subject-years) in subjects treated with EU-approved adalimumab. TEAEs were most frequently reported in the SOCs of Infections and infestations and Gastrointestinal disorders.

TEAEs in the Infections and infestations SOC were reported in 131/319 (41.1%, EAIR 171.1/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 24/71 (33.8%, EAIR 139.7/100 subject-years) in subjects treated with US-licensed adalimumab, and 38/88 (43.2%, EAIR 180.0/100 subject-years) in subjects treated with EU-approved adalimumab. TEAEs in the Gastrointestinal disorders SOC were reported in 27/319 (8.5%, EAIR 28.9/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 5/71 (7.0%, EAIR 24.1/100 subject-years) in subjects treated with US-licensed adalimumab, and 4/88 (4.5%, EAIR 15.2/100 subject-years) in subjects treated with EU-approved adalimumab.

The table below presents the frequency and EAIR for adverse reactions identified in Pool S1.

Table 55: Adverse Reactions Identified in Pool S1, Initial Treatment Period Trial PS0008

	BKZ Total N=319 100 subject yrs=0.98 n (%) EAIR (95% CI)	ADA US-Licensed N=71 100 subject-yrs=0.22 n (%) EAIR (95% CI)	ADA EU-Approved N=88 100 subject-yrs=0.27 n (%) EAIR (95% CI)
Upper Respiratory Infections[a]	68 (21.3) 77.9 (60.5, 98.8)	13 (18.3) 65.6 (34.9, 112.1)	35 (39.8) 161.7 (112.6, 224.9)
Candida Infections[b]	33 (10.3) 35.1 (24.2, 49.3)	0	0
Headache	9 (2.8) 9.3 (4.3, 17.7)	4 (5.6) 19.0 (5.2, 48.7)	1 (1.1) 3.7 (0.1, 20.7)
Injection Site Reactions[c]	7 (2.2) 7.2 (2.9, 14.9)	2 (2.8) 9.4 (1.1, 34.1)	0
Tinea Infections[d]	8 (2.5) 8.3 (3.6, 16.3)	1 (1.4) 4.6 (0.1, 25.9)	0
Gastroenteritis[e]	16 (5.0) 16.8 (9.6, 27.3)	4 (5.6) 19.2 (5.2, 49.2)	5 (5.7) 18.7 (6.1, 43.6)
Herpes Simplex Infections[f]	3 (0.9) 3.1 (0.6, 8.9)	0	1 (1.1) 3.7 (0.1, 20.6)
Acne	0	0	1 (1.1) [1] 3.7 (0.1, 20.6)
Folliculitis	7 (2.2) 7.2 (2.9, 14.8)	1 (1.4) 4.6 (0.1, 25.9)	1 (1.1) 3.7 (0.1, 20.5)
Fatigue	2 (1.3) 4.14 (0.50, 14.96)	1 (1.4) [1] 4.69 (0.12, 26.11)	1 (1.1) [1] 3.71 (0.09, 20.70)

Abbreviations: BKZ=bimekizumab, ADA=adalimumab; CI=confidence interval, Q4W=every four weeks, Q8W=every eight weeks, TEAE=treatment-emergent adverse event, yrs=years, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Clinical Reviewer's Table

Because the overall numbers of subjects who received US-licensed adalimumab is small, it is difficult to draw clinically meaningful conclusions regarding the safety of bimekizumab in comparison to US-licensed adalimumab.

Trial PS0009

For the Initial Treatment Period of Trial PS0009, subjects were randomized to bimekizumab 320 mg Q4W, ustekinumab, or placebo. For ustekinumab, subjects weighing ≤100kg at Baseline received 45 mg SC initially and 4 weeks later; subjects weighing > 100 kg received 90 mg SC initially and 4 weeks later. During the Maintenance Treatment Period, subjects who were randomized to bimekizumab 320 mg Q4W continued on this dosage, subjects who were randomized to placebo switched to bimekizumab 320 mg Q4W, and subjects who were randomized to ustekinumab continued ustekinumab. Subjects weighing ≤100kg at Baseline received 45 mg SC Q12W, and subjects weighing > 100 kg received 90 mg SC Q12W. To evaluate the comparative safety of bimekizumab to US-licensed and EU-approved ustekinumab, this review will consider both the Initial and Maintenance Treatment Periods as both treatment periods included the respective treatment arms.

During the Initial Treatment Period of Trial PS0009 (Week 0-16), TEAEs were reported in 181/321 (56.4%, EAIR 287.3/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 10/34 (29.4%, EAIR 113.9/100 subject-years) in subjects treated with US-licensed ustekinumab, 73/129 (56.6%, EAIR 295.1/100 subject-years) in subjects treated with EU-approved ustekinumab, and 39/83 (47.0%, EAIR 238.4/100 subject-years) in subjects treated with placebo. TEAEs were most frequently reported in the SOCs of Infections and infestations and Skin and subcutaneous disorders.

TEAEs in the SOC of Infections and infestations were reported in 111/321 (34.6, EAIR 137.1/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 3/34 (8.8%, EAIR 29.1/100 subject-years) in subjects treated with US-licensed ustekinumab, 31/129 (24.0%, EAIR 88.8/100 subject-years) in subjects treated with EU-approved ustekinumab, and 18/83 (21.7%, EAIR 83.4/100 subject-years in subjects treated with placebo. TEAEs in the SOC of Skin and subcutaneous disorders were reported in 46/321 (14.3%, EAIR 50.6/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 2/34 (5.9%, EAIR 19.3/100 subject-years) in subjects treated with US-licensed ustekinumab, 13/129 (10.1%, EAIR 34.8/100 subject-years) in subjects treated with EU-approved ustekinumab, and 9/83 (10.8%, EAIR 38.5/100 subject-years) in subjects treated with placebo.

The table below presents the frequency and EAIRs during the Initial Treatment Period of Trial PS0009 for adverse reactions identified in Pool S1.

Table 56: Adverse Reactions Identified in Pool S1, Initial Treatment Period Trial PS0009

	Placebo N=83 100 subject yrs=0.25 n (%) EAIR (95% CI)	BKZ 320mg Q4W N=321 100 subject yrs=0.99 n (%) EAIR (95% CI)	Uste US-Licensed N=34 100 subject-yrs=0.11 n (%) EAIR (95% CI)	Uste EU-Approved N=129 100 subject-yrs=0.39 n (%) EAIR (95% CI)
Upper Respiratory Infections[a]	10 (12.0) 43.1 (20.7, 79.3)	49 (15.3) 53.2 (39.3, 70.3)	1 (2.9) 9.6 (0.2, 53.3)	21 (16.3) 57.9 (35.9, 88.5)
Candida Infections[b]	0	36 (11.2) 38.2 (26.8, 52.9)	0	1 (0.8) 2.5 (0.1, 14.2)
Headache	0	11 (3.4) 11.4 (5.7, 20.3)	0	7 (5.4) 18.3 (7.4, 37.8)
Injection Site Reactions[c]	1 (1.2) 4.0 (0.1, 22.2)	9 (2.8) 9.2 (4.2, 17.6)	0	2 (1.6) 5.1 (0.6, 18.6)
Tinea Infections[d]	0	8 (2.5) 8.2 (3.5, 16.1)	0	0
Gastroenteritis[e]	5 (6.0) 20.2 (6.6, 47.2)	15 (4.7) 15.7 (8.8, 25.9)	0	2 (1.6) 5.1 (0.6, 18.5)
Herpes Simplex Infections[f]	0	5 (1.6) 5.1 (1.7, 11.9)	0	3 (2.3) 7.7 (1.6, 22.4)
Acne	0	8 (2.5) [8] 8.2 (3.5, 16.1)	0	0
Folliculitis	0	5 (1.6) 5.2 (1.7, 11.9)	0	0
Fatigue	0	5 (1.6) [5] 5.09 (1.65, 11.88)	0	0

Abbreviations: BKZ=bimekizumab, Uste=Ustekinumab; CI=confidence interval, Q4W=every four weeks, Q8W=every eight weeks, TEAE=treatment-emergent adverse event, yrs=years, adj.=adjusted, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Clinical Reviewer's Table

In the Maintenance Treatment Period of Trial PS0009 (Week 16-52), TEAEs were reported in 283/380 (74.5%, EAIR 224.0/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 22/34 (64.7%, EAIR 151.5/100 subject-years) in subjects treated with US-licensed ustekinumab, and 81/123 (65.9%, 175.7/100 subject-years) in subjects treated with EU-

approved ustekinumab. TEAEs were most frequently reported in the SOCs of Infections and infestations and Skin and subcutaneous disorders.

TEAEs in the SOC of Infections and infestations were reported in 214/380 (56.3%, EAIR 129.4/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 12/34 (35.3%, EAIR 66.8/100 subject-years) in subjects treated with US-licensed ustekinumab, and 53/123 (43.1%, EAIR 87.7/100 subject-years) in subjects treated with EU-approved ustekinumab. TEAEs in the SOC of Skin and subcutaneous disorders were reported in 58/380 (15.3%, EAIR 24.9/100 subject-years) in subjects treated with bimekizumab 320 mg Q4W, 2/34 (5.9%, EAIR 9.3/100 subject-years) in subjects treated with US-licensed ustekinumab, and 12/123 (9.8%, EAIR 15.0/100 subject-years) in subjects treated with EU-approved ustekinumab.

The table below presents the frequency and EAIRs during the Maintenance Treatment Period of Trial PS0009 for adverse reactions identified in Pool S1.

Table 57: Adverse Reactions Identified in Pool S1, Maintenance Treatment Period Trial PS0009

	BKZ 320mg Q4W N=380 100 subject yrs=2.59 n (%) EAIR (95% CI)	Uste US-Licensed N=34 100 subject-yrs=0.22 n (%) EAIR (95% CI)	Uste EU-Approved N=123 100 subject-yrs=0.84 n (%) EAIR (95% CI)
Upper Respiratory Infections[a]	129 (33.9) 53.2 (44.4, 63.2)	8 (23.5) 36.3 (15.7, 71.6)	43 (35.0) 55.2 (40.0, 74.4)
Candida Infections[b]	59 (15.5) 23.3 (17.7, 30.0)	0	1 (0.8) 1.2 (0.0, 6.6)
Headache	6 (1.6) 2.3 (0.9, 5.1)	1 (2.9) 4.7 (0.1, 26.0)	2 (1.6) 2.4 (0.3, 8.6)
Injection Site Reactions[c]	4 (1.1) 1.5 (0.4, 4.0)	0	0
Tinea Infections[d]	5 (1.3) 1.9 (0.6, 4.5)	0	2 (1.6) 2.4 (0.3, 8.5)
Gastroenteritis[e]	16 (4.2) 6.2 (3.5, 10.0)	0	5 (4.1) 6.0 (1.9, 13.9)
Herpes Simplex Infections[f]	5 (1.3) 1.9 (0.6, 4.5)	0	3 (2.4) 3.6 (0.7, 10.4)
Acne	3 (0.8) 1.2 (0.2, 3.4)	0	0
Folliculitis	14 (3.7) 5.5 (3.0, 9.2)	1 (2.9) 4.6 (0.1, 25.5)	0
Fatigue	3 (0.8) [3] 1.16 (0.24, 3.40)	0	1 (0.8) [1] 1.19 (0.03, 6.62)

Abbreviations: BKZ=bimekizumab; Uste=ustekinumab; CI=confidence interval, Q4W=every four weeks, Q8W=every eight weeks, TEAE=treatment-emergent adverse event, yrs=years, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
Note: BKZ Q4W arm also includes subjects that switched from Placebo to BKZ (only events after switch)

[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Clinical Reviewer's Table

Because the overall numbers of subjects who received US-licensed ustekinumab is small, it is difficult to draw clinically meaningful conclusions regarding the safety of bimekizumab in comparison to US-licensed ustekinumab.

Laboratory Findings

During the development program for bimekizumab, evaluation of systemic safety included assessment of clinical laboratory data, which included hematology, serum chemistry, and urinalysis. Liver biochemistries and leukopenia, including neutropenia, will be discussed in Section 8.2.5 of this review. Excluding these parameters, the Applicant reported no clinically meaningful changes from baseline in laboratory values.

The review team evaluated TEAEs related to laboratory abnormalities. In Pool S1, only 3 PTs were reported in more than one subject in the bimekizumab group. These were Blood glucose increased, Crystal urine present, and Protein urine, each reported in 2/670 (0.3%, EAIR 1/100 subject-years) and no subjects in the placebo group. TEAEs associated with laboratory abnormalities did not increase with extended exposure to bimekizumab. In Pool S2B, there were no increases in EAIRs for TEAE PTs associated with laboratory abnormalities.

In Pool S2C, these were no dose-dependent increases in TEAEs associated with laboratory abnormalities in the bimekizumab Q4W group compared with the bimekizumab Q8W group.

Vital Signs

The Applicant's evaluation of safety included periodic assessment of vital signs. In Pool S1, the Applicant reported increases in systolic BP <180 mmHg and increase of ≥20 mmHg from Baseline in 2/670 (0.3%) subjects in the bimekizumab group and 2/169 (1.2%) in the placebo group. For the same period, the Applicant reported increases in diastolic BP >105 mmHg and increase of ≥15 mmHg from Baseline in 6/670 (0.9%) subjects in the bimekizumab group and 3/169 (1.8%) in the placebo group. Also, in Pool S1, decreases in systolic BP <90 mmHg or diastolic BP<50 occurred in <1% of subjects in either treatment group.

The Applicant also reported that for the pooled Phase 3 trials, increases in diastolic BP >105 mmHg and increase of ≥15 mmHg from Baseline occurred in 36/1493 (2.4%) of subjects in the combined bimekizumab groups. The remaining BP parameter changes described in the preceding paragraph occurred in <1% of subjects in the combined bimekizumab groups.

The review team also evaluated TEAE PTs related to changes in vital signs. In Pool S1, Hypertension was reported in 11/670 (1.6%) of subjects treated with bimekizumab and 2/169 (1.2%) of subjects treated with placebo. As discussed in Section 8.2.4 of this review, the imbalance between bimekizumab and placebo is <0.5%, which is unlikely to be clinically meaningful. For the PT of Hypertension, the EAIR during Pool S1 was 5.3/100 subject-years. In Pool S2B, the EAIR for Hypertension was 3.4/100 subject-years, so no exposure related increase was noted. In Pool S2C, the adjusted EAIRs for the bimekizumab Q4W and Q8W groups were 3.69 and 3.71/100 subject-years, respectively, so no dose related increase in Hypertension was noted.

Otherwise, the only PTs related to vital signs reported more frequently in the bimekizumab group in Pool S1 were Pyrexia in 5/670 (0.7%, EAIR 2.4/100 subject-years) and body temperature increased in 1/670 (0.1%, EAIR 0.5/100 subject-years). Neither PT was reported in the placebo group. In Pool S2B, the adjusted EAIR for Pyrexia was 0.5/100 subject-years for the combined bimekizumab Q4W and Q8W groups. In Pool S2C, the adjusted EAIR for Pyrexia was 1.56/100 subject-years for the bimekizumab Q4W group and 0/100 subject-years for the Q8W group.

Electrocardiograms (ECGs)

During the development program, the Applicant evaluated the effect of bimekizumab on ECG parameters. Effects on the corrected QT interval (QTc) are discussed in the subsection below. No clinically meaningful trends were observed in ECG parameters during the phase 3 trials.

The review team also evaluated TEAEs related to ECG findings. In Pool S1, the PTs Bundle branch block right, Defect conduction intraventricular, Left ventricular hypertrophy, and Electrocardiogram ST segment depression were reported in 1/670 (0.1%) of subjects in the bimekizumab group and no subjects in the placebo group. In Pool S2B, a TEAE of tachycardia was reported in 1/488 (0.2%) subject in the bimekizumab Q4W group. In Pool S2C, no clinically meaningful differences were noted between the Q4W and Q8W treatment arms. In the Q4W arm, the PTs Nodal rhythm, Sinus node dysfunction, and Tachycardia were reported in 1/261 (0.4%) subject each. In the Q8W arm, the PTs Bundle branch block left, and Electrocardiogram T wave amplitude decreased were reported in 1/257 (0.4%) subject each.

QT

The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and

proarrhythmic potential for nonantiarrhythmic drugs does not specifically address QT assessments for biologic agents. Because of their large size and high target specificity, mAbs such as bimekizumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

Although a thorough QT study was not performed for bimekizumab, the Applicant nonetheless explored a relationship between bimekizumab concentrations and QTc during the development program. In Pool S1, no trend in QTc was observed and no subjects had QT interval corrected for heart rate (Fridericia's formula) (QTcF) >500ms. In Pool S2, one subject (PS0008-(b) (6) (1/1271, <0.1%) had a QTcF >500 ms. The subject was asymptomatic, had no TEAEs related to this finding, and continued in the trial.

Immunogenicity

Because therapeutic proteins have the potential to elicit an immune response, the Applicant evaluated for the presence of anti-drug antibodies (ADAb) during the development program. During phase 3 trials, this included the evaluation of neutralizing antibodies (NAb). The assessment of immunogenicity is discussed in more detail in Sections 6.3 and 19.4.5 of this review.

In the pooled Phase 3 trials, the overall incidence of ADAb was 22.6% during the Initial Treatment Period. After 1 year of treatment, the incidence of ADAb was 37.6% in subjects receiving bimekizumab 320mg Q4W throughout and 45.1% in subjects who switched from bimekizumab 320mg Q4W to 320mg Q8W at Week 16. In subjects who switched from Q4W to Q8W at Week 16, a total of 34% of subjects who were ADAb positive were also NAb positive. For NAb, the overall incidence after 1 year of treatment was 14.6% in the bimekizumab Q4W group and 15.6% in the group that switched from Q4W to Q8W at Week 16.

In subjects who were ADAb negative, 726/926 (78.4%) reported 2797 TEAEs. The EAIR was 241.8/100 subject-years, and the event rate was 363.8 events/100 subject-years. In subjects who were ADAb positive, 183/286 (64.0%) reported 577 TEAEs beginning on or after the first ADAb positive result. The EAIR was 230.9/100 subject-years, and the event rate was 342.6 events/100 subject-years.

In subjects who were ADAb positive but NAb negative, 215/262 (82.1%) reported 875 TEAEs. The EAIR was 229.0/100 subject-years, and the event rate was 347.0 events/100 subject-years. In subjects who were ADAb and NAb positive, 131/150 (87.3%) reported 542 TEAEs. The EAIR was 277.6/100 subject-years, and the event rate was 383.9 events/100 subject-years. Although the frequency and event rates for TEAEs were higher overall for NAb-positive subjects, there was no clear trend for any specific SOCs.

Although no TEAEs of drug hypersensitivity were reported in subjects who were NAb positive, we compared the rates of injections site reactions between NAb positive and negative subjects.

The event rates for injection site reactions were similar between NAb positive (3.5 events/100 subject-years) and NAb negative subjects (3.2 events/100 subject-years).

Candida infections occurred more commonly in NAb negative subjects, in which 55/262 (21.0%) reported 105 events. The EAIR was 25.1/100 subject-years, and the event rate was 41.6/100 subject-years. In NAb positive subjects, 21/150 (14.0%) reported 37 events. The EAIR was 16.5/100 subject-years, and the event rate was 26.2/100 subject-years. This difference could be related to decreased IL-17A and IL-17F blockade, with consequent reduction in immunosuppression in NAb positive subjects.

Overall, the presence of ADAb and NAb had no clinically meaningful effect on the safety of bimekizumab. The following is recommended for inclusion in Section 6.2 (Immunogenicity) in labeling:

> "Up to 56 weeks, approximately 45% of subjects treated with BIMZELX at the recommended dose developed antidrug antibodies. Of the subjects who developed antidrug antibodies, approximately 34% (16% of all subjects treated with BIMZELX) had antibodies that were classified as neutralizing. No clinically meaningful differences in the clinical response or safety profile of bimekizumab were observed in subjects who tested positive for anti-bimekizumab antibody."

8.2.5. Analysis of Submission-Specific Safety Issues

During the development program, Adverse Events of Special Interest (AESI) were identified. AESIs were events which were potentially related to the proposed mechanism of action for bimekizumab (immunomodulation via cytokine blockade, specifically IL-17A and IL-17F), class effects associated with other anti-cytokine antibody therapies (including anti-IL-17A), and the specific risks and co-morbidities observed in the target population. The following were identified as AESIs:

- Infections
- Inflammatory Bowel Disease
- Hepatotoxicity/DILI
- Malignancies
- Major Adverse Cardiovascular Events (MACE)
- Neutropenia
- Suicidal Ideation/Behavior (SI/B)
- Hypersensitivity and Injection Site Reactions

Information regarding these AESIs will be summarized and discussed in the subsections below.

8.2.5.1. Infections

Overall Infections

The Applicant reported that during the combined Initial, Maintenance, and Open-label extension periods of the phase 3 trials, infections were reported in 63% of subjects treated with bimekizumab (EAIR 120.4/100 subject-years). In addition, serious infections were reported in 1.5% of subjects treated with bimekizumab (EAIR 1.6/100 subject-years. The review team conducted additional analyses to compare the rate of infections between short-term (Pool S1) and long-term (Pool S2B) exposure to bimekizumab (up to 52 weeks), as well as between the Q4W and Q8W treatment regimens (Pool S2C). Results of these analyses are presented below.

In Pool S1, TEAEs from the SOC of Infections and Infestations were reported in 241/670 (36%, EAIR 141.7/100 subject-years) in the bimekizumab group and 38/169 (22.5%, 84.6/100 subject-years) in the placebo group. We pooled PTs for clinically similar infections, which included upper respiratory infections (URI), Candida infections, Herpes simplex infections, lower respiratory tract infections, tinea infections, and urinary tract infections. Infections comprising these pooled PTs which were reported more frequently in the bimekizumab group compared to the placebo group are presented in the table below. These will be included in Section 6 (Adverse Reactions) in product labeling).

Table 58: Infections (Pooled PTs) Reported More Commonly in the Bimekizumab Group, Pool S1

Pooled Term	**BKZ 320mg Q4W N=670 100 subject yrs=2.08 n (%) [EAIR]**	**Placebo N=169 100 subject yrs=0.52 n (%) [EAIR]**
URI	102 (15.2) [52.8]	24 (14.2) [50.8]
Candida Infections	66 (9.9) [33.2]	1 (0.6) [1.9]
Tinea Infections	18 (2.7) [8.8]	1 (0.6) [1.9]
Herpes Simplex Infections	9 (1.3) [4.4]	0 (0) [0]

Abbreviations: BKZ=bimekizumab, Q4W=every four weeks, TEAE=treatment-emergent adverse event, yrs=years, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
Source: Statistical and Clinical Reviewer's Table

In Pool S2B, which allows comparison of incidence rates between short term (Week 0-16) and long term (Week 16-52) exposure to bimekizumab, TEAEs from the SOC of Infections and Infestations were reported in 268/488 (54.9%, EAIR 124.1/100 subject-years) of subjects treated with bimekizumab Q4W. This demonstrates that the frequency of overall TEAEs related to infection did not increase with increased exposure. Data regarding specific infections of interest (Candida, Tinea, and Herpes Simplex infections) will be presented below in the discussion of opportunistic and fungal infections.

In Pool S2C, which allows for direct comparison of the bimekizumab Q4W and Q8W treatment arms, TEAEs from the SOC of Infections and Infestations were reported in 141/261 (54%, EAIR

118.2/100 subject-years) subjects treated with bimekizumab Q4W and 150/257 (58.4%, EAIR 133.1/100 subject-years) in subjects treated Q8W, which demonstrates that the frequency of overall TEAEs related to infection was not increased with the Q4W dosing regimen. The frequency (%) and EAIRs were adjusted for study size.

Serious Infections

In Pool S1, SAEs from the SOC of Infections and Infestations were reported in 2/670 (0.3%, EAIR 1.0/100 subject-years) in the bimekizumab group and no subjects in the placebo group. PTs for these serious infections included Enteroviral infection and Pneumonia. Each was reported in 1/670 subject (0.1%, EAIR 0.5/100 subject years).

In Pool S2B, serious infections were reported in 6/488 (1.2%, EAIR 1.8/100 subject-years) of subjects treated with bimekizumab Q4W. These included the PTs Gastroenteritis, Esophageal candidiasis, Otitis media chronic, Infective tenosynovitis, Necrotizing fasciitis, and Subglottic laryngitis. Each was reported by 1 subject (1/488, 0.2%, EAIR 0.3/100 subject-years). The EAIR of serious infections was slightly higher with longer exposure to bimekizumab.

In Pool S2C, serious infections were reported in 2/261 (0.8%, EAIR 1.0/100 subject-years) in the Q4W group and 2/257 (0.8%, EAIR 1.0/100 subject-years) in the bimekizumab Q8W group. PTs in the Q4W group included Otitis media chronic and Subcutaneous abscess, each reported in 1 subject (1/261, 0.4%, EAIR 0.5/100 subject-years). PTs in the Q8W group included Appendicitis and Erysipelas, each reported in 1 subject (1/257, 0.4%, EAIR 0.5/100 subject-years). Based on the EAIRs, treatment with bimekizumab Q4W did not increase the risk of serious infection. The frequency (%) and EAIRs were adjusted for study size.

Narratives for subjects who experienced serious infections are presented in Section 8.2.4 of this review under Serious Adverse Events.

Opportunistic Infections and TB

During the development program, opportunistic infections were primarily mucocutaneous fungal infections. Pooled Herpes simplex infections will be discussed in this subsection as well. For our analysis of mucocutaneous fungal infections, we pooled PTs for Candida infections and Tinea Infections.

As presented in the table above, in Pool S1, Candida infections were reported in 66/670 subjects (9.9%, EAIR 33.2/100 subject-years) in the bimekizumab group and 1/169 subject (0.6%, EAIR 1.9/100 subject-years) in the placebo group. Tinea infections were reported in 18/670 subjects (2.7%, EAIR 8.8/100 subject-years) in the bimekizumab group and 1/169 subject (0.6%, EAIR 1.9/100 subject-years) in the placebo group. Herpes simplex infections were reported in 9/670 subjects (1.3%, EAIR 4.4/100 subject-years) in the bimekizumab group and no subjects in the placebo group.

In Pool S2B, in subjects treated with bimekizumab Q4W, Candida infections were reported in 78/488 subjects (16.0%, EAIR 25.6/100 subject-years). Tinea infections were reported in 10/488 subjects (2.0%, EAIR 3.0/100 subject-years). Herpes simplex infections were reported in 7/488 subjects (1.4%, EAIR 2.1/100 subject-years). Based on the EAIRs, the frequency of Candida, Tinea, and Herpes simplex infections did not increase with longer exposure to bimekizumab.

In Pool S2C, Candida infections were reported in 45/261 subjects (17.2%, EAIR 26.0/100 subject-years) in the Q4W group and 32/257 subjects (12.4%, EAIR 18.1/100 subject-years) in the Q8W group. Tinea infections were reported in 10/261 subjects (3.8%, EAIR 5.3/100 subject-years) in the Q4W group and 11/257 subjects (4.3%, EAIR 5.9/100 subject years) in the Q8W group. Herpes simplex infections were reported in 4/261 subjects (1.5%, EAIR 2.1/100 subject-years) in the Q4W group and 3/257 subjects (1.2%, EAIR 1.6/100 subject years) in the Q8W group. For Candida infections, the EAIRs were greater in the Q4W group compared to the Q8W group. This was not the case for Tinea or Herpes simplex infections. The frequency (%) and EAIRs were adjusted for study size. As previously discussed, oropharyngeal Candida infections and other Candida infections will be pooled separately for labeling.

Although subjects with active TB were excluded from clinical trials, subjects with latent TB could be enrolled provided they began prophylactic treatment prior to the beginning of the trial. No subjects developed new onset TB infection during the clinical trials. A total of 14 subjects with latent TB were enrolled in the phase 3 trials and received prophylactic treatment for TB. None of these subjects developed active TB.

We recommend the following for inclusion in Sections 5 (Warnings and Precautions) and 6 (Adverse Reactions) of labeling for bimekizumab:

> 5.1 Infections
>
> BIMZELX may increase the risk of infections. In clinical trials in subjects with plaque psoriasis, infections occurred in 36% of the BIMZELX group compared to 23% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections, Candida infections, tinea infections, gastroenteritis, and Herpes Simplex infections occurred more frequently in the BIMZELX group than in the placebo group. [*see Adverse Reactions (6.1)*].
>
> Serious infections occurred in 0.3% of subjects treated with BIMZELX and 0% treated with placebo. (b) (4)
>
> In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing BIMZELX. If a patient develops such an infection or is not responding to standard therapy, discontinue BIMZELX until the infection resolves.

5.2 Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with BIMZELX. Avoid the use of BIMZELX in patients with active TB infection. Initiate treatment of latent TB prior to administering BIMZELX. (b) (4) Consider anti-TB therapy prior to initiation of BIMZELX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Closely monitor patients treated with BIMZELX for signs and symptoms of active TB during and after treatment.

6 Adverse Reactions

Specific Adverse (b) (4) Reactions

Infections

During the placebo-controlled period of Trials Ps-1 and Ps-2, infections were reported in 36% of subjects (141.7 per 100 patient-years) treated with BIMZELX compared with 23% of subjects (84.6 per 100 patient-years) treated with placebo. Serious infections occurred in 0.3% of subjects (1.0 per 100 patient-years) treated with BIMZELX and 0% treated with placebo.

The most common infections were upper respiratory tract infections and Candida infections, including oral candidiasis (oral candidiasis, oropharyngeal candidiasis, oral fungal infection, fungal pharyngitis, and oropharyngitis fungal) occurring in 9% (30.6 per 100 patient-years) of subjects treated with BIMZELX and other Candida infections (vulvovaginal candidiasis, vulvovaginal mycotic infection, skin candida, and genital candidiasis) in 1% (3.4 per 100 patient-years) of subjects treated with BIMZELX compared to 0% and 1%, respectively, of subjects treated with placebo.

During the combined initial, maintenance, and open-label extension treatment periods of trials Ps-1, Ps-2, Ps-3, and the open-label extension trial, infections were reported in 63% of subjects treated with BIMZELX (120.4 per 100 patient-years). Serious infections were reported in 1.5% of subjects treated with BIMZELX (1.6 per 100 patient-years).

8.2.5.2. Inflammatory Bowel Disease (IBD)

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors and is included in Section 5 (Warnings and Precautions) of labeling for ant-IL-17A mAbs secukinumab and ixekizumab, as well as anti-IL-17A Receptor mAb brodalumab. The Applicant also conducted a proof-of-concept trial to evaluate bimekizumab for the treatment of active, moderate to severe ulcerative colitis (UC). However, this trial was terminated early based on an on an imbalance in TEAEs and SAEs between bimekizumab and placebo treatment together with an observed increase in clinical signs of UC.

We evaluated the potential risk of IBD associated with treatment with bimekizumab in conjunction with consultants from the Division of Gastroenterology (DG). Refer to the Consult Review by Dr. Anil Nayyar dated March 22, 2021.

Subjects with a history of IBD could be enrolled in the clinical trials as long as they had no active symptomatic disease at Screening or Baseline. A total of 3 such subjects were enrolled in the phase 3 trials. In the phase 2 and phase 3 trials, one subject (1/1789, EAIR 0.05/100 subject-years) treated with bimekizumab 320 mg Q4W developed new-onset ulcerative colitis which was serious, led to discontinuation, and was considered related to treatment by the investigator. A narrative for this subject is provided in Section 8.2.4 of this review under Serious Adverse Events.

The consultant from DG also reviewed data from clinical trials evaluating bimekizumab for other indications and provided the following comment:

> *"A small number of patients reported new onset of CD and UC as well exacerbation of preexisting IBD during the clinical studies evaluating safety and efficacy of BKZ in patients with AS and PsA. The majority of IBD events were reported in Study AS0008 and its open label extension Study AS0009. Due to a small number of reports of IBD and blinded treatment for the ongoing Studies PA0010 and AS00011, no meaningful comparisons of the incidence rates with the comparators (placebo and other IL-17 inhibitor groups) can be made at this stage. The risk of exacerbation/flare of pre-existing IBD cannot be ascertained/evaluated due to limited enrollment of patients with pre-existing IBD in these trials."*

We recommend the following for inclusion in Sections 5 (Warnings and Precautions) and 6 (Adverse Reactions) of labeling for bimekizumab:

> 5.4 Inflammatory Bowel Disease
>
> Cases of inflammatory bowel disease (IBD) have been reported in patients treated with IL-17 inhibitors, including BIMZELX [*see Adverse Reactions (6.1)].* Avoid use of BIMZELX in patients with active IBD. During BIMZELX treatment, monitor patients for signs and symptoms of IBD and discontinue treatment if worsening of signs and symptoms occurs.
>
> 6.1 Clinical Trials Experience
>
> Specific Adverse (b) (4) Reactions
>
> In clinical trials in subjects with plaque psoriasis, subjects with active inflammatory bowel disease were excluded. In these trials, which included (b) (4) subjects exposed to BIMZELX accounting for (b) (4) patient-years, (b) (4) In clinical development programs for other disease conditions, new cases of

Crohn's disease (CD) and UC, some serious, and exacerbations of pre-existing CD and UC, were reported with BIMZELX use.

8.2.5.3. Hepatotoxicity/DILI

During the review of safety data, the review team discovered potential cases of drug-induced liver injury associated with treatment with bimekizumab. In Pool S1, pooled TEAE PTs involving liver enzyme elevations were reported in 10/670 (1.5%, EAIR 4.9/100 subject-years) subjects treated with bimekizumab and 2/169 (1.2%, EAIR 3.9/100 subject-years) subjects in the placebo group. In Pool S2B, which allows for evaluation of long-term safety by direct comparison with Pool S1, liver enzyme elevations were reported in 12/488 (2.5%, EAIR 3.6/100 subject-years) subjects treated with bimekizumab Q4W. Based on the EAIRs, TEAEs associated with liver enzyme elevations did not increase with longer exposure to bimekizumab.

In Pool S2C, which allows for direct comparison of the Q4W and Q8W dosing regimens, liver enzyme elevations were reported in 10/261 (3.8%, EAIR 5.4/100 subject-years) subjects in the Q4W group and 5/257 (1.9%, EAIR 2.6/100 subject years) subjects in the Q8W group. The frequencies and EAIRs were adjusted for study size. Based on the EAIRs, TEAEs related to liver enzyme elevations occurred more frequently in the Q4W group in this pooled dataset.

The review team evaluated potential hepatotoxicity in conjunction with consultants from the DILI team from the Division of Hepatology and Nutrition. Refer to the consult review dated August 6, 2021 by Paul Hayashi, MD, MPH. In addition, in an Information Request dated March 22, 2021, we requested the Applicant to convene an Independent Hepatology Assessment Committee (HAC) to evaluate potential cases of DILI and to provide an overall summary of the risk of DILI associated with treatment with bimekizumab.

The DILI team provided an analysis of transaminase elevations >3x the upper limit of normal (ULN) in Pool S1. Transaminase elevations >3x ULN occurred in 7/670 (1.0%) of subjects treated with bimekizumab and 1/169 (0.6%) of subjects treated with placebo. The DILI team also analyzed liver enzyme elevations using Pool S2, which consisted of pooled data from the phase 2 and phase 3 clinical trials. The DILI team provided a summary of transaminase elevations in the following tables.

Table 59: Summary of Transaminase Elevations, Pool S2

ALT Counts and Percents

	TRT01A																	
	Adalimumab 40mg Q2W		BKZ 64mg		BKZ 160mg		BKZ 160mg w/ LD		BKZ 320mg		BKZ 320mg Q4W		BKZ 480mg		Ustekinumab		BKZ 320mg + PBO		Placebo	
ALT Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	143	96.0%	36	92.3%	73	91.3%	37	92.5%	355	93.2%	700	95.4%	33	76.7%	135	99.3%	29	90.6%	147	94.8%
Between 2x and 5x ULN	6	4.0%	3	7.7%	5	6.3%	3	7.5%	23	6.0%	30	4.1%	8	18.6%	1	0.7%	3	9.4%	7	4.5%
Between 5x and 10x ULN	0	0.0%	0	0.0%	2	2.5%	0	0.0%	3	0.8%	2	0.3%	2	4.7%	0	0.0%	0	0.0%	1	0.6%
Between 10x and 20x ULN	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
20x ULN or Greater	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
All	149	100.0%	39	100.0%	80	100.0%	40	100.0%	381	100.0%	734	100.0%	43	100.0%	136	100.0%	32	100.0%	155	100.0%

AST Counts and Percents

	TRT01A																	
	Adalimumab 40mg Q2W		BKZ 64mg		BKZ 160mg		BKZ 160mg w/ LD		BKZ 320mg		BKZ 320mg Q4W		BKZ 480mg		Ustekinumab		BKZ 320mg + PBO		Placebo	
AST Elevations	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects	Subject Count	% of Subjects
Less than 2x ULN	138	92.6%	37	94.9%	72	90.0%	37	92.5%	352	92.4%	674	91.8%	38	88.4%	131	96.3%	32	100.0%	144	92.9%
Between 2x and 5x ULN	9	6.0%	2	5.1%	7	8.8%	3	7.5%	23	6.0%	55	7.5%	4	9.3%	5	3.7%	0	0.0%	10	6.5%
Between 5x and 10x ULN	2	1.3%	0	0.0%	1	1.3%	0	0.0%	6	1.6%	2	0.3%	1	2.3%	0	0.0%	0	0.0%	0	0.0%
Between 10x and 20x ULN	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	1	0.1%	0	0.0%	0	0.0%	0	0.0%	1	0.6%
20x ULN or Greater	0	0.0%	0	0.0%	0	0.0%	0	0.0%	0	0.0%	2	0.3%	0	0.0%	0	0.0%	0	0.0%	0	0.0%
All	149	100.0%	39	100.0%	80	100.0%	40	100.0%	381	100.0%	734	100.0%	43	100.0%	136	100.0%	32	100.0%	155	100.0%

Source: Dili Team Consult Review, Table 2, p. 10

The DILI team provided summaries for five subjects who the DILI team or the Applicant's HAC considered to have probable or possible DILI:

> "4.9.1 PS0008-(b) (6) (Possible DILI due to BKZ per HAC and DILI team assessment; potential Hy's Law case)
>
> *Summary*: This is a 22-year-old woman enrolled in Poland (study PS0008). She had an acute hepatocellular injury 27 weeks after starting BKZ and 20 days after last dose.
>
> She screened failed initially due to an AST of 134 and ALT of 68 on (b) (6) but LDH was also up at 359 (ULN 220). No alcohol in the 6 months prior to enrollment. Her BMI was 35. Enzymes fell to normal, and she started BKZ (320 SC q4w) on (b) (6) On (b) (6) dosing interval decreased to q8wk.
>
> On (b) (6) she received ciprofloxacin for abdominal pain, but liver enzymes were documented as normal on (b) (6) and (b) (6). Ultrasound on (b) (6) was "normal". No gallstones mentioned. Pain resolved.
>
> She did well until (b) (6) when she developed nausea and vomiting. She was given itopride (pro-kinetic). By (b) (6) (3 weeks after last BKZ dose), she had a fever,

pruritus, and jaundice with an hepatocellular liver injury (ALT 624, AST 361, AP 166, bilirubin 4.6). She was admitted and BKZ was held (last dose: (b) (6)). BP 138/90. Enzymes peaked four days later (ALT 824, AST 474). No mention of rash. Ultrasound showed "slightly" wider biliary tree at the hilum, but “hepatic ducts less than 5mm". No gallstones. Cholangiogram done (b) (6) when ALT still rising, and bilirubin 3.65 mg/dL showed no gallstones or dilated intrahepatic ducts. Common bile duct was 8.6 mm (mild dilation) but no filling defects were seen. Hepatitis A, B and C tests were "negative". CMV IgM was negative and no mention of other viral serologies. She was on four concurrent medications (levothyroxine, itopride, trimebutine, cipro). Herbal dietary supplements unmentioned as pertinent negatives or positives. Liver enzymes quickly fell after admission.
Assessment: This case is possible DILI due to BKZ. Passage of a gallstone competes in this obese, young woman. The lack of stones on cholangiogram at the time of elevations and an ultrasound done two months prior hurt the case for gallstones though. Symptoms of abdominal pain, nausea, vomiting, and fever favor gallstone disease. The prior liver enzyme elevations during screening and the markedly rapid fall in liver enzymes also favors passage of a stone. DILI from monoclonal biologics typically have a longer washout.

4.9.2 PS0014-(b) (6) (Possible DILI due to BKZ per HAC and DILI team assessment; potential Hy’s Law case)

Summary: This is a 38-year-old Asian woman who developed a prolonged course of elevated transaminases and jaundice about 20 weeks after BKZ start and 35 days after last dose.

She had no known liver disease. BMI was 22 kg/m^2. No diabetes, hypertension or hyperlipidemia are mentioned. She has a history of chronic anemia. She did not drink alcohol for the 6 months prior to enrollment. Her ALT was 32, AST 28, AP 85 and bilirubin <1.0 at baseline. She started BKZ at 320 mg SC q4w on (b) (6). The dosing interval was decreased to q8w after 100 days.

She had oral candidiasis on (b) (6), for which she got miconazole nitrate ((b) (6) She was placed on famotidine for dyspepsia on (b) (6). She had been on this medication previously without issues.

Elevated liver enzymes were noted on routine follow-up, (b) (6). She was otherwise asymptomatic. BKZ was held with last dose 35 days prior to injury onset. Enzymes rose a bit more through (b) (6) and then fell to the 80s by (b) (6) However, they rose again on (b) (6) with ALT peaking at 460 and ALT 698. Bilirubin would go on to peak at 4.4 a couple weeks later.

On this second rise, evaluation was done, including negative HAV IgM, HBsAg, anti-HBc IgM, HCV antibody, HCV RNA, HEV IgM, EBV and CMV IgM. Ultrasound was unremarkable. Anti-smooth muscle antibody (ASMA) was positive and anti-nuclear antibody (ANA) negative. Liver biopsy on (b) (6) showed changes consistent with autoimmune hepatitis (AIH) versus DILI. No mention of plasma cells. There was "peripheral" fibrosis. From (b) (6) through (b) (6), she received prednisolone, but dose and taper not given. Her liver tests declined, though the narrative says "poor response to systemic steroids." At last follow-up, (b) (6) (57 days after last prednisolone), liver tests were normal.

Assessment: This is possible DILI with autoimmune injury phenotype. De novo autoimmune hepatitis (AIH) competes. Biopsy was without significant fibrosis and was unable to discern DILI from AIH. Patient had a poor dechallenge and was treated with steroids. If patient remains stable off steroids over longer term follow-up, then the case for DILI strengthens.

4.9.3 PS0009-(b) (6) (Probable DILI due to BKZ per DILI team, Possible per HAC assessment)

Summary: This is a 61-year-old Caucasian woman who developed elevated liver enzymes and jaundice 4 weeks after BKZ start.

She had a common bile duct perforation in (b) (6) and repair with cholecystectomy in (b) (6). However, at baseline her ALT was 16, AST 20, AP 75, bilirubin <1.0. She denied alcohol use. Her BMI was 39 kg/m^2. She was diabetic, hypertensive and had chronic upper abdominal pain. She initially randomized to placebo but then re-randomized to BKZ 320 mg every 4 weeks and started on (b) (6). She developed fatigue and loss of appetite 10- 11 days after BKZ start. Elevated liver enzymes and bilirubin were noted on (b) (6) (ALT 494, AST 486, AP 328, bilirubin 6.1). She developed abdominal pain the next day. BKZ was stopped with the last dose given on (b) (6)

Hepatitis A and B serologies negative. No mention of HCV or HEV testing. ANA titer was 1:40. No mention of anti-smooth muscle antibody. MRI/MRCP (b) (6), was "negative" showing "intrahepatic and extrahepatic biliary tree" as "nondistended with no intraluminal abnormalities". Concomitant medications were non-contributory. On (b) (6) (after normalization of ALT, AST and bilirubin) a liver biopsy showed NASH (Gr 0-1/Stage 0-1). Thereafter, all liver tests returned to normal.

Assessment: This case is possible, if not probable DILI due to BKZ. Latency fits. De-challenge was rapid but uneven. Evaluation for other causes incomplete though. No mention of HEV or HCV testing, so these could compete. Passage of biliary sludge or stones is also possible although MRCP suggested chronic changes only without filling defects or stones. Symptoms of abdominal pain came on *after* the peak in enzymes and

bilirubin, and she had a history of chronic abdominal pain. There was a second rise transaminase to low 200s on (b) (6), before finally settling to normal, fitting repeated stone or sludge passage.

This case does not meet Hy's Law due to the AP elevation to 2.78x ULN and nR Hy's Law value being less than 5. In other words, it was a mixed liver injury and not purely hepatocellular.

4.9.4 PS0009-(b) (6) (Probable DILI due to BKZ per DILI team and HAC assessment)

Summary: This is a 35-year-old Asian man who developed elevated ALT and AST without jaundice 8 weeks after drug start.

His BMI was 30 kg/m^2. He had a history of hypertension, hyperlipidemia and non-alcoholic fatty liver disease (NAFLD). Alcohol intake was seven alcohol equivalents per week, but none in the six months prior to study entry. His baseline liver tests were normal. He started BKZ 320 mg every 4 weeks on (b) (6).

On (b) (6), he had elevated transaminases without mention of liver related symptoms (ALT 168, AST 129, AP 145, bilirubin 1.99). He had received a dose of BKZ on the same day and it was held thereafter. On (b) (6), prednisone was given for "treatment of DILI". The prednisone is listed as "ongoing" with no further mention of course, taper or dosing.

Liver enzymes did fall to normal, but then rose again 4 months later, at the time of severe epistaxis episode with "shock" and drop in Hgb.

Concomitant medications were taken for at least five months prior to screening, and most were continued. Evaluation for viral and autoimmune testing "negative". No imaging was mentioned.

Assessment: This is possible due to BKZ. Latency and de-challenge consistent with DILI, but use of prednisone confuses the picture. Seronegative AIH becomes plausible due to possible response to steroids and no data on when steroids were stopped. Later rise in liver enzymes concurrent with shock liver, but recurrent AIH is also possible. Evaluation testing lack detail. No imaging results mentioned.

4.9.5 PS0014 (b) (6) (Possible DILI due to BKZ; Probable per HAC assessment)

Summary: This is 34-year-old Asian man with history of latent tuberculosis (TB) and "occasional" alcohol use, BMI of 37 kg/m^2 and fatty liver. He had a significant rise in liver tests 28 weeks after first injection and 31 days after last.

Latent tuberculosis was diagnosed in screening, and he failed entry. He was treated with isoniazid [redacted], but it was stopped due to elevated liver tests. Liver tests fell and rifampicin started [redacted] He passed second screen and started BKZ 320 every 4 weeks on [redacted] At baseline, his ALT was 22, AST 18, AP 92, bilirubin less than 1 mg/dL. On [redacted] dose interval was increased to every eight weeks, but on [redacted] ALT was up at 58. Rifampicin held, but by [redacted], ALT was 78 and AST 42. On [redacted] his liver tests were significantly higher (ALT 230, AST 114, AP normal and bilirubin 0.94 mg/dL). Last dose of BKZ was 31 days prior. Eosinophilia was present.

He was asymptomatic but was admitted for evaluation. Ultrasound was negative except for fatty liver. HAV, HBV, HCV, HEV serologies all negative; HCV RNA negative; EBV and CMV testing negative. ANA titer was 1:40; antismooth muscle antibody negative. On [redacted], liver biopsy showed NAFLD and fibrosis "around the central vein."

Assessment: This is possible DILI due to BKZ. Evaluation for other causes was complete. Timing and de-challenge consistent for a biologic long latency & slow washout. Eosinophilia favors DILI. Alcohol competes less well with ALT greater than AST consistently. No gallstones or dilated ducts seen on imaging. Rifampicin competes poorly because latency of 150 days is long for this drug, and ALT continued to rise after stopping. Liver biopsy suggests NAFLD, but wide variance in ALT argues against NAFLD as primary cause of acute rise (20's at baseline up to over 300 and then back to 20's). However, the second rise at last f/u [redacted] (ALT 90, AST 49) raises the possibility of a non-DILI diagnoses such as autoimmune hepatitis, or gallstone disease. No further liver tests provided."

In addition, the DILI team provided the following summary in the consult review:

"In the pooled dataset (Pool S2), elevation of transaminases occurred more in the bimekizumab (BKZ) arms compared to placebo or other approved treatments. The imbalance was seen at ALT 2-5x ULN. The median percentage of patients with such ALT elevation was 7.5% (range 4.1-18.6) across dosing arms versus 4.5% for placebo. There was no clear dose-response relationship. The imbalance persisted for 5x-10x ULN but was smaller. The median percent with ALT 5-10x ULN was 0.3% (0-4.7) for BKZ arms versus 0% for placebo. BKZ arms also had markedly higher rates of hepatic TEAE per 100-patient-years of exposure (18.3 for BKZ versus 1.6 for ustekinumab and 0.7 for adalimumab.

Pool S2 had 8-9 BKZ patients for every 1 placebo, so evaluation of drug-induced serious hepatotoxicity (eDISH) plots were less able to show obvious imbalances between arms. However, all BKZ cases in Hy's Law quadrant or ALT > 5x ULN regardless of bilirubin were assessed by the DILI Team. There were 30. Three were considered probable and seven possible DILI due to BKZ by either the DILI Team or the Hepatology Assessment

> Committee (HAC) chartered by the sponsor. The rest of the 30 were unlikely DILI. There were no fatalities due to hepatic injury and no liver transplants. While 5 cases were in Hy's Law quadrant, none were probable or definite hepatocellular DILI. Two of the 5 were unlikely DILI, and 2 were possible DILI with alternative diagnoses. The fifth was probable DILI, but the alkaline phosphatase was 2-3x ULN and nR-value (pattern of injury) suggest mixed, not hepatocellular injury.
>
> For the 10 at least possible DILI cases, there was no clear DILI phenotype. The median latency was long at 164 days but with a wide range (28 to 338 days). DILI long latency with a broad range is reported with monoclonal antibodies. The nR values also had a wide range (2.1 to 14.3). Therefore, we agree with the HAC assessment that there were no clear Hy's Law cases nor uniform DILI phenotype. Restricting to the 3 probable cases yields a latency of 28 to 198 days and nR-values of 3.9 to 7.3. Most patients were asymptomatic, so following symptoms to instigate liver tests will not be helpful. Thus, checking baseline liver tests and restricting BKZ use to patients without cirrhosis, and avoiding use in patients with active liver disease or moderate to heavy alcohol use would be prudent. Monitoring liver tests, especially for patients with chronic liver disease, should be considered.
>
> The sponsor excluded patients with hepatitis B infection (HBsAg and/or anti-HBc positive) their studies. Therefore, we cannot assess reactivation risk in this BLA. However, the first approved monoclonal antibody directed against IL-17A, secukinumab, has been associated with a significant rate of reactivation. Close monitoring for reactivation with or without prophylactic treatment in patients with chronic hepatitis B (positive HBsAg) or past exposure (negative HBsAg, positive anti-HBc) should be considered. Hepatitis B reactivation is an increasingly recognized form of DILI (indirect DILI) from immunosuppressant medications.
>
> Overall, we do not see a DILI risk that would hold up approval of BKZ, if the efficacy and need are clear. We believe the risk of DILI can be managed with proper labeling and standard post market safety surveillance."

As described above, the DILI team also noted that reactivation of Hepatitis B virus (HBV) has been reported in postmarketing studies of secukinumab, which is an IL-17A blocker. This risk was also evaluated by consultants from the Division of Pharmacovigilance I (DPV) and Division of Epiemiology I (DEPI). Based on their analyses, consultants from the DILI team, DPV, and DEPI recommended inclusion of a recommendation for pretreatment evaluation for HBV infection in labeling for bimekizumab. However, because subjects with serologic evidence of HBV infection were excluded from clinical trials in the development program for bimekizumab, no data are available regarding the potential risk of HBV reactivation in patients treated with bimekizumab. As such, a recommendation for pretreatment evaluation for HBV will not be included in product labeling at this time. However, HBV reactivation will be included as an outcome of interest in an observational, long-term postmarketing safety study.

The review team recommends the inclusion of the following in labeling for bimekizumab:

> Section 2.1- Recommended Evaluations and Immunization Prior to Treatment Initiation:
> Test liver enzymes, alkaline phosphatase and bilirubin prior to initiating treatment with BIMZELX *[see Warnings and Precautions (5.3)]*.
>
> Section 5.3 (W&P):
> 5.3 Liver Biochemical Abnormalities
>
> Treatment with BIMZELX was associated with increased incidence of liver enzyme elevations compared to treatment with placebo in randomized clinical trials. Liver serum transaminase elevations > 3 times the upper limit of normal were reported in subjects treated with BIMZELX [*see Adverse Reactions (6.1)*]. Elevated liver serum transaminases resolved after discontinuation of BIMZELX. The time to onset of these adverse reactions varied between 28 and 198 days after starting BIMZELX treatment.
>
> Test liver enzymes, alkaline phosphatase and bilirubin at baseline and periodically during treatment with BIMZELX. If treatment-related increases in liver enzymes occur and drug-induced liver injury is suspected, interrupt BIMZELX until a diagnosis of liver injury is excluded. Permanently discontinue BIMZELX in patients with causally associated combined elevations of transaminases and bilirubin. Patients with acute liver disease or cirrhosis may be at increased risk for severe hepatic injury; avoid use of BIMZELX in these patients.
>
> Section 6.1 Clinical Trials Experience
>
> Specific Adverse (b) (4) Reactions
>
> *Liver Biochemical Abnormalities*
>
> During the placebo-controlled period of Trials Ps-1 and Ps-2, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.0% of subjects treated with BIMZELX versus 0.6% of subjects treated with placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

8.2.5.4. Malignancies

Subjects with any active malignancy or history of malignancy within 5 years prior to the Screening Visit were excluded from phase 3 trials. The only exceptions to the exclusion criteria were cutaneous squamous or basal cell carcinoma that were treated and considered cured, or in situ cervical cancer. Overall, the frequency or malignancies were low during the development

program. This review will focus on comparison of malignancy rates during Pool S1 and Pool S2 (pooled phase 2/3 trials).

In Pool S1, malignancy was reported by 1/670 (0.1%, EAIR 0.5/100 subject-years) in the bimekizumab group and 1/169 (0.6%, EAIR 1.9/100 subject years) in the placebo group. The reported malignancy PTs were esophageal adenocarcinoma in the placebo group and basal cell carcinoma in the bimekizumab group. The basal cell carcinoma was considered not related to treatment with bimekizumab.
In Pool S2, malignancies were reported in 15/1789 (0.8%, EAIR 0.8/100 subject-years) subjects treated with any dose of bimekizumab. These included 7/1789 subjects (0.4%, EAIR 0.4/100 subject years) with basal cell carcinoma and 2/1789 subjects (0.4%, EAIR 0.4/100 subject-years) with colon cancer. In addition, the following malignancies were each reported in 1/1789 subjects (<0.1%, EAIR 0.1/100 subject-years): anal squamous cell carcinoma, gastric cancer, acute myeloid leukemia, squamous cell carcinoma, squamous cell carcinoma of lung, squamous cell carcinoma of skin, and keratoacanthoma. Investigators considered none of the malignancies related to treatment with bimekizumab. The TEAEs of colon cancer and gastric cancer were classified as SAEs. Narratives for these subjects are provided in Section 8.2.4 of this review under Serious Adverse Events.

Because of the long latency period associated with malignancy, this will be an outcome of interest in the prospective long-term safety study which will be a PMR. In addition, the risk of lymphoma will be evaluated via Active Risk and Identification Analysis (ARIA) system.

8.2.5.5. Major Adverse Cardiovascular Events (MACE)

In view of the epidemiologic associations between psoriasis and cardiovascular (CV) comorbidities, and the potential association between anti-cytokine therapies used in the treatment of moderate-to-severe psoriasis and CV events, the Applicant conducted analyses on all events related to the CV system. The Applicant also established a Cardiovascular Clinical Event Adjudication Committee (CV-CAC) for adjudication of CV TEAEs. MACE was defined as cardiovascular death, nonfatal myocardial infarction (MI), and stroke.

The Applicant also evaluated extended MACE, which was defined as all MACE, plus adjudicated event types of hospitalization for unstable angina with urgent revascularization, hospitalization for heart failure, coronary revascularization procedures (percutaneous coronary intervention [PCI], coronary artery bypass grafting [CABG]) or urgent revascularization procedures (i.e., due to symptoms of brain ischemia or pending infarction).

Subjects with stable CV disease were not excluded from the clinical trials unless they had a history of MI or stroke within 6 months prior to Screening. Risk factors for CV disease were common in the phase 2/3 population. The majority of subjects were obese or overweight. A total of 7.5% had a BMI $\geq$40kg/m^2, 35.0% had a BMI $\geq$30 to <40kg/m^2, and 32.6% had a BMI $\geq$25 to <30kg/m^2. In addition, approximately half of the population were current or past smokers,

more than 30% had a medical history of hypertension, and approximately 20% had a history of dyslipidemia.

The review team evaluated MACE events in conjunction with consultants from the Division of Cardiology and Nephrology (DCN). Refer the Consult Review by Selena DeConti, PharmD, MPH. Per Dr. DeConti's review, in Pool S1 adjudicated MACE for bimekizumab was infrequent, occurring in one subject (1/670, 0.1%; 0.05/100 subject-years); the subject had multiple CV risk factors and experienced a fatal outcome 4 days after a non-STEMI which was considered resolved. (A narrative for this subject is provided in Section 8.2.4 of this review under Deaths.) Of note, no MACE was reported in the initial treatment period for the other controlled phase 3 trial, PS0008 (not included in Pool S1 because it was not placebo-controlled), or controlled phase 2 trials.

Dr. DeConti also reviewed MACE events for Pool S2 (the combined phase 2/3 trials). Although the information was not included in the consult review, Dr. DeConti provided the following information (email communication dated August 5, 2021):

> "In Pool S2, we noted a higher proportion of subject reporting the MedDRA preferred term (PT), myocardial infarction, in the bimekizumab group (0.4%) compared with the comparator groups (0). However, a subgroup analysis of individual trials did not reveal an imbalance during the initial or extended treatment periods. Our team reviewed the cases and all cases had multiple CV risk factors (obesity, hypertension, hyperlipidemia, atherosclerosis, and long-time current or previous smoker). Two of the cases occurred after the last study dose (35 days and 100 days) during the post-treatment period. All cases were reported resolved and did not result in study treatment discontinuation. No trend was observed with respect to the time to onset of the CV event or MACE with longer term exposure up to 52 weeks."

Based on her review, Dr. DeConti concluded, "There is no clinical concern from the cardiovascular perspective and no labeling language is necessary."

8.2.5.6. Neutropenia

Per the Applicant, reduction in neutrophil counts is a possible pharmacodynamic effect of blockade of IL-17A. In Pool S1, 4/670 (0.6%) of subjects treated with bimekizumab and 1/169 (0.6%) of subjects treated with placebo experienced neutrophil counts $<1.0 \times 10^9$/L. However, for the subject in the placebo group, the Applicant did not report the low neutrophil count as a TEAE. The Applicant reported that in Pool S1, neutropenia TEAEs occurred in 5/670 subjects (0.7%, EAIR 2.4/100 subject-years) in the bimekizumab group and no subjects in the placebo group. In Pool S2 (pooled phase 2/3 data), neutropenia TEAEs occurred in 22/1789 subjects (0.7%, EAIR 1.2/100 subject-years). Based on the EAIRs reported by the Applicant, neutropenia TEAEs did not occur more frequently with longer exposure to bimekizumab.

The review team conducted additional analyses to compare the rate of TEAEs related to leukopenias, including neutropenia, between short-term (Pool S1) and long-term (Pool S2B) exposure to bimekizumab, as well as between the Q4W and Q8W treatment regimens (Pool S2C). Results of these analyses are presented below.

In Pool S1, pooled leukopenia TEAEs were reported in 7/670 subjects (1.0%, EAIR 3.4/100 subject-years) in the bimekizumab group and none in the placebo group. However, as previously stated, 1 subject (0.6%) in the placebo group had Grade 3 neutropenia that was not reported as an AE. Pooled leukopenia TEAEs and the associated PTs reported in Pool S1 are presented in the table below.

Table 60: Pooled PT Leukopenia TEAEs Pool S1

Preferred Term	BKZ 320mg Q4W N=670 100 subject yrs=2.08 n (%) [EAIR]	Placebo N=169 100 subject yrs=0.52 n (%) [EAIR]
Pooled Leukopenias	7 (1) [3.4]	0 (0) [0]
Neutrophil count decreased	3 (0.4) [1.4]	0 (0) [0]
Neutropenia	2 (0.3) [1]	0[a] (0) [0]
Lymphopenia	2 (0.3) [1]	0 (0) [0]
White Blood cell count decreased	2 (0.3) [1]	0 (0) [0]

Abbreviations: BKZ=bimekizumab, NA= not available, Q4W=every four weeks, TEAE=treatment-emergent adverse event, yrs=years, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
[a] one (1/169, 0.6%) subject in the placebo group experienced Grade 3 neutropenia which was not reported as an AE by the Applicant
Source: Statistical and Clinical Reviewer's Table

The result of our analysis for Pool S1 are similar to those presented by the Applicant. The overall frequency of neutropenia in subjects treated with bimekizumab was similar to that in the placebo group.

In Pool S2B, pooled leukopenia TEAEs were reported in 4/488 (0.8%, EAIR 1.2/100 subject-years) subjects treated with bimekizumab Q4W. Pooled leukopenia TEAEs and the associated PTs reported in Pool S2B are presented in the table below.

Table 61: Pooled PT Neutropenia and Leukopenia TEAEs Pool S2B

Preferred Term	Phase 3 BKZ 320mg Q4W N=488 100 subject yrs=3.36 n (%) [EAIR]	Phase 3 BKZ 320mg Q8W N=103 100 subject yrs=0.76 n (%) [EAIR]	Phase 3 BKZ Total N=591 100 subject yrs=4.12 n (%) [EAIR]
Pooled Leukopenias	4 (0.8) [1.2]	1 (1) [1.3]	5 (0.8) [1.2]
Neutropenia	1 (0.2) [0.3]	1 (1) [1.3]	2 (0.3) [0.5]
Neutrophil count decreased	1 (0.2) [0.3]	0 (0) [0]	1 (0.2) [0.2]
WBC count decreased	2 (0.4) [0.6]	0 (0) [0]	2 (0.3) [0.5]

Abbreviations: BKZ=bimekizumab, Q4W=every four weeks, Q8W=every eight weeks, TEAE=treatment-emergent adverse event, yrs=years, EAIR=exposure-adjusted incidence rate.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/Preferred Term.
Source: Statistical and Clinical Reviewer's Table

EAIRs for PTs related to neutropenia were lower than those reported during the placebo-controlled period. Thus, TEAEs related to neutropenia did not increase in frequency with longer exposure to bimekizumab.

In Pool S2C, there were insufficient numbers of TEAEs related to leukopenia to discern a difference between the bimekizumab Q4W and Q8W treatment arms. TEAEs in Pool S2C included one subject with neutropenia and one subject with lymphopenia (1/257, 0.4%, EAIR 0.5/100 subject-years). Both were treated with bimekizumab Q8W.

In the placebo-controlled period, neutropenia did not occur more frequently in subjects treated with bimekizumab compared to placebo. The frequency with which neutropenia occurred did not increase with longer exposure to bimekizumab. These data do not demonstrate a treatment-related risk of neutropenia related to treatment with bimekizumab. Therefore, neutropenia is not recommended for inclusion in labeling.

8.2.5.7. Suicidal Ideation/Behavior

Patients with psoriasis are at higher risk for depression and suicide than the general population. Subjects who met the following criteria were excluded from the phase 3 trials:

- Active suicidal ideation or suicidal ideation within the month prior to Screening
- History of suicide attempt within the past 5 years prior to screening
- Moderately severe major depression or severe major depression indicated by a score of ≥15 using the screening Patient Health Questionnaire-9 (PHQ-9)

The Applicant's safety assessments for neuropsychiatric events during the phase 3 trials included administration of the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) and PHQ-9 at Screening and Baseline and periodically throughout the trials. In addition, the Applicant established an independent Neuropsychiatric Adjudication Committee which evaluated neuropsychiatric TEAEs as well as subjects with scores on the eC-SSRS or PHQ-9 which met withdrawal criteria. Subjects who developed active suicidal ideation or severe major depression were withdrawn from the trial.

We evaluated neuropsychiatric AEs in conjunction with consultants from the Division of Psychiatry. Refer to the consult review by Shamir N. Kalaria, PharmD, PhD dated December 17, 2021. Dr. Kalaria reviewed data from the phase 2 and phase 3 trials and provided the following conclusion and recommendations:

> "Based on the review of the pooled clinical data from phase 2 and 3 psoriasis trials for bimekizumab, we did not observe any clear association of an increased risk for SI/B or psychiatric AEs in patients treated with bimekizumab. The overall rare incidence of SI/B and psychiatric events limits the ability to detect a significant signal. During the bimekizumab program, the eC-SSRS was used to prospectively evaluate SI/B throughout the initial, maintenance, and open-label extension periods of phase 2 and 3 trials. No

SI/B-related deaths or suicidal behavior events were observed in any patient. Although the number of suicidal ideation events was greater for bimekizumab as compared to other studies, the majority of events were mild and the use of the eC-SSRS may increase suicidal ideation ascertainment. The rate of adjudicated SI/B was considered low for this program overall, given the increased background rate in the PSO population. Prospective monitoring using the HADS (Hospital Anxiety and Depression Scale) and PHQ-9 questionnaires also suggested no significant association for an increased risk of depression and anxiety with bimekizumab. We observed the majority of psychiatric AEs in patients with a prior psychiatric medical history. No apparent demographic characteristics or potential prognostic factors were shown to be potentially predictive of SI/B or psychiatric AEs.

Recommendations:

1. We do not recommend specific psychiatric warning language in the bimekizumab label at this time. Analysis of clinical trial data from phase 2 and 3 trials suggest no clear evidence of an increased risk of SI/B or other psychiatric AEs.
2. We continue to recommend that any future study protocol should include prospective assessment for SI/B and psychiatric disorders (e.g., depression and anxiety) given the history of possible SI/B signals in this drug class and in the background population with PSO. We recommend a mental health professional (psychiatrist or clinical psychologist) be involved in the screening process to review all prospective SI/B and psychiatric rating scales and determine whether participants are eligible for enrollment."

8.2.5.8. Hypersensitivity and Injection Site reactions

No cases of anaphylaxis or angioedema related to treatment with bimekizumab were reported during the development program. In Pool S1, there were no SAEs related to hypersensitivity. A total of 3/670 (0.4%) subjects discontinued because of TEAEs considered related to hypersensitivity by the Applicant. These included 2/670 (0.3%) with eczema and 1/670 (0.1%) with hypersensitivity (verbatim term dermal hypersensitivity upper trunk). Narratives for these subjects are provided in Section 8.2.4 of this review under Dropouts and/or Discontinuations Due to Adverse Effects. Investigators considered one TEAE of eczema and the TEAE of hypersensitivity related treatment with bimekizumab. In addition, 2 subjects had TEAEs of urticaria in Pool S1. Neither were related to treatment with bimekizumab nor led to discontinuation.

In Pool S2, 2/1789 subjects (0.1%, EAIR 0.1/100 subject-years) had TEAEs with a PT of hypersensitivity that were considered related to treatment with bimekizumab. A total of 13/1789 subjects (0.7%, EAIR 0.8/100 subject-years) had TEAEs of urticaria. However, none led to discontinuation and are thus unlikely to represent hypersensitivity to bimekizumab.

Injection Site Reactions

Injection site reactions were reported under multiple PTs. To better characterize the overall frequency of injection site reactions, the review team pooled PTs for these TEAEs. In Pool S1, injection site reactions were reported in 19/670 (2.8%, EAIR 9.4/100 subject-years) subjects treated with bimekizumab and 2/169 (1.2%, EAIR 3.9/100 subject-years) in the placebo group. In subjects treated with bimekizumab in Pool S1, the most commonly reported PTs included injection site erythema and injection site reaction. Each was reported by 6/670 subjects (0.9%, EAIR 2.9/100 subject-years).

In Pool S2B, 6/488 (1.2%, EAIR 1.8/100 subject-years) subjects treated with bimekizumab Q4W reported injection site reactions. The most commonly reported PTs were injection site erythema in 3/488 subjects (0.6%, EAIR 0.9/100 subject years) and injection site pain in 2/488 subjects (0.4%, EAIR 0.6/100 subject-years). Based on comparison of the EAIRs between Pool S1 and S2B, the frequency of injection site reactions did not increase with longer exposure to bimekizumab.

In Pool S2C, Injection site reactions were reported in 3/261 (1.1%, EAIR 1.6/100 subject-years) subjects in the Q4W group and 4/257 (1.5%, EAIR 2.1/100 subject-years) in the Q8W group. PTs reported by >1 subject included injection site erythema in 2/261 (0.8%, EAIR 1.0/100 subject-years) subjects in the Q4W group and injection site pain in 2/257 (0.8%, EAIR 1.0/100 subject-years) subjects in the Q8W group. Based on comparison of the EAIRs between the bimekizumab Q4W and Q8W treatment arms, there was no apparent dose-response relationship for injection site reactions.

As discussed in Section 8.2.4 of this review, injection site reactions will be included Section 6 (Adverse Reactions) in labeling for bimekizumab.

8.2.6. Clinical Outcome Assessment (COA) Analyses Informing Safety/Tolerability

There were no patient-reported outcome assessments that measured safety parameters. Refer to Section 8.1.7 for COA analyses informing efficacy, as well as the DCOA consult review by Dr. Mira Patel dated April 18, 2021.

8.2.7. Safety Analyses by Demographic Subgroups

The review team conducted additional analyses to evaluate the safety of bimekizumab in demographic subgroups. We conducted these analyses on adverse reactions (ARs) identified during the placebo-controlled periods of Trials PS0009 and PS0013 (Pool S1). We analyzed the most common adverse reactions (AR) by sex, age group (18-<40 years, 40-<65 years, and ≥65 years), and race. The results are presented in the tables below.

Table 62: Adverse Reactions occurring in **≥1%** of Subjects Treated with Bimekizumab and more frequently in Bimekizumab 2 mg than Placebo, by Sex, Pool S1

Adverse Reaction	Bimekizumab 320mg Q4W: Female n=186	Bimekizumab 320mg Q4W: Male n=484	Placebo: Female n=51	Placebo: Male n=118
Upper Respiratory Infections[a]	37 (19.9%)	65 (13.4%)	9 (17.6%)	15 (12.7%)
Candida Infections[b]	23 (12.4%)	43 (8.9%)	1 (2.0%)	0 (0.0%)
Headache	8 (4.3%)	14 (2.9%)	0 (0.0%)	0 (0.0%)
Injection Site Reactions[c]	8 (4.3%)	11 (2.3%)	1 (2.0%)	1 (0.8%)
Tinea Infections[d]	1 (0.5%)	17 (3.5%)	0 (0.0%)	1 (0.8%)
Gastroenteritis[e]	9 (4.8%)	20 (4.1%)	3 (5.9%)	3 (2.5%)
Herpes Simplex Infections[f]	5 (2.7%)	4 (0.8%)	0 (0.0%)	0 (0.0%)
Acne	4 (2.2%)	4 (0.8%)	0 (0.0%)	0 (0.0%)
Folliculitis	1 (0.5%)	7 (1.4%)	0 (0.0%)	0 (0.0%)
Fatigue	2 (1.1%)	5 (1.0%)	0 (0.0%)	0 (0.0%)

[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Cinical Reviewer's table

Table 63: Adverse Reactions occurring in **≥1%** of Subjects Treated with Bimekizumab and more frequently in Bimekizumab 2 mg than Placebo, by Age Group, Pool S1

Adverse Reaction	BKZ 320mg Q4W: <40 yrs n=249	BKZ 320mg Q4W: 40 - <65 yrs n=366	BKZ 320mg Q4W: >=65 yrs n=55	Placebo: <40 yrs n=54	Placebo: 40 - <65 yrs n=101	Placebo: >=65 yrs n=14
Upper Respiratory Infections[a]	50 (20.1%)	47 (12.8%)	5 (9.1%)	13 (24.1%)	10 (9.9%)	1 (7.1%)
Candida Infections[b]	24 (9.6%)	32 (8.7%)	10 (18.2%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Headache	12 (4.8%)	9 (2.5%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection Site Reactions[c]	9 (3.6%)	8 (2.2%)	2 (3.6%)	2 (3.7%)	0 (0.0%)	0 (0.0%)
Tinea Infections[d]	8 (3.2%)	9 (2.5%)	1 (1.8%)	0 (0.0%)	1 (1.0%)	0 (0.0%)
Gastroenteritis[e]	14 (5.6%)	13 (3.6%)	2 (3.6%)	3 (5.6%)	2 (2.0%)	1 (7.1%)
Herpes Simplex Infections[f]	7 (2.8%)	1 (0.3%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acne	4 (1.6%)	4 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Folliculitis	4 (1.6%)	4 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Adverse Reaction	BKZ 320mg Q4W: <40 yrs n=249	BKZ 320mg Q4W: 40 - <65 yrs n=366	BKZ 320mg Q4W: >=65 yrs n=55	Placebo: <40 yrs n=54	Placebo: 40 - <65 yrs n=101	Placebo: >=65 yrs n=14
Fatigue	4 (1.6%)	2 (0.5%)	1 (1.8%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

BKZ-bimekizumab
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling
[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Cinical Reviewer's table

Table 64: Adverse Reactions occurring in **≥1%** of Subjects Treated with Bimekizumab and more frequently in Bimekizumab 2 mg than Placebo, by Race, Pool S1

Adverse Reaction	BKZ 320mg Q4W: Asian n=84	BKZ 320mg Q4W: Black n=15	BKZ 320mg Q4W: Other n=10	BKZ 320mg Q4W: White n=561	Placebo: Asian n=25	Placebo: Other n=2	Placebo: White n=142
Upper Respiratory Infections[a]	14 (16.7%)	1 (6.7%)	3 (30.0%)	84 (15.0%)	2 (8.0%)	1 (50.0%)	21 (14.8%)
Candida Infections[b]	7 (8.3%)	1 (6.7%)	0 (0.0%)	58 (10.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Headache	1 (1.2%)	0 (0.0%)	0 (0.0%)	21 (3.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Injection Site Reactions[c]	3 (3.6%)	0 (0.0%)	0 (0.0%)	16 (2.9%)	1 (4.0%)	0 (0.0%)	1 (0.7%)
Tinea Infections[d]	5 (6.0%)	0 (0.0%)	0 (0.0%)	13 (2.3%)	0 (0.0%)	0 (0.0%)	1 (0.7%)
Gastroenteritis[e]	7 (8.3%)	1 (6.7%)	0 (0.0%)	21 (3.7%)	2 (8.0%)	0 (0.0%)	4 (2.8%)
Herpes Simplex Infections[f]	0 (0.0%)	0 (0.0%)	0 (0.0%)	9 (1.6%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Acne	4 (4.8%)	0 (0.0%)	0 (0.0%)	4 (0.7%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Folliculitis	2 (2.4%)	0 (0.0%)	0 (0.0%)	6 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Fatigue	0 (0.0%)	1 (6.7%)	0 (0.0%)	6 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

BKZ-bimekizumab
[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza
[b] Candida Infections include oral candidiasis, oropharyngeal candidiasis, vulvovaginal candidiasis, vulvovaginal mycotic infection, oral fungal infection, oropharyngitis fungal, skin candida, genital candidiasis, and fungal pharyngitis
[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling

[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis
[e] Gastroenteritis includes gastroenteritis, gastroenteritis viral, gastroenteritis bacterial, enterovirus infection, diarrhea, nausea, vomiting, enteritis, enterocolitis, and gastritis
[f] Herpes Simplex Infections include herpes simplex and oral herpes
Source: Statistical and Cinical Reviewer's table

Although imbalances in certain ARs between demographic subgroups were noted, because of the small subgroup sample sizes, it cannot be concluded that these differences are clinically meaningful.

8.2.8. Specific Safety Studies/Clinical Trials

In addition to the phase 3 trials, the Applicant also submitted data from the following clinical trials:

- One phase 1 trial
- Four phase 2 trials
- Two clinical -use studies to evaluate device platforms
- One vaccine trial (influenza) conducted in healthy volunteers
- Two PK trials

Phase 1 Trial UP0008

Trial UP0008 was conducted outside the United States and not under the IND. This was a phase 1, first-in-human, randomized, subject-blind, investigator-blind, placebo-controlled, single-dose, dose-escalating study to evaluate the safety, PK, and pharmacodynamics (PD) of bimekizumab administered as a single iv infusion to subjects with mild-to-moderate plaque psoriasis. Mild to moderate plaque psoriasis was defined as ≤5% involved BSA and a minimum of 2 psoriatic plaques. Subjects were enrolled and randomized to bimekizumab or placebo in the following cohorts:

- Bimekizumab 8 mg- 4 subjects, placebo-2 subjects
- Bimekizumab 40 mg- 4 subjects, placebo-2 subjects
- Bimekizumab 160 mg- 6 subjects, placebo-3 subjects
- Bimekizumab 480 mg- 6 subjects, placebo-3 subjects
- Bimekizumab 640 mg- 6 subjects, placebo-3 subjects

Subjects were admitted to the study center on Day -2 for pre-dose assessments and remained in the clinic until Day 2. Subjects returned for assessments at 72 and 96 hours postdose, then weekly from Week 1-4, then every 2 weeks until Week 12, then every 4 Weeks until week 20. Subjects received a single dose of study product at the assigned dose via IV infusion over at least 60 minutes. A safety review group reviewed data from each cohort prior to advancing to the subsequent cohort. Safety assessments included:

- AEs

- Vital signs (blood pressure [BP], heart rate [HR], respiratory rate [RR], and temperature)
- ECGs
- Clinical laboratory studies (clinical chemistry, hematology, and urinalysis)
- Coagulation/hemostasis tests
- Fecal occult blood (FOB)

No deaths occurred and no severe TEAEs were reported. One subject in the bimekizumab 40 mg group had an SAE of vomiting which occurred 37 days post-dose. The event resolved after 4 days and the investigator considered the event not related to treatment. The most frequently observed TEAEs are presented in the table below:

Table 65: TEAEs most Frequently Reported by SOC, PT, and Treatment Group, Trial UP0008

MedDRA (version 16.1) SOC PT	Placebo N=13 n (%)	UCB4940 8mg N=4 n (%)	UCB4940 40mg N=4 n (%)	UCB4940 160mg N=6 n (%)	UCB4940 480mg N=6 n (%)	UCB4940 640mg N=6 n (%)	UCB4940 total N=26 n (%)
Any TEAE	10 (76.9)	1 (25.0)	4 (100)	5 (83.3)	6 (100)	6 (100)	22 (84.6)
Gastrointestinal disorders	3 (23.1)	0	3 (75.0)	3 (50.0)	0	1 (16.7)	7 (26.9)
Abdominal distension	0	0	0	2 (33.3)	0	0	2 (7.7)
Abdominal pain	0	0	0	2 (33.3)	0	0	2 (7.7)
Vomiting	0	0	1 (25.0)	1 (16.7)	0	0	2 (7.7)
General disorders and administration site conditions	2 (15.4)	0	3 (75.0)	1 (16.7)	1 (16.7)	1 (16.7)	6 (23.1)
Fatigue	0	0	1 (25.0)	1 (16.7)	0	0	2 (7.7)
Medical device site reaction	0	0	2 (50.0)	0	0	1 (16.7)	3 (11.5)
Infections and infestations	4 (30.8)	0	0	2 (33.3)	0	4 (66.7)	6 (23.1)
Ear infection	0	0	0	0	0	2 (33.3)	2 (7.7)
Nasopharyngitis	1 (7.7)	0	0	1 (16.7)	0	3 (50.0)	4 (15.4)
Nervous system disorders	2 (15.4)	0	1 (25.0)	0	4 (66.7)	3 (50.0)	8 (30.8)
Dizziness	0	0	0	0	0	2 (33.3)	2 (7.7)
Headache	2 (15.4)	0	1 (25.0)	0	4 (66.7)	1 (16.7)	6 (23.1)
Respiratory, thoracic, and mediastinal disorders	0	1 (25.0)	1 (25.0)	1 (16.7)	2 (33.3)	3 (50.0)	8 (30.8)
Oropharyngeal pain	0	1 (25.0)	1 (25.0)	1 (16.7)	2 (33.3)	0	5 (19.2)

MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event; UCB4940=bimekizumab
Note: N=number of subjects in each group (FAS); n=number of subjects reporting at least 1 TEAE in that SOC/PT; (%) =percentage of subjects among total N.
Source: Table 8-2, UP0008 CSR, p.69

Most of the TEAEs were mild in intensity. Investigators reported no infusion reactions. One subject in the bimekizumab 480 mg group had neutropenia ($0.97x10^9$/L) at Week 3. This was not associated with any TEAEs of infection. This subject also had low neutrophil counts ($<2.0x10^9$/L) at all other study visits. Otherwise, no notable differences or clinically meaningful changes from Baseline in laboratory parameters were noted. In addition, investigators reported no clinically significant ECG findings or physical examination abnormalities.

Phase 2 Trials

Trial PS0010

This was a phase 2, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging trial in subjects with moderate to severe plaque psoriasis. Moderate to severe plaque psoriasis was defined as an Investigator Global Assessment (IGA) score of ≥3 on a 5-point scale, Psoriasis Area and Severity Index (PASI) score ≥12, and involved body surface area (BSA) of ≥10%. The trial included a Screening Period, as 12-week Treatment Period, and 20-week Safety Follow-up Period. Investigators enrolled 250 subjects and randomized them 1:1:1:1:1:1 to the following blinded treatment regimens:

- Bimekizumab 64mg SC Q4W
- Bimekizumab 160mg SC Q4W
- Bimekizumab 320mg SC loading dose (LD) at Baseline followed by 160mg SC Q4W
- Bimekizumab 320mg SC Q4W
- Bimekizumab 480mg SC Q4W
- Placebo SC Q4W

After the 12-week Treatment Period, eligible subjects were allowed to enroll in an extension study (PS0011). Safety assessments included:

- AEs/SAEs
- Physical examination
- Vital signs (BP, HR, and temperature)
- Clinical laboratory studies (clinical chemistry, hematology, and urinalysis)
- ECGs
- Pregnancy testing
- Screening for neuropsychiatric events (suicidal ideation/behavior [SIB])
    - Electronic Columbia Suicide Severity Rating Scale (eC-SSRS)
    - Hospital Anxiety and Depression Scale (HADS)

In addition, the following were considered AEs of special interest (AESIs):

- Serious infections, including TB and opportunistic infections
- Malignancies, including lymphoma
- Major adverse cardiovascular events (MACE)
- Cytopenias
- Neuropsychiatric events
- Inflammatory bowel disease (IBD)
- Anaphylactic reactions
- Hepatic events and DILI

No deaths were reported during the trial. Two subjects treated with bimekizumab had SAEs. A 68 y/o male in the bimekizumab 480 mg group had SAEs of large intestine polyp of moderate intensity and colon cancer of severe intensity on Day 14. The subject was discontinued. The

SAE of large intestine polyp was resolved, and colon cancer was resolving at the time of the study report. Investigators considered the SAEs unrelated to treatment. A 53 y/o female with a history of tobacco use, obesity, hypercholesterolemia, and Type 2 DM had an SAE of myocardial infarction 35 days after the final dose of bimekizumab 64 mg. The SAE was moderate in intensity and was reported as resolved. The SAE was adjudicated as a MACE event by the CV adjudication committee. The investigator considered the event unrelated to treatment.
A total of 10 subjects treated with bimekizumab and 1 subject in the placebo group discontinued because of AEs. These are presented in the table below:

Table 66: Discontinuations Because of AEs during the Treatment Period, Trial PS0010

MedDRA (Version 19.0) SOC PT	Placebo N=42 n (%)	BKZ 64mg N=39 n (%)	BKZ 160mg N=43 n (%)	BKZ 160mg w/LD N=40 n (%)	BKZ 320mg N=43 n (%)	BKZ 480mg N=43 n (%)	All BKZ N=208 n (%)
Any TEAE	1 (2.4)	1 (2.6)	3 (7.0)	3 (7.5)	1 (2.3)	2 (4.7)	10 (4.8)
Blood and lymphatic system disorders	0	0	0	1 (2.5)	0	0	1 (0.5)
Eosinophilia	0	0	0	1 (2.5)	0	0	1 (0.5)
Infections and infestations	1 (2.4)	0	0	0	0	0	0
Meningitis viral	1 (2.4)	0	0	0	0	0	0
Investigations	0	1 (2.6)	3 (7.0)	3 (7.5)	1 (2.3)	1 (2.3)	9 (4.3)
Gamma-glutamyltransferase increased	0	0	2 (4.7)	1 (2.5)	1 (2.3)	0	4 (1.9)
Alanine aminotransferase increased	0	0	1 (2.3)	0	0	0	1 (0.5)
Aspartate aminotransferase increased	0	0	1 (2.3)	0	0	0	1 (0.5)
Blood bilirubin increased	0	0	0	0	0	1 (2.3)	1 (0.5)
Hepatic enzyme increased	0	0	0	1 (2.5)	0	0	1 (0.5)
False positive tuberculosis test	0	1 (2.6)	0	0	0	0	1 (0.5)
Blood creatinine increased	0	0	0	1 (2.5)	0	0	1 (0.5)
Neutrophil count decreased	0	0	1 (2.3)	0	0	0	1 (0.5)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	1 (2.3)	1 (0.5)
Colon cancer	0	0	0	0	0	1 (2.3)	1 (0.5)

BKZ=bimekizumab; LD=loading dose; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; sc=subcutaneously; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: BKZ was administered sc Q4W, with the exception of the LD as follows: BKZ 320mg LD administered sc at Baseline followed by BKZ 160mg dose administered sc Q4W.
Note: Percentages are based on the number of subjects in the SS; n=number of subjects reporting at least 1 TEAE leading to discontinuation within SOC/PT.
Note: The Treatment Period was defined as the time period from the first dose at Baseline through Week 12.
Source: Table 11-8, PS0010 CSR, pp. 192-193

Overall, TEAEs occurred more frequently in subjects in the bimekizumab groups (129/208, 60.6%) than the placebo group (15/42, 35.7%). The frequency of TEAEs by bimekizumab treatment groups were 27/39 (69.2%) for 64 mg Q4W, 24/43 (55.8%) for 160 mg Q4W, 24/40 (60.0%) for 320mg LD/160mg Q4W, 26/43 (60.5%) for 320 mg Q4W, and 25/43 (58.1%) for 480 mg Q4W. The most commonly reported TEAEs (>5%) are presented in the table below:

Table 67: Most Commonly Reported TEAEs by PT, Trial PS0010

MedDRA (Version 19.0)	Placebo	BKZ 64mg	BKZ 160mg	BKZ 160mg w/LD	BKZ 320mg	BKZ 480mg	All BKZ
	N=42	N=39	N=43	N=40	N=43	N=43	N=208
PT	n (%) [Events]						
Any TEAE	8 (19.0) [9]	16 (41.0) [29]	12 (27.9) [14]	12 (30.0) [13]	14 (32.6) [20]	10 (23.3) [14]	64 (30.8) [90]
Nasopharyngitis	2 (4.8) [2]	5 (12.8) [5]	3 (7.0) [3]	3 (7.5) [3]	6 (14.0) [6]	4 (9.3) [5]	21 (10.1) [22]
Upper respiratory tract infection	1 (2.4) [1]	5 (12.8) [5]	2 (4.7) [3]	3 (7.5) [3]	2 (4.7) [2]	0	12 (5.8) [13]
Arthralgia	0	2 (5.1) [2]	0	1 (2.5) [1]	1 (2.3) [3]	3 (7.0) [5]	7 (3.4) [11]
Gamma-glutamyltransferase increased	1 (2.4) [1]	0	3 (7.0) [3]	2 (5.0) [2]	1 (2.3) [2]	0	6 (2.9) [7]
Neutropenia	0	2 (5.1) [2]	0	1 (2.5) [1]	2 (4.7) [3]	0	5 (2.4) [6]
Respiratory tract infection	1 (2.4) [1]	2 (5.1) [2]	1 (2.3) [1]	1 (2.5) [1]	1 (2.3) [1]	0	5 (2.4) [5]
Hypertension	3 (7.1) [3]	1 (2.6) [1]	1 (2.3) [1]	1 (2.5) [1]	0	1 (2.3) [1]	4 (1.9) [4]
Oral candidiasis	0	0	0	1 (2.5) [1]	3 (7.0) [3]	0	4 (1.9) [4]
Rhinitis	1 (2.4) [1]	2 (5.1) [2]	1 (2.3) [1]	0	0	1 (2.3) [1]	4 (1.9) [4]
Tonsillitis	0	2 (5.1) [3]	2 (4.7) [2]	0	0	0	4 (1.9) [5]
Leukopenia	0	2 (5.1) [3]	0	0	0	1 (2.3) [1]	3 (1.4) [4]
Headache	0	2 (5.1) [2]	0	0	0	1 (2.3) [1]	3 (1.4) [3]
Vomiting	0	2 (5.1) [2]	0	0	0	0	2 (1.0) [2]

BKZ=bimekizumab; LD=loading dose; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; sc=subcutaneously; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: BKZ was administered sc Q4W, with the exception of the LD as follows: BKZ 320mg LD administered sc at Baseline followed by BKZ 160mg dose administered sc Q4W.
Note: Percentages are based on the number of subjects in the SS; n=number of subjects reporting at least 1 TEAE within PT.
Note: The Treatment Period was defined as the time period from the first dose at Baseline through Week 12.
Source: Table 11-3, PS0010 CSR, pp.183-184

AESIs

A total of 9/208 (4.3%) subjects treated with bimekizumab reported TEAEs of fungal infection. No fungal infections were reported in the placebo group. Fungal infection PTs included oral candidiasis, tinea pedis, oral fungal infection, and vulvovaginal mycotic infection. Fungal infections occurred in 1-2 subjects/treatment group except for bimekizumab 320 mg Q4W, in which 4/43 (9.3%) had TEAEs of fungal infection. Otherwise, there were no TEAEs of opportunistic infection, latent TB, or active TB.

The only malignancy reported during the trial was a subject with an SAE of colon cancer, which was discussed above. The only adjudicated MACE event was a subject with an SAE of MI during the Safety Follow-up Period, which was also discussed above.

TEAEs related to cytopenias include the following:

- Leukopenia: bimekizumab 64mg, 2 subjects (3 events); bimekizumab 480mg, 1 subject (1 event)
- Lymphocyte count decreased: bimekizumab 160mg w/LD, 1 subject (1 event)
- Lymphopenia: bimekizumab 160mg w/LD, 1 subject (1 event)
- Neutropenia: bimekizumab 64mg, 2 subjects (2 events); bimekizumab 160mg w/LD, 1 subject (1 event); bimekizumab 320mg, 2 subjects (3 events)
- Neutrophil count decreased: bimekizumab 160mg, 1 subject (1 event); bimekizumab 160mg w/ 320 mg LD, 1 subject (1 event)
- White blood cell count decreased: bimekizumab 160mg w/LD, 1 subject (1 event)

One subject, a 36 y/o male with unremarkable history in the 160 mg Q4W group discontinued because of a TEAE of neutrophil count decreased. His neutrophil count at Baseline was 1.5 x 10^9/L at Baseline and reached its lowest value at 1.3 x 10^9/L at Week 2. By Week 4 his neutrophil count had risen to 2.2 x 10^9/L and the investigator considered the AE resolved. The investigator considered the AE moderate in severity and related to treatment with bimekizumab.

No TEAEs related to neuropsychiatric events or IBD occurred during the trial. No anaphylactic reactions occurred. However, one subject in the bimekizumab 64 mg Q4W had 2 TEAEs of Type IV delayed type hypersensitivity 3 days after the second dose at Week 4 and 2 days after the Week 8 dose. The subject had developed anti-drug antibodies at Week 4. The AEs resolved and the subject continued treatment with bimekizumab and went on to enroll in the extension Trial PS0011. The investigator considered the events related to treatment with bimekizumab.

A total of 13/208 (6.3%) of subjects treated with any dose of bimekizumab experienced 18 TEAEs related to hepatic events, compared to 1/42 (2.4%) in the placebo group. No subjects met Hy's Law criteria (AST or ALT ≥ 3x ULN and total bilirubin ≥ 2x ULN), although AST or ALT ≥ 3x ULN occurred in 3 subjects treated with bimekizumab. These included 1 subject (1/42, 2.4%) in the 160 mg Q4W group, 1 subject (1/40, 2.5%) in the 160 mg Q4W with 320 mg LD, and 1 subject (1/43, 2.3%) in the 480 mg Q4W group. Hepatic TEAEs occurred in all bimekizumab groups except for 64 mg Q4W. There was no apparent dose-response for hepatic TEAEs. In subjects treated with any dose of bimekizumab (except for 64 mg Q4W), the PTs of hepatic function abnormal, hepatic steatosis, nonalcoholic fatty liver, nonalcoholic steatohepatitis, and steatohepatitis were reported in 1 subject each. Nine of the 18 hepatic TEAEs were resolved within 8 to 36 days. Of the remaining events 2 were reported as resolving, 5 were not resolved, 1 was worsened, and 1 had an unknown outcome. The hepatic TEAEs that were not resolved or worsened included the following:

- Benign hepatic cyst, not resolved, 480 mg Q4W
- Hepatic steatosis, not resolved, 480 mg Q4W
- Hepatic steatosis, not resolved, 160mg Q4W w/ 320 mg LD
- Hepatic enzyme increased, not resolved, occurred 146 days after the first and most recent injection, 160mg Q4W
- Steatohepatitis, not resolved, 160mg Q4W w/ 320 mg LD
- GGT increased, worsened, 320 mg Q4W, did not lead to discontinuation

Four subjects with hepatic TEAEs were discontinued. The PTs and dosing group are listed below:

- GGT increased, bimekizumab 160mg Q4W
- GGT increased, bimekizumab 160mg Q4W w/ 320 mg LD
- GGT increased, bimekizumab 320mg Q4W
- Blood bilirubin increased, bimekizumab 480mg Q4W

Trial PS0011

This was a multicenter, 48-week, double-blind, parallel-group extension trial. Subjects who completed Week 12 of PS0010 were eligible for enrollment. Investigators assigned subjects to dosing regimens based on their assigned dose in Trial PS0010 and whether PASI 90 was achieved. A total of 217 subjects were enrolled and assigned to the following treatment regimens:

- Bimekizumab 64mg Q4W- 15 subjects
- Bimekizumab 160mg Q4W- 111 subjects
- Bimekizumab 320mg Q4W- 91 subjects

Two deaths occurred during Trial PS0011. Narratives for these subjects are provided in Section 8.2.4 of this review. A total of 15/217 subjects (6.9%, 9.22 events/100 subject-years) had 23 SAEs. In the 64 mg Q4W group, 1/15 (6.7%, 5.43 events/100 subject-years) had 1 SAE. In the 160 mg Q4W group, 7/111 (6.3%, 7.86 events/100 subject-years) had 10 SAEs. In the 320 mg Q4W group, 7/91 (7.7%, 11.57 events/100 subject-years) had 12 SAEs. SAEs were most frequently reported in the SOCs of Infections and infestations, Renal and urinary disorders, and Vascular disorders (2 subjects [0.9%] each). No SAE PT was reported in more than 1 subject. The only SAE considered by the investigator as related to treatment was an event of hepatic enzyme increased in a subject in the 160mg Q4W group. The event was severe in intensity, was resolving, and did not lead to discontinuation.

A total of 14/217 (6.5%) subjects experienced 16 AEs leading to discontinuation. This included 7/111 (6.3%) of subjects with 8 AEs in the 160 mg Q4W group and 7/91 (7.7%) of subjects with 8 AEs in the 320mg Q4W group. The most common SOC for AEs leading to discontinuation was Investigations. PTs in this SOC included GGT increased, ALT increased, Blood bilirubin increased, Hepatic enzyme increased, and Transaminases increased. TEAEs of GGT increased

leading to discontinuation occurred in 2/91 (2.2%) of subjects in the 320 mg Q4W group. The remaining PTs were reported in 1 subject in the 160 mg Q4W and 320 mg Q4W groups. There was no apparent dose-response for AEs leading to discontinuation.

Overall, TEAEs occurred in 184/217 subjects (84.8%, 263.50 events/100 subject-years). This included 10/15 subjects (66.7%, 190.01 events/100 subject-years) in the 64 mg Q4W group, 98/111 (88.3%, 257.84 events /100 subject-years) in the 160 mg Q4W group, and 76/91 subjects (83.5%, 283.59 events/100 subject-years) in the 320mg Q4W group. The most common SOC in which TEAEs were reported was Infections and Infestations, with 119/217 subjects with 241 events (54.8%, 96.66 events/100 subject-years) overall. This included 8/15 subjects with 17 events (53.3%, 92.29 events/100 subject-years) in the 64 mg Q4W group, 61/111 subjects with 118 events (55.0%, 92.76 events/100 subject-years) in the 160 mg Q4W group, and 50/91 subjects with 106 events (54.9%, 102.21 events/100 subject years) in the 320 mg Q4W group. The most commonly reported PT in this SOC was Oral candidiasis, with 29/217 subjects with 38 events (13.4%, 15.24 events/100 subject-years) overall. This included 1/15 subjects with 2 events (6.7%, 10.86 events/100 subject-years) in the 64 mg Q4W group, 13/111 subjects with 17 events (11.7%, 13.36 events/100 subject-years) in the 160 mg Q4W group, and 15/91 subjects with 19 events (16.5%, 18.32 events/100 subject years) in the 320 mg Q4W group.

AESIs

There were no cases of latent or active TB reported. There were 2 SAEs of infection. One subject in the 160 mg Q4W group had a staphylococcal abscess and 1 subject in the 320 mg Q4W group had otitis externa bacterial. Overall, a total of 39/217 subjects (18%, 22.46 events/100 subject-years) experienced 56 TEAEs of fungal infections. This included 3/15 subjects with 5 events (20.0%, 27.14 events/100 subject-years) in the 64 mg Q4W group, 15/111 subjects with 22 events (13.5%, 17.29 events/100 subject-years) in the 160 mg Q4W group, and 21/91 subjects with 29 events (23.1%, 27.96 events/100 subject years) in the 320 mg Q4W group. Oral candidiasis was the most commonly reported PT for fungal infections, which were discussed above. All TEAEs of fungal infection were mild or moderate in intensity. The only fungal infection TEAE that led to discontinuation was esophageal candidiasis in one subject in the 320 mg Q4W group. Otherwise, no opportunistic infections were reported.

Two malignancies occurred during the trial. One subject in the 160 mg Q4W group had acute myeloid leukemia which was reported at the time of the final dose of bimekizumab. This was resolved with sequelae. The investigator considered the event not related to treatment with bimekizumab and attributed it to previous chemotherapy the subject had received. One subject in the 320 mg Q4W group had basal cell carcinoma with onset 211 days after the first dose of bimekizumab. The event was resolved but led to discontinuation. The investigator considered the event not related to treatment with bimekizumab.

No adjudicated MACE events or AEs of inflammatory bowel disease occurred during Trial PS0011.

No SAEs related to cytopenias were reported during Trial PS0011. TEAEs related to cytopenias were reported by PT and treatment group as follows:

- Leukopenia: 1 subject with 1 event, 160mg Q4W; 1 subject with 1 event, 320mg Q4W
- Lymphopenia: 1 subject with 1 event, 160mg Q4W
- Platelet count decreased: 1 subject with 1 event, 160mg Q4W
- Lymphocyte count decreased: 1 subject with 1 event, 320mg Q4W

Neutropenia (all Grade 1; <LLN - 1.5 x 10^9 /L) occurred in 1/15 subjects (6.7%) in the 64 mg Q4W group, 5/111 subjects (4.5%) in the 160 mg Q4W group, and 3/91 subjects (3.3%) in the 320 mg Q4W group. These were not reported as TEAEs.

No adjudicated SIB events occurred during the trial. Neuropsychiatric TEAEs occurred in a total of 3/217 subjects (1.4%). In the 320 mg Q4W group, 1/91 subject (1.1%) had a TEAE of hypersomnia. The event was moderate in severity and did not lead to discontinuation. The investigator considered the event related to treatment. In the 160mg Q4W group, 1/111 (0.9%) subject had a TEAE of affect lability and 1 subject had a TEAE of depression. Both were moderate in intensity, and neither led to discontinuation. The investigator considered neither of these events to be related to treatment.

No anaphylaxis occurred during the trial. One subject (1/111, 0.9%) in the 160 mg Q4W group had 1 TEAE of delayed type hypersensitivity. This subject also had delayed type hypersensitivity during the feeder Trial PS0010 and is discussed above. The event was moderate in severity, resolved, and did not lead to discontinuation. The investigator considered the event related to treatment.

Hepatic TEAEs were reported in the SOCs of Investigations and Hepatobiliary disorders. No subjects met the criteria for Hy's Law in Trial PS0011. Overall, 22/217 subjects (10.1%, 11.63 events/100 subject-years) treated with any dose of bimekizumab experienced 29 TEAEs related to hepatic events. This included 1/15 subjects with 2 events (6.7%, 10.86 events/100 subject-years) in the 64 mg Q4W group, 8/111 subjects with 10 events (7.2%, 7.86 events/100 subject-years) in the 160 mg Q4W group, and 14/91 subjects with 17 events (14.3%, 16.39 events/100 subject years) in the 320 mg Q4W group. The most commonly reported PT was gamma-glutamyl transferase increased, in which 8/217 subjects (3.7%, 4.41 events/100 subject-years) treated with any dose of bimekizumab experienced 11 TEAEs. This included 1/15 subjects with 1 event (6.7%, 5.43 events/100 subject-years) in the 64 mg Q4W group, 4/111 subjects with 6 events (3.6%, 4.72 events/100 subject-years) in the 160 mg Q4W group, and 3/91 subjects with 4 events (3.3%, 3.86 events/100 subject years) in the 320 mg Q4W group. One subject had an SAE of Hepatic enzyme increased and was discussed above. Discontinuations because of hepatic TEAEs were also discussed above.

A total of 7/217 (3.2%) subjects had ALT or AST ≥3x ULN, with 3/111 (2.7%) in the 160 mg Q4W group and 4/91 (4.4%) in the 320 mg Q4W group. ALT or AST ≥5x ULN occurred in 4/217 (1.8%) subjects, with 2/111 (1.8%) in the 160 mg Q4W group and 2/91 (2.2%) in the 320 mg Q4W group.

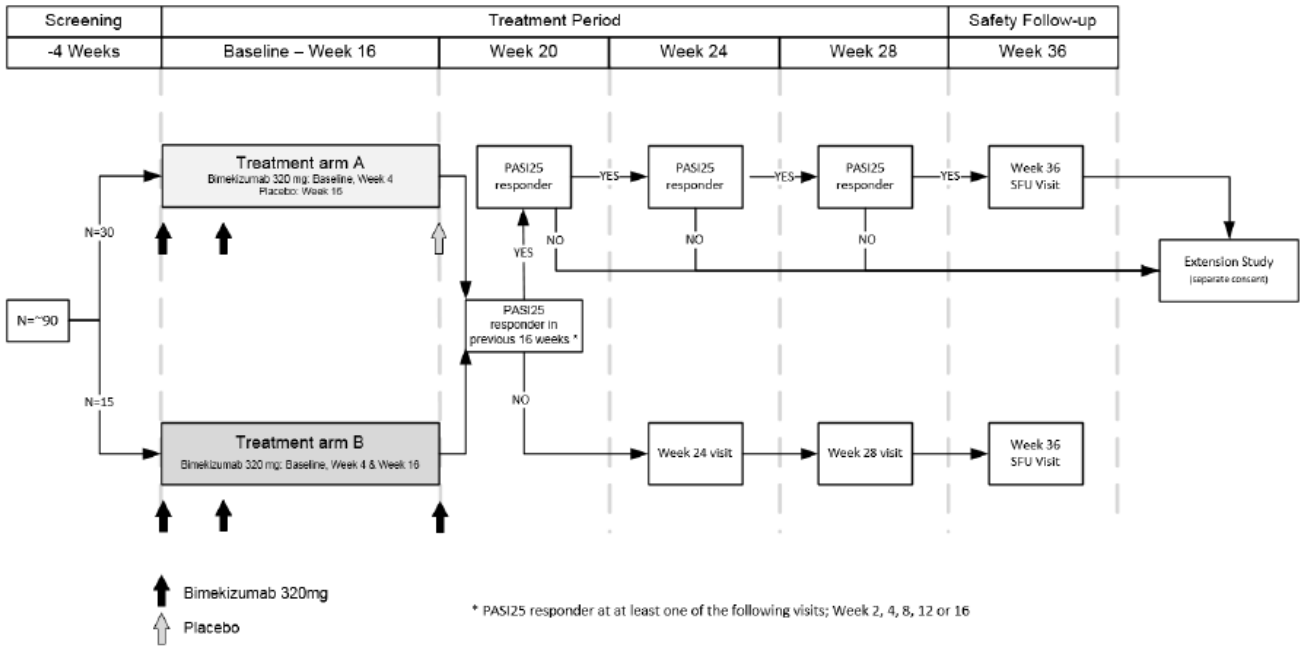
Trial PS0016

This was a phase 2, multicenter, randomized, subject-blind and investigator-blind trial in subjects with moderate to severe plaque psoriasis, defined as IGA score ≥3, PASI ≥12, and involved BSA ≥10%. The trial included a Screening Period, a 28-week Treatment Period, and a Safety Follow-up (SFU) Period of 20 weeks following the final dose of bimekizumab. Subjects were randomized 2:1 to the following regimens:

- Treatment arm A: Bimekizumab 320 mg SC at Baseline and Week 4, and placebo at Week 16 (32 subjects)
- Treatment arm B: Bimekizumab 320 mg SC at Baseline and Weeks 4 and 16 (17 subjects)

From Week 20-28, subjects who had achieved PASI25 response (i.e. experienced 25% improvement from Baseline PASI score) by Week 16 were evaluated every 4 weeks off treatment. If the subject relapsed (defined as loss of PASI25 response), they were eligible to enter extension trial PS0018. Subjects not achieving PASI25 response by Week 20 were assessed at Weeks 24, 28, and the SFU visit at Week 36 and were not eligible to enroll in the extension trial. The schematic diagram for Trial PS0016 is presented below:

Figure 19: Schematic Diagram of Trial PS0016



IMP=investigational medicinal product; PASI=Psoriasis Area and Severity Index; SFU=Safety Follow-up
Source: Figure 3-1, PS0016 CSR, p. 37

No deaths occurred during Trial PS0016. Two subjects experienced 3 SAEs during the Treatment Period. A 61 y/o male in the 320 mg + placebo group (Treatment arm A) experienced peripheral sensorimotor neuropathy on Day 95. The SAE was severe in intensity, resolved within 5 days, and did not lead to discontinuation. The investigator considered the event not related to treatment. A 30 y/o female in the 320 mg group (Treatment arm B) had SAEs of cholecystitis acute and pancreatitis on Day 68. Both events were severe in intensity, resolved within 5 days, and did not lead to discontinuation. The investigator considered the events not related to treatment. One subject experienced an SAE during the Post-Treatment Period. A 65 y/o male had syncope on Day 114. The event was mild in intensity and resolved within 3 days. The investigator considered the event not related to treatment.

A total of 2 subjects experienced 4 TEAEs leading to discontinuation. Both subjects were in the 320 mg group (Treatment arm B). A 31 y/o male discontinued because of TEAEs of ALT and GGT increased on Day 15 and 29. The TEAE of ALT increased was mild and resolved within 15 days. The TEAE of GGT increased at Day 15 was severe in intensity, resolved, then recurred at Day 29 at moderate intensity with the final outcome unknown. The investigator considered the events not related to treatment. A 45 y/o female discontinued because of a TEAE of lymphocyte count decreased (Grade 3) on Day 29. The event was severe in intensity and was resolved on Day 142. The investigator considered the event related to treatment.

In the 320mg + placebo group, 24/32 subjects (75.0%) reported 57 TEAEs. In the 320 mg group, 15/17 subjects (88.2%) reported 44 TEAEs. Overall, the SOCs in which TEAEs were reported most frequently were Infections and infestations (53.1% of all subjects) and Investigations (28.6% of all subjects). The most commonly reported PTs among all subjects were upper respiratory tract infection (9 subjects [18.4%]) and gamma glutamyl transferase (GGT) increased (5 subjects [10.2%]). The most common TEAEs (reported by ≥2 subjects in either treatment group) are presented in the table below:

Table 68: TEAEs reported by **≥2** Subjects in any Treatment Group, Trial PS0016

MedDRA (Version 19.0) PT	BKZ 320mg+PBO N=32 n (%) [#]	BKZ 320mg N=17 n (%) [#]	All Subjects N=49 n (%) [#]
Any TEAE	24 (75.0) [57]	15 (88.2) [44]	39 (79.6) [101]
Upper respiratory tract infection	6 (18.8) [7]	3 (17.6) [3]	9 (18.4) [10]
Nasopharyngitis	2 (6.3) [2]	1 (5.9) [1]	3 (6.1) [3]
Urinary tract infection	4 (12.5) [4]	0	4 (8.2) [4]
Viral upper respiratory tract infection	2 (6.3) [2]	1 (5.9) [1]	3 (6.1) [3]
Blood cholesterol increased	1 (3.1) [1]	2 (11.8) [2]	3 (6.1) [3]
GGT increased	2 (6.3) [3]	3 (17.6) [3]	5 (10.2) [6]
AST increased	2 (6.3) [2]	2 (11.8) [2]	4 (8.2) [4]
ALT increased	1 (3.1) [1]	2 (11.8) [2]	3 (6.1) [3]
White blood cell count decreased	1 (3.1) [1]	3 (17.6) [4]	4 (8.2) [5]
Neutrophil count decreased	0	2 (11.8) [2]	2 (4.1) [2]
Hyperkalaemia	2 (6.3) [4]	1 (5.9) [1]	3 (6.1) [5]
Arthralgia	1 (3.1) [1]	1 (5.9) [1]	2 (4.1) [2]
Headache	2 (6.3) [2]	0	2 (4.1) [2]

ALT=alanine aminotransferase; AST=aspartate aminotransferase; BKZ=bimekizumab; GGT= gamma glutamyl transferase; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: Treatment Period TEAEs were defined as all TEAEs with onset at the time of or after the first administration of IMP up until the Week 20 visit. For any subjects who discontinued prior to Week 20, Treatment Period TEAEs were cut off at 140 days relative to the first dose.
Source: Table 11-3, PS0016 CSR, p. 120

AESIs

No cases of latent TB, active TB, or SAEs of infections occurred during Trial PS0016. No Fungal infection TEAEs were reported in the 320 mg group. In the 320mg+ placebo group, 3/32 subjects (9.4%) had 4 TEAEs of fungal infection. One subject (1/32, 3.1%) had 1 TEAE of oral candidiasis and 1 TEAE of candida infection, 1 subject had 1 TEAE of oral candidiasis, and 1 subject had 1 TEAE of vulvovaginal candidiasis. Investigators considered the oral candidiasis and Candida infection events to be related to treatment and the vulvovaginal candidiasis to be not related to treatment. All the fungal infections were resolved, and none led to discontinuation. Otherwise, there were no TEAEs of opportunistic infections.
No SAEs related to cytopenias were reported. One subject was discontinued because of a TEAE of lymphocyte count decreased and is discussed above. In the 320mg + placebo group, there

were 3 TEAEs related to cytopenia along with 12 in the 320 mg group. The preferred terms, number of subjects and events, and treatment groups were as follows:

- Neutrophil Count decreased: 1 subject with 1 event in the 320 mg + placebo group; 3 subjects with 3 events in the 320 mg group
- White blood cell count decreased: 2 subjects with 2 events in the 320 mg + placebo group; 3 subjects with 5 events in the 320 mg group
- Lymphocyte count decreased: 1 subject with 1 event in the 320 mg group
- Platelet count decreased: 1 subject with 3 events in the 320 mg group

No subject in either treatment group met Hy's Law criteria. There were no SAEs related to hepatic TEAEs. One subject discontinued because of hepatic TEAEs and was discussed above. TEAEs related to hepatic events occurred in 3/32 subjects with 9 events (9.4%, 37.50 events/100 subject years) in the 320mg + placebo group and 7/17 subjects with 16 events (41.2%, 125.00 events/100 subject years) in the 320 mg group. Most hepatic TEAEs were in the SOC of investigations. In the 320 mg + placebo group, PTs included ALT increased, Gamma glutamyl transferase increased, and AST increased, each occurring in 2/32 subjects (6.3%). In the 320 mg group, PTs included ALT increased and Gamma glutamyl transferase increased, both in 3/17 subjects (17.6%); AST increased in 2/17 subjects (11.8%), and Blood bilirubin increased in 1/17 subject (5.9%). A total of 21/25 of the hepatic TEAEs were resolved, with time to resolution ranging from 12-125 days. Hepatic TEAEs that were not resolved included:

- 31 y/o male with Gamma glutamyl transferase increased, outcome unknown, subject discontinued
- 41 y/o male with Gamma glutamyl transferase increased, not resolved
- 46 y/o male with Blood bilirubin increased, not resolved
- 55 y/o male with non-alcoholic fatty liver, not resolved

There were no TEAEs related to malignancy, MACE events, neuropsychiatric events, anaphylactic reactions, or IBD during Trial PS0016.

Trial PS0018

This was a multicenter, 48-week, open-label extension trial in which subjects from PS0016 were eligible to enroll. A total of 43 subjects were enrolled, and 37 completed the trial. Of the 6 subjects who discontinued, 1 was because of AE, 1 because of protocol violation, 1 lost to follow-up, and 3 withdrew consent. All subjects began treatment with bimekizumab 160 mg Q4W. Investigators had the option to increase the dosage to 320 mg Q4W if a subject's PASI response was reduced by ≥50% to <75% from Baseline of Trial PS0016 at Week 12 or later. In addition, if a subject's disease was adequately controlled on a dosage of 320 mg Q4W, investigators had the option to reduce the dosage to 160 mg Q4W. Subjects who did not achieve a PASI50 response at Week 12 or later were withdrawn from the trial. A total of 5 subjects had their dose increased from 160 to 320 mg Q4W during the trial. None of these subjects had their dosage reduced back to 160 mg Q4W during the trial.
No deaths occurred during Trial PS0018. A total of 3/43 subjects treated with 160 mg Q4W had 3 SAEs during the trial. One subject had an Acute myocardial infarction, 1 had Anemia

postoperative, and 1 had Syncope. All 3 events were resolved, and none led to discontinuation. None of the SAEs were considered by investigators as related to treatment.

One subject (1/43, 2.3%) treated with 160 mg Q4W had an AE which led to discontinuation. This subject discontinued because of a TEAE of Otitis media bacterial which occurred 60 days after the first dose of bimekizumab in Trial PS0018. The investigator considered the event related to treatment.

A total of 38/43 subjects (88.4%) experienced 142 TEAEs. The most common SOCs in which TEAEs were reported were Infections and infestations and Investigations. The most common TEAEs occurring in >5% of subjects are presented in the table below:

Table 69: TEAEs Occurring in >5% of Subjects in Trial PS0018

MedDRA (Version 19.0)	BKZ 160mg Q4W N=43 100 participant-yrs=0.44	BKZ 320mg Q4W N=5 100 participant-yrs=0.06	All BKZ N=43 100 participant-yrs=0.50
SOC PT	n (%) [Events]		
Any TEAE Incidence rate (CI) Event rate	35 (81.4) [136] 79.55 (55.4, 110.6) 309.09	4 (80.0) [6] 66.67 (18.2, 170.7) 100.00	38 (88.4) [142] 76.00 (53.8, 104.3) 284.00
Infections and infestations	30 (69.8) [66]	1 (20.0) [1]	31 (72.1) [67]
Upper respiratory tract infection	8 (18.6) [12]	0	8 (18.6) [12]
Nasopharyngitis	7 (16.3) [10]	0	7 (16.3) [10]
Viral upper respiratory tract infection	5 (11.6) [6]	0	5 (11.6) [6]
Oral candidiasis	4 (9.3) [6]	0	4 (9.3) [6]
Staphylococcal pharyngitis	3 (7.0) [3]	0	3 (7.0) [3]
Pharyngitis	3 (7.0) [3]	0	3 (7.0) [3]
Investigations	9 (20.9) [20]	0	9 (20.9) [20]
GGT increased	5 (11.6) [7]	0	5 (11.6) [7]
ALT increased	4 (9.3) [5]	0	4 (9.3) [5]

ALT=Alanine aminotransferase; BKZ=Bimekizumab; CI=Confidence Interval; GGT=Gamma-glutamyl transferase; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; Q4W=every 4 weeks; SS=Safety Set; SOC=System Organ Class; TEAE=Treatment-Emergent Adverse Event.
Note: n=number of study participants reporting at least 1 TEAE within SOC/PT.
Note: [#] is the number of individual occurrences of the TEAE.
Note: Incidence=Incidence of new cases per 100 participant-years and associated 95% CI.
Note: Event Rate=event rate per 100 participant-years.
Note: The bimekizumab 320mg Q4W group consisted of all study participants who received bimekizumab 320mg Q4W at any point in the study.
Source: Table 8-3, PS0018 CSR, p. 86

AESIs

No cases of latent or active TB and no SAEs related to infection were reported during the trial. A total of 6/43 (14.0%) subjects reported 8 TEAEs of fungal infection. All were treated with 160 mg Q4W. Fungal infection PTs included 4/43 subjects (9.3%) with 6 events of Oral candidiasis, 1/43 subject (2.3%) with 1 event of Oropharyngeal candidiasis, and 1/43 subject (2.3%) with 1 event of Tinea versicolor. All were mild or moderate in intensity, resolved, and did not lead to discontinuation. The TEAE of Oropharyngeal candidiasis and 4/6 TEAEs of oral candidiasis were considered by investigators as related to treatment. The TEAE of Tinea versicolor and 2/6 TEAEs of Oral candidiasis were considered not related to treatment. Otherwise, no opportunistic infections were reported during the trial.

One malignancy was reported during Trial PS0018. A subject treated with 320 mg Q4W had a TEAE of keratoacanthoma. The event was classified as moderate in intensity and the subject continued in the trial. The investigator considered the event not related to treatment.

One subject had an adjudicated MACE event of Acute myocardial infarction. This was an SAE and is discussed above.

TEAEs related to cytopenias were reported in 3 subjects, all treated with 160 mg Q4W. One subject had Anemia, one had platelet count decreased, and one had White blood cell count decreased. All were mild in intensity and did not lead to discontinuation. The TEAEs of anemia and white blood cell count decreased were resolved. The TEAE of platelet count decreased was not resolved. Investigators considered none of the events related to treatment.

No TEAEs related to neuropsychiatric events, inflammatory bowel disease, or anaphylactic reactions occurred during Trial PS0018.

No subject in either treatment group met Hy's Law criteria. TEAEs related to hepatic events occurred in 7/43 subjects with 19 events. All were treated with 160 mg Q4W. Most hepatic TEAEs were in the SOC of investigations. PTs in this SOC included:

- GGT increased: 7 events in 5/43 subjects (11.6%)
- ALT increased: 5 events in 4/43 subjects (9.3%)
- Hepatic enzyme increased: 3 events in 2/43 subjects (4.7%)
- AST increased: 2 events in 2 subjects (4.7%)
- Liver function test abnormal: 1 event in 1/43 subjects (2.3%)

All hepatic TEAEs were mild or moderate in intensity and none led to discontinuation. All were resolved except 1/3 events of Hepatic enzyme increased and the event of Non-alcoholic fatty liver which occurred in 1 subject. Investigators considered both TEAEs of AST increased, 5 of the 7 events of GGT increased, and 1 of the 3 events of hepatic enzyme increased as related to treatment.

Vaccine Trial 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 adults. A total of 56 subjects were randomized 1:1 to receive bimekizumab 320 mg or no treatment, followed 2 weeks later by a single dose of inactivated influenza vaccine. Subjects were then followed until Day 140.

A seroconversion response was defined as either a pre-vaccination hemagglutination inhibition (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. There was no significant difference in the rate of seroconversion between subjects treated with bimekizumab and subjects who received no treatment.

No deaths, SAEs, or discontinuation because of AEs occurred during the trial. TEAEs reported during Trial UP0034 are presented in the table below:

Table 70: TEAEs by System-Organ Class and Preferred Term in Trial UP0034

MedDRA (v19.0) SOC PT	No treatment N=28 n (%) [#]	BKZ 320mg N=28 n (%) [#]
Any TEAE	11 (39.3) [16]	14 (50.0) [38]
Nervous system disorders	1 (3.6) [1]	4 (14.3) [9]
Headache	1 (3.6) [1]	3 (10.7) [7]
Musculoskeletal and connective tissue disorders	2 (7.1) [2]	2 (7.1) [2]
Myalgia	2 (7.1) [2]	2 (7.1) [2]
Gastrointestinal disorders	2 (7.1) [2]	1 (3.6) [2]
Nausea	2 (7.1) [2]	0
Infections and infestations	1 (3.6) [1]	6 (21.4) [9]
Viral infection	0	2 (7.1) [2]
Injury, poisoning, and procedural complications	1 (3.6) [1]	4 (14.3) [5]
Arthropod bite	0	2 (7.1) [2]
Psychiatric disorders	0	2 (7.1) [3]
Anxiety	0	2 (7.1) [3]

BKZ=bimekizumab; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; sc=subcutaneous; SOC=system organ class; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=Number of study participants reporting at least 1 TEAE in that category. #=Number of individual occurrences of the TEAE.
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.
Source: Table 10-2, UP0034 CSR, p. 63

No TEAEs in any of the AESI categories occurred during the trial. The Applicant reported no clinically significant changes in hematology or serum chemistry laboratory values.

PK Studies

UP0042

This was a phase 1, randomized, double-blind, placebo-controlled, single-dose, parallel-group study to evaluate the safety, tolerability, and PK of bimekizumab administered to Japanese and Caucasian healthy subjects. Investigators enrolled a total of 48 healthy male subjects. Subjects were randomized to 4 treatment groups for each ethnic group. The trial evaluated doses of 80mg, 160mg, and 320mg as well as placebo administered by sc injection. Safety results from this trial will be discussed here.

No deaths, SAEs, or discontinuation because of AEs occurred during this trial. Overall, 15/48 subjects (31.3%) reported 22 TEAEs. A total of 8/24 (33.3%) Japanese subjects reported 13 TEAEs. This included 3/6 (50%) in the placebo group, 3/6 (50%) in the bimekizumab 160mg group, and 2/6 (33.3%) in the bimekizumab 320mg group. A total of 7/24 (29.2%) Caucasian subjects reported 9 TEAEs. This included 1/6 (16.7%) in the placebo group, 4/6 (66.7%) in the bimekizumab 80mg group, 1/6 (16.7%) in the bimekizumab 160mg group, and 1/6 (16.7%) in the bimekizumab 320mg group. TEAEs by SOC, PT, and treatment group are presented in the tables below.

Table 71: TEAEs by SOC, PT, and Treatment Group, Japanese Subjects, Trial UP0042

MedDRA (v19.0) SOC PT	Placebo N=6 n (%)	BKZ 80mg N=6 n (%)	BKZ 160mg N=6 n (%)	BKZ 320mg N=6 n (%)	BKZ Total N=18 n (%)
Any TEAE	3 (50.0)	0	3 (50.0)	2 (33.3)	5 (27.8)
Gastrointestinal disorders	0	0	0	1 (16.7)	1 (5.6)
Toothache	0	0	0	1 (16.7)	1 (5.6)
Infections and infestations	0	0	2 (33.3)	2 (33.3)	4 (22.2)
Nasopharyngitis	0	0	1 (16.7)	1 (16.7)	2 (11.1)
Gastroenteritis	0	0	1 (16.7)	0	1 (5.6)
Pharyngitis	0	0	0	1 (16.7)	1 (5.6)
Injury, poisoning and procedural complications	0	0	1 (16.7)	0	1 (5.6)
Contusion	0	0	1 (16.7)	0	1 (5.6)
Excoriation	0	0	1 (16.7)	0	1 (5.6)
Wound	0	0	1 (16.7)	0	1 (5.6)
Investigations	1 (16.7)	0	0	0	0
Alanine aminotransferase increased	1 (16.7)	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (16.7)	0	1 (16.7)	0	1 (5.6)
Myalgia	1 (16.7)	0	1 (16.7)	0	1 (5.6)
Muscle fatigue	1 (16.7)	0	0	0	0
Skin and subcutaneous tissue disorders	1 (16.7)	0	0	0	0
Miliaria	1 (16.7)	0	0	0	0

BKZ=bimekizumab; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE within an SOC/PT.
Note: Placebo refers to the placebo subjects pooled across dose levels for each ethnic group.
Note: BKZ Total is all BKZ pooled for the ethnic group.
Source: Table 9-2, UP0042 CSR, p.95

Table 72: TEAEs by SOC, PT, and Treatment Group, Caucasian Subjects, Trial UP0042

MedDRA (v19.0) SOC PT	Placebo N=6 n (%)	BKZ 80mg N=6 n (%)	BKZ 160mg N=6 n (%)	BKZ 320mg N=6 n (%)	BKZ Total N=18 n (%)
Any TEAE	1 (16.7)	4 (66.7)	1 (16.7)	1 (16.7)	6 (33.3)
Gastrointestinal disorders	0	1 (16.7)	1 (16.7)	0	2 (11.1)
Abdominal pain upper	0	1 (16.7)	0	0	1 (5.6)
Diarrhoea	0	0	1 (16.7)	0	1 (5.6)
Infections and infestations	1 (16.7)	2 (33.3)	1 (16.7)	1 (16.7)	4 (22.2)
Nasopharyngitis	1 (16.7)	0	1 (16.7)	1 (16.7)	2 (11.1)
Gastroenteritis	0	1 (16.7)	0	0	1 (5.6)
Otitis media	0	0	1 (16.7)	0	1 (5.6)
Tinea infection	0	1 (16.7)	0	0	1 (5.6)
Nervous system disorders	0	1 (16.7)	0	0	1 (5.6)
Headache	0	1 (16.7)	0	0	1 (5.6)

BKZ=bimekizumab; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event
Note: n=number of subjects reporting at least 1 TEAE within an SOC/PT.
Note: Placebo refers to the placebo subjects pooled across dose levels for each ethnic group.
Note: BKZ Total is all BKZ pooled for the ethnic group
Source: Table 9-3, UP0042 CSR, p.96

In both ethnic groups, the most common SOC in which TEAEs occurred was Infections and infestations. There were no significant differences in the frequency or pattern of TEAEs between ethnic groups.

No TEAEs in any of the AESI categories occurred during the trial. The Applicant reported no clinically significant changes in hematology or coagulation laboratory values. Increases in bilirubin occurred in both ethnic groups. Among Japanese subjects, 3/6 subjects (50%) in the 80 mg group, 4/6 subjects (66.7%) in the 160 mg group, and 3/6 subjects (50%) in the 320mg group had an increase in bilirubin ≥ULN at any time during the trial. One subject (1/6, 16.7%) in the 80 mg group and 1/6 (16.7%) in the 160 mg group had an increase in bilirubin ≥1.5x ULN at any time during the trial. No other increases from Baseline in liver enzymes occurred in Japanese subjects during the trial.

Among Caucasian subjects, 3/6 subjects (50%) in the placebo group, 1/6 subject (16.7%) in the 80 mg group, 3/6 subjects (50%) in the 160 mg group, and 3/6 subjects (50%) in the 320 mg group had an increase in bilirubin ≥ULN at any time during the trial. A total of 1/6 subject (16.7%) in the 80 mg group, 2/6 subjects (33.3%) in the 160 mg group, and 3/6 subjects (50%) in the 320 mg group had an increase in bilirubin ≥1.5x ULN at any time during the trial. No other increases from Baseline in liver enzymes occurred in Caucasian subjects during the trial.

UP0033

This was a phase 1, open-label, parallel-group, randomized, 3-arm, single-dose study in healthy male and female participants to confirm the BE between bimekizumab administered SC using manufacturing process (b) (4) drug substance in the bimekizumab-(b) (4) device prefilled syringe (PFS) presentation, and manufacturing process (b) (4) drug substance in the bimekizumab-safety syringe (SS)-1mL and bimekizumab-autoinjector (AI)-1mL device presentations.
A total of 189 healthy adult subjects were randomized 1:1:1 to the following treatment arms:

- Bimekizumab-(b) (4): bimekizumab 320mg administered SC with bimekizumab-(b) (4) (b) (4) drug substance)
- Bimekizumab-SS-1mL: bimekizumab 320mg administered SC with bimekizumab-SS-1mL (b) (4) drug substance)
- Bimekizumab-AI-1mL: bimekizumab 320mg administered SC with bimekizumab-AI-1mL (b) (4) drug substance)

For more information regarding the trial design and PK findings, refer to Section 6.2.1 of this review. Safety results will be discussed here.
No deaths or TEAEs leading to discontinuation occurred. One subject in the AI-1mL group had 2 SAEs of musculoskeletal chest pain on Day 64 and acute kidney injury on Day 66. Both AEs were moderate in intensity and resolved. The investigator considered neither event related to treatment with bimekizumab.

In the [(b)(4)] group, 33/63 subjects (55.6%) reported 78 TEAEs. In the SS-1 mL group, 40/63 subjects (63.5%) reported 101 TEAEs. In the AI-1 mL group, 33/63 subjects (52.4%) reported 73 TEAEs. No subject in any treatment group reported any adverse device effect (ADE). In all treatment groups, the most common SOC in which TEAEs occurred was Infections and infestations. The most commonly reported TEAEs, which occurred in ≥5% of subjects in any treatment group, are presented in the table below:

Table 73: Most Commonly Reported TEAEs (≥5% in any treatment group) by SOC, PT, and Treatment Group, Trial UP0033

MedDRA (v19.0) SOC PT	BKZ-[(b)(4)] N=63 n (%) [#]	BKZ-SS-1mL N=63 n (%) [#]	BKZ-AI-1mL N=63 n (%) [#]
Any TEAE	35 (55.6) [78]	40 (63.5) [101]	33 (52.4) [73]
Gastrointestinal disorders	**9 (14.3) [10]**	**8 (12.7) [15]**	**8 (12.7) [10]**
Diarrhoea	1 (1.6) [2]	4 (6.3) [6]	3 (4.8) [3]
Infections and infestations	**19 (30.2) [24]**	**23 (36.5) [28]**	**17 (27.0) [19]**
Nasopharyngitis	16 (25.4) [19]	13 (20.6) [17]	14 (22.2) [15]
Musculoskeletal and connective tissue disorders	**7 (11.1) [9]**	**8 (12.7) [8]**	**4 (6.3) [4]**
Back pain	4 (6.3) [4]	3 (4.8) [3]	2 (3.2) [2]
Nervous system disorders	**11 (17.5) [15]**	**12 (19.0) [17]**	**10 (15.9) [16]**
Headache	10 (15.9) [12]	9 (14.3) [13]	9 (14.3) [14]
Respiratory, thoracic and mediastinal disorders	**5 (7.9) [5]**	**5 (7.9) [5]**	**6 (9.5) [6]**
Oropharyngeal pain	1 (1.6) [1]	2 (3.2) [2]	5 (7.9) [5]

BKZ=bimekizumab; BKZ-AI-1mL=BKZ 320mg Process [(b)(4)] drug substance administered using 2x1mL autoinjector; BKZ-SS-1mL=BKZ 320mg Process [(b)(4)] drug substance administered using 2x1mL safety syringe; BKZ-[(b)(4)]=BKZ 320mg Process [(b)(4)] drug substance administered u[illegible]ng 2x1mL [(b)(4)] syringe; MedDRA=Medical Dictionary for Regulatory Activities; PT=preferred term; SOC=system organ class; TEAE=treatment-emergent adverse event.
Note: n=number of study participants reporting at least 1 TEAE within SOC or PT.
Note: [#] was the number of individual occurrences of the TEAE.
Source: Table 10-2, UP0033 CSR, p. 62

AESIs

One subject had a TEAE of vulvovaginal mycotic infection on Day 36. The TEAE was mild in intensity, resolved, and the investigator considered the event related to treatment with bimekizumab. Otherwise, no TEAEs related to infections (serious, opportunistic, or TB), neutropenia, hypersensitivity, suicidal ideation and behavior, depression, major cardiovascular events, malignancies, or inflammatory bowel diseases occurred during Trial PS0033.
The Applicant reported no clinically significant changes from Baseline in hematology or coagulation laboratory values. One subject (1/63, 1.6%) in the SS-1mL group had an elevation of AST ≥3xULN on Day 13. Total bilirubin was <2xULN and the Applicant reported no temporally associated symptoms of hepatitis or hypersensitivity. The event resolved within 6 days. The

investigator considered the event not related to treatment and attributed the event to "heavy physical activity". One additional subject (1/63, 1.6%) in the SS-1mL group also had a TEAE of AST increased on Day 25 which resolved and was considered not related to treatment by the investigator. Additional TEAEs related to abnormal serum chemistry values are summarized below.

A total of 2 subjects had TEAEs of hepatic enzyme increased. One subject (1/63, 1.6%) in the SS-1mL group had the TEAE on Day 9. The event was moderate in intensity and resolved. The investigator considered the event related to treatment. One subject (1/63, 1.6%) in the AI-1mL group had the TEAE on Day 25. The event was of mild intensity and resolved.

A total of 3 subjects had TEAEs of liver function test increased. These included 2/63 (3.2%) subjects in the SS-1mL group and 1/63 (1.6%) in the AI-1mL group. Two of the TEAEs occurred on day 56 and 1 on Day 80. All were mild in intensity and resolved. The investigator considered all the events not related to treatment.

A total of 4 subjects had TEAEs of Elevated blood creatine phosphokinase. The TEAE occurred in 1/63 (1.6%) subject in the (b) (4) group and 3/63 (4.8%) subjects in the ss-1mL group. The TEAEs occurred on Days 7, 8, 56, and 84. All events were of moderate intensity and all resolved. The investigator considered all of the events not related to treatment.

A total of 2 subjects had TEAEs of Blood creatinine increased. These included 1/63 (1.6%) subjects in the SS-1mL group and 1/63 (1.6%) in the AI-1mL group. Both were of moderate intensity and resolved. The investigator considered the events not related to treatment.

Clinical Use Studies

DV0002

This was a phase 3, open-label, randomized, noncomparator, North America-only substudy to the ongoing open-label extension trial PS0014. In Trail PS0014, subjects were assigned to treatment with bimekizumab 320 mg Q4W or Q8W depending on their dosing regimen and PASI response from the feeder trial. The primary objective of the substudy was to evaluate the ability of subjects with moderate to severe plaque psoriasis to safely and effectively self-inject bimekizumab 8 weeks after training in the self-injection technique using the bimekizumab-SS-1mL or the bimekizumab-AI-1mL. A total of 134 subjects were randomized to use the SS-1mL (N=66) or AI-1mL (N=68). Subjects self-administered bimekizumab as 2 injections of 160 mg/mL at Weeks 0 and 8 of DV0002 using their assigned devices.

TEAEs and adverse drug reactions will be reported in the PS0014 CSR as the trial is ongoing. There were no ADEs reported during Trial DV0002. A total of 6 subjects had 8 TEAEs of injection site reactions. Four TEAEs of injection site reaction occurred with each device presentation. All were mild or moderate in intensity and none led to discontinuation.

Investigators considered none of these TEAEs to be device-related, and the events will be reported as TEAEs with the data from PS0014.

DV0006

This was a phase 3, open-label, randomized, noncomparator, substudy to the ongoing open-label extension trial PS0014. Trial DV0006 was conducted in the EU and Japan (b) (4)

As with Trial DV0002, TEAEs and adverse drug reactions will be reported in the PS0014 CSR as the trial is ongoing. There were no ADEs reported during Trial DV0006. One subject in the SS-1mL reported a TEAE of injection site reaction. The event was mild in intensity and did not lead to discontinuation. The investigator considered the event not related to the device, and the event will be reported as a TEAE with the data from PS0014.

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Because they are large proteins, monoclonal antibodies are not expected to gain access to the nucleus and directly interact with DNA to promote carcinogenesis. Bimekizumab will be catabolized to peptides and constituent amino acids via normal metabolic pathways. However, for any product that produces immunosuppression, and which is indicated for chronic administration, there is a theoretical risk of increased malignancy. In patients with psoriasis, this risk may be potentiated by prior exposure to other immunosuppressive agents or other therapies that may enhance tumor development such as phototherapy.

No animal studies have been conducted to evaluate the carcinogenic or mutagenic potential of bimekizumab. Refer to Section 5.5.3 for a discussion of the carcinogenicity risk from a Pharmacology /Toxicology perspective.

The data available to date do not support the conclusion that chronic administration of bimekizumab is associated with an increased risk of carcinogenesis. However, the limited duration of observation during the drug development program is unlikely to allow detection of rare events with a long latency period such as malignancy. Therefore, postmarketing data are needed to evaluate the long-term risk of malignancy in patients with psoriasis receiving bimekizumab. Refer to Section 13 of this review for a summary of the required post-marketing studies.

Human Reproduction and Pregnancy

Female subjects of childbearing potential were required to have a negative pregnancy test at Screening and to use a highly effective method of birth control. Pregnancy testing was performed at appropriate intervals, and study drug was discontinued as per pre-specified withdrawal criteria if they became pregnant. Wherever possible, subjects who were pregnant were followed until delivery. The Applicant considered the following pregnancy outcomes to be SAEs:

- Miscarriage
- Elective abortion when medically indicated (e.g. when pregnancy is endangering life or health of woman or when fetus will be born with severe abnormalities)
- Unintended pregnancy after hormonal contraceptive failure (if the hormonal contraceptive was correctly used)
- Ectopic pregnancy
- Fetal demise
- Any congenital anomaly/birth defect of the baby.

During the phase 1 and phase 2 trials, male subjects with partners of childbearing potential were required to use a condom when sexually active during the trials. Because the level of transfer of bimekizumab to seminal fluid and the extent of vaginal absorption was low, the requirement was lifted during the phase 3 trials. The Applicant did not track pregnancies in partners of male subjects.

In the initial BLA submission and 120-day safety update (data through April 15, 2020), the Applicant reported a total of 11 pregnancies in the development program for psoriasis, with the following outcomes:

- 6 with live birth of a healthy infant (gestational age at delivery not reported)
- 2 spontaneous abortions during the 1st trimester
- 1 induced abortion during the 1st trimester (due to unintended pregnancy)
- 2 unknown outcomes (lost to follow-up)

No congenital anomalies or major maternal complications were reported. The information that will be conveyed in labeling (Section 8.1 Pregnancy and Section 8.2 Lactation) regarding the risks of exposure to bimekizumab during pregnancy and lactation is presented in Section 19.3 of this review. In addition, refer to the review dated February 5, 2021 by Kristie Baisden, D.O., Division of Pediatric and Maternal Health (DPMH), for recommendations regarding post marketing requirements (PMRs) to evaluate the risks of exposure to bimekizumab during pregnancy and lactation.

Per Dr. Baisden's review, the available data "are insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes." As such, DPMH recommends PMRs for a prospective pregnancy exposure registry, a retrospective cohort pregnancy study, and a lactation study. Refer to Section 13 (Postmarketing

Requirements and Commitments) of this review for more details regarding the PMRs and proposed timelines.

Pediatrics and Assessment of Effects on Growth

The Applicant has not evaluated the safety and efficacy of tildrakizumab in the pediatric population. Because the product is a new active ingredient, approval of bimekizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c). The Applicant submitted an initial Pediatric Study Plan (iPSP) on August 10, 2017 and submitted the final Agreed iPSP on June 26, 2018. The Agency agreed with the iPSP (letter dated July 19, 2018).

In the [redacted] (b) (4) BLA submission, the Applicant requested a partial waiver for studies in the pediatric population from birth to less than 6 years of age. The waiver was requested because the necessary studies are impossible or highly impracticable (Section 505B (a)(4)(B)(i) of the Act) due to the low prevalence of moderate to severe psoriasis in this population. The Applicant requested a deferral of studies in the pediatric population age 6 years to less than 18 years until the safety and efficacy data from the Phase 3 trials in the adult population was submitted and reviewed. (Section 505B(a)(3)(A)(ii) of the Act).

In the discussion with the Pediatric Review Committee (PeRC) on April 20, 2021, the Division conveyed their agreement with the proposed pediatric development program in the Agreed iPSP and the proposed timeline. However, the Division also noted that the potential of bimekizumab to cause drug-induced liver injury (DILI) was still under review by consultants from the DILI team. As such, the Division and PeRC planned to revisit the timeline after the evaluation for DILI was complete, and the impact on the benefit-risk profile of bimekizumab was more clearly understood.

An updated Pediatric Assessment was provided to the PeRC on September 22, 2021, in which the Division conveyed their agreement with the proposed timeline. The PeRC reevaluated the pediatric development program at their meeting on September 28, 2021. The PeRC agreed with granting a partial waiver for for pediatric subjects 0 to <6 years of age because studies would be impossible or highly impractical and a deferral for pediatric subjects 6 to <18 years of age until the safety and efficacy data from the phase 3 trials in the adult population are submitted and reviewed. The PeRC also asked whether the proposed PMR for a PK, safety, and efficacy study in adolescent subjects was necessary. The Division responded that we consider this trial necessary to find the optimal dosing regimen for pediatric subjects. Refer to Section 13 (Postmarketing Requirements and Commitments) for the pediatric study requirements under PREA.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

Overdose

The Applicant reported that no accidental or intentional overdoses occurred during the clinical development program, and that single doses of bimekizumab up to 640 mg IV in subjects with psoriasis and 640 mg SC in subjects with HS have been administered during clinical trials without dose-limiting toxicity.

(b) (4)

Abuse, Withdrawal, and Rebound

There is no data to support an association of monoclonal antibodies including bimekizumab with the potential for addiction or abuse. Therefore, the Applicant did not evaluate abuse potential.

The Applicant reported that "no clear withdrawal effects after cessation of treatment have been observed in any PSO clinical study." The Applicant evaluated rebound during the Randomized-Withdrawal Period of Trial PS0013. The Applicant defined rebound as a ≤25% increase from the Initial Treatment Period Baseline in PASI score occurring within 2 months (60 days) of stopping therapy (i.e., being re-randomized to placebo). Per the Applicant, no cases of rebound occurred in subjects who were re-randomized to placebo in Trial PS0013.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

Bimekizumab is not currently marketed in any jurisdiction. Therefore, no postmarketing safety data are available.

Expectations on Safety in the Postmarket Setting

The comprehensive analysis of the safety data for bimekizumab identified no safety concerns that are expected to change the favorable benefit/risk assessment nor lead to increased risk with administration of bimekizumab in the postmarket setting. However, additional data are needed to characterize the safety profile of bimekizumab in special populations (e.g., pregnant and lactating females and the pediatric population age ≥ 6 years) and assess the risk of adverse events associated with long latency periods (e.g., malignancy). Refer to Section 13 of this review for the postmarketing requirements and commitments.

8.2.11. Integrated Assessment of Safety

The safety profile of bimekizumab was adequately characterized during the drug development program. The overall safety database consisted of 1789 subjects enrolled in the phase 2 and phase 3 trials (Pool S2). Of these subjects, 1591 were exposed to bimekizumab for ≥8 months and 1371 for ≥12 months. The primary analysis dataset (Pool S1) for the review of safety of bimekizumab included pooled data from the Initial Treatment Period (Week 0-16) of the placebo-controlled phase 3 Trials PS0009 and PS0013.

Treatment with bimekizumab did not appear to increase the risk of mortality. The Applicant reported 6 deaths in subjects treated with bimekizumab. These included one subject with dyspnea, respiratory failure, and circulatory collapse; one subject each with hypovolemic shock from a gastrointestinal hemorrhage, cardiac arrest, cardiorespiratory failure after hip replacement, myocardial infarction, and one subject from an unknown cause. Treatment with bimekizumab was not associated with an increased incidence of treatment-related adverse reactions in the categories of suicidal ideation and behavior (SIB) and major adverse cardiovascular events (MACE).

During the placebo-controlled period of Trials PS0009 and PS0013 (Pool S1), SAEs were reported by 11/670 (1.6%, EAIR 5.3/100 subject-years) of subjects treated with bimekizumab and 4/169 (2.4%, EAIR 7.8/100 subject-years) treated with placebo. In Pool S2B (Maintenance Period of Trials PS0009 and PS0013), SAEs were reported in 23/488 (4.7%, EAIR 7.0/100 subject-years) subjects treated with bimekizumab 320 mg Q4W. In Pool S2C (Maintenance Period of Trial PS0009 and Randomized Withdrawal Period of Trial PS0013), SAEs were reported by 8/261 (3.1%, EAIR 4.2/100 subject-years) of subjects treated with bimekizumab 320 mg Q4W and 11/257 (4.3%, EAIR 5.8/100 subject-years) of subjects treated with bimekizumab 320 mg Q8W. No cases of anaphylaxis, angioedema, or serious hypersensitivity reactions related to treatment with bimekizumab were reported during the development program.

In Pool S1, the most common adverse reactions (ARs) were upper respiratory infections (15%), oral candidiasis (9%), headache (3%), injection site reactions (3%), Tinea infections (3%), gastroenteritis (2%), Herpes simplex infections (1%), acne (1%), folliculitis (1%), other Candida infections (1%), and fatigue (1%). These ARs are recommended for inclusion in Section 6 (Adverse Reactions) of labeling for bimekizumab and are discussed in more detail in Section 8.2.4 of this review. Because of the small sample sizes for demographic subgroups, it was not possible to detect clinically meaningful imbalances in ARs between the subgroups.

Infections were reported more frequently in subjects treated with bimekizumab than placebo. In Pool S1, TEAEs from the SOC of Infections and Infestations were reported in 241/670 (36%, EAIR 141.7/100 subject-years) in the bimekizumab group and 38/169 (22.5%, 84.6/100 subject-years) in the placebo group. The most commonly reported infections were upper respiratory infections, Candida infections, Tinea infections, and Herpes simplex infections. Comparison of EAIRs for infections with Pool S2B did not demonstrate an increased frequency of infection with

increased exposure. Comparison of EAIRs for infections with Pool S2C did not demonstrate an increased frequency of infection with the 320 mg Q4W regimen compared to the 320 mg Q8W regimen.

In Pool S1, SAEs from the SOC of Infections and Infestations were reported in 2/670 (0.3%, EAIR 1.0/100 subject-years) in the bimekizumab group and no subjects in the placebo group. In Pool S2B, the EAIR for serious infections was 1.8/100 subject-years. In Pool S2c, the EAIRs for serious infections were 1.0/100 subject-years for both the bimekizumab 320 mg Q4W and Q8W regimens. A total of 14 subjects with latent TB were enrolled in the phase 3 trials and received prophylactic treatment for TB. None of these subjects developed active TB.

Because of the mechanism of action of bimekizumab, malignancy is a potential risk. During the development program for bimekizumab, the overall rates of malignancy were low. In Pool S1, malignancy was reported by 1/670 (0.1%, EAIR 0.5/100 subject-years) in the bimekizumab group and 1/169 (0.6%, EAIR 1.9/100 subject-years) in the placebo group. In Pool S2, malignancies were reported in 15/1789 (0.8%, EAIR 0.8/100 subject-years) subjects treated with any dose of bimekizumab. However, because the risk of malignancy is biologically plausible and may exhibit a long latency effect after initial exposure, more long-term data are needed to characterize the risk of malignancy. Consultants from the Office of Surveillance and Epidemiology (OSE) evaluated the sufficiency of the Active Risk and identification Analysis system (ARIA) to address the long-term risk of malignancy. ARIA is considered to be sufficient to assess the short-term risk for lymphoma. The long-term risk of other types of malignancies will be evaluated via a prospective, observational, long-term safety study.

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. Subjects with a history of IBD could be enrolled in the clinical trials as long as they had no active symptomatic disease at Screening or Baseline. In the phase 2 and phase 3 trials, one subject (1/1789, EAIR 0.05/100 subject-years) treated with bimekizumab 320 mg Q4W developed new-onset ulcerative colitis which was serious, led to discontinuation, and was considered related to treatment by the investigator. IBD will be included in Sections 5 (Warnings and Precautions) and 6 (Adverse Reactions) of labeling for bimekizumab and will be evaluated as an outcome of interest in a prospective, observational, long-term safety study.

During the review of safety data, the review team discovered potential cases of drug-induced liver injury (DILI) associated with treatment with bimekizumab. There were no fatalities due to hepatic injury and no liver transplants. In Pool S1, elevations of transaminases > 3 times the upper limit of normal were reported in 1.0% of subjects treated with bimekizumab and 0.6% of subjects treated with placebo. Consultants from the DILI team of the Division of Hepatology and Nutrition (DHN) identified 5 subjects who were considered to have possible or probable DILI by the DILI team or the Applicant's Hepatology Assessment Committee. Based on recommendations from the DILI team, labeling for bimekizumab will include Liver Biochemical Abnormalities in Section 5 (Warnings and Precautions), including a statement advising prescribers to avoid use of bimekizumab in patients with acute liver disease or cirrhosis

because such patients may be at increased risk for severe hepatic injury. Labeling will also include recommendations for testing of liver enzymes, alkaline phosphatase, and bilirubin prior to and periodically during treatment with bimekizumab. Data from Pool S1 for elevated transaminases will be conveyed in Section 6.1 of product labeling. In addition, elevated liver enzymes/DILI will be evaluated as an outcome of interest in a prospective, observational, long-term safety study.

The DILI team also noted that reactivation of Hepatitis B virus (HBV) has been reported in postmarketing studies of secukinumab, which is an IL-17A blocker. This risk was also evaluated by consultants from the Division of Pharmacovigilance I (DPV) and Division of Epiemiology I (DEPI). Based on their analyses, consultants from the DILI team, DPV, and DEPI recommended inclusion of a recommendation for pretreatment evaluation for HBV infection in labeling for bimekizumab. However, because subjects with serologic evidence of HBV infection were excluded from clinical trials in the development program for bimekizumab, no data are available regarding the potential risk of HBV reactivation in patients treated with bimekizumab. As such, a recommendation for pretreatment evaluation for HBV will not be included in product labeling at this time. However, HBV reactivation will be included as an outcome of interest in an observational, long-term postmarketing safety study.

The Applicant reported a total of 11 pregnancies occurring during the development program. Pregnancy outcomes included 6 with live birth of a healthy infant, 2 spontaneous abortions during the first trimester, 1 induced abortion during the first trimester (due to unintended pregnancy), and 2 with outcome unknown (subjects were lost to follow-up). The effect of bimekizumab on human reproduction and pregnancy is discussed in further detail in Section 8.2.9 of this review. Because the available data are insufficient to evaluate the risk of major birth defects, miscarriage, or adverse fetal or maternal outcomes associated with treatment with bimekizumab, we will require post-approval prospective and retrospective studies assessing maternal, fetal and neonatal outcomes of women exposed to bimekizumab during pregnancy compared to an unexposed control population. Refer to Section 13 (Postmarketing Requirements and Commitments) for further details.

The safety data currently available demonstrate that bimekizumab is safe for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. Postmarketing risk management will include professional labeling (including a Medication Guide), prescription status and routine pharmacovigilance. In addition, the ARIA system will be used to assess the risk of lymphoma. The long-term risk of other malignancy will be assessed by a long-term observational study. In addition, inflammatory bowel disease and elevated liver enzymes/DILI will also be evaluated in the long-term observational study. The maternal, fetal, and infant outcomes of women exposed to tildrakizumab during pregnancy will be evaluated by a registry based observational exposure cohort study.

8.3. Summary and Conclusions

8.3.1. Statistical Issues

There were no major statistical issues affecting overall conclusions. The treatment effects for bimekizumab were large and generally consistent across endpoints. A slightly higher treatment effect is observed in Trial PS0013 compared to Trial PS0009 for both co-primary efficacy endpoints. It is noted that Trial PS0009 had a lower proportion of White subjects and a slightly larger amount of missing data in the placebo arm compared to Trial PS0013. Also, Trial PS0009 included an active-comparator. The amount of missing data was relatively small (≤5%) at Week 16 (i.e., the primary efficacy timepoint), and the results were similar across the various methods investigated to impute the missing data (see Table 20 and Table 21).

There were no substantial differences in efficacy among subgroups. Approximately 89% and 94% of subjects were 18 to 64 years of age in Trials PS0009 and PS0013, respectively; therefore, it would be difficult to detect any differences in efficacy between this subgroup and its complement (i.e., ≥65 years). For sex, the treatment effect was slightly larger in females compared to males for IGA 0/1 in Trial PS0013; however, the treatment effect was larger in males in Trial PS0009. For PASI 90, treatment effect was generally consistent across these subgroups in Trial PS0013; however, the treatment effect was larger in females in Trial PS009. For race, the treatment effect was slightly higher in White subjects compared to non-White subjects for both co-primary endpoints in Trial PS0013, while treatment effect was generally consistent in Trial PS0009. However, it should be noted that in both trials the sample size for the non-White subgroup was relatively small. For weight, the treatment effect was larger in those that weighed <100 kg compared to ≥100 kg for both co-primary endpoints in both trials. For baseline disease severity, the treatment effect tended to be larger for subjects with more disease severity (i.e., IGA score of 4[severe]) in Trial PS0009; however, there was more variability in treatment effect across these subgroups in Trial PS0013. The treatment effect was larger for subjects who had prior use of systemic therapy use compared to subjects who didn't in both trials.

8.3.2. Conclusions and Recommendations

To establish the effectiveness of bimekizumab, the Applicant submitted data from 2 pivotal phase 3 trials, PS0009 and PS0013. Trial PS0009 is a multicenter, randomized, double-blind, placebo- and active comparator-controlled, parallel-group, phase 3 trial with ustekinumab as a comparator. Trial PS0013 is a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial. The trials included subjects 18 years of age and older who had moderate to severe plaque psoriasis with PASI score ≥ 12, Investigator Global Assessment (PGA) score of ≥3 ("moderate") and a minimum body surface area (BSA) of involvement of ≥10%. The co-primary efficacy endpoints were the proportion of subjects achieving ≥90% improvement in PASI from Baseline to Week 16 (PASI90) and the proportion of subjects achieving IGA score of 0

("clear") or 1 ("almost clear") with at least a 2-grade of improvement from Baseline to Week 16. Bimekizumab was statistically superior to placebo (p-values < 0.001) for the co-primary efficacy endpoints in both trials.

Key secondary endpoints for both trials included the proportion of subjects achieving: PASI100 at Week 16, IGA of 0 ("clear") at Week 16, Scalp IGA score of 0 ("clear") or 1 ("almost clear") with a 2-grade improvement from Baseline, and PASI75 at Week 4. In addition, secondary endpoints included assessment of psoriasis symptoms (itching, pain, and scaling) measured by the Patient Symptom Diary (PSD) at Week 16. In both trials, bimekizumab was statistically superior to placebo (p-values < 0.001) for all of these key secondary efficacy endpoints.

Trial PS0008 included adalimumab as an active comparator and Trial PS0009 included ustekinumab as an active comparator. In Trial PS0008, all subjects randomized to adalimumab in the North American sites (i.e., U.S. and Canada) received US-licensed adalimumab. Subjects randomized to adalimumab at all other sites received EU-approved adalimumab. In Trial PS0009, US-licensed ustekinumab was used in all sites in the US; all other sites received EU-approved ustekinumab. Because the Applicant did not establish a scientific bridge between the US-licensed and EU-approved comparator products, there were considered distinct products in this review. In both trials, bimekizumab was statistically superior (p-values < 0.001) to the active control in both the overall population and the US-licensed subgroup for all efficacy endpoints. However, data regarding comparative efficacy vs adalimumab and ustekinumab will not be included in labeling because the lack of replication of findings for each of the active comparators, as well as the lack of a scientific bridge between US-licensed and EU-approved products.

In the phase 3 trials, subjects received bimekizumab 320 mg Q4W through Week 16. After Week 16, the treatment arms included bimekizumab 320 mg Q4W and 320 mg Q8W during the maintenance period. The recommended dosage is 320 mg (given as 2 subcutaneous injections of 160 mg each) at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For patients weighing ≥ 120 kg, a dose of 320 mg every 4 weeks after Week 16 may be considered. Initially, the Applicant did not propose a body weight cutoff for the Q4W dosing regimen after Week 16. The Clinical Pharmacology review team noted that body weight was found to be an intrinsic factor that could impact clinical response. Patients with a higher body weight may have a lower clinical response due to lower plasma concentrations with the same dose compared to a lower body weight patient. Therefore, the Clinical Pharmacology team recommended that a dosage of 320 mg Q4W after Week 16 may be considered for patients with body weight ≥120 kg. This will be reflected in product labeling.

To support the safety of bimekizumab, the Applicant submitted data from 4 phase 2 and 3 phase 3 trials. Pooling of data from the phase 3 trials allowed for comparison of safety vs placebo, short- vs long-term exposure, and bimekizumab 320 mg Q4W vs 320 mg Q8W regimens. The Applicant conducted a comprehensive assessment of safety of bimekizumab in

the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions.

Safety and efficacy data submitted by the Applicant support approval of this BLA for bimekizumab for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. However, because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356) by the Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing (OPMA/DBM), the application cannot be approved at this time. The review team recommends a Complete Response for BLA 761151. Satisfactory resolution of the identified deficiencies is required before the application may be approved.

9 Advisory Committee Meeting and Other External Consultations

The Agency held no Advisory Committee Meeting regarding this application because the safety profile was expected to be comparable to that of other biologic products approved for this indication.

10 Pediatrics

Refer to the following sections of this review for the proposed development program for bimekizumab in the pediatric population:

- Section 8.2.9 *Pediatrics and Assessment of Effects on Growth* for a discussion regarding the Pediatric Study Plan
- Section 13 *Postmarketing Requirements and Commitments* for the deferred pediatric studies, which are required under the Pediatric Research Equity Act (PREA) (21 CFR 314.55(b) and 601.27(b)).

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI) and carton/container labels for BIMZELX (bimekizumab) injection. The review team provided recommendations regarding the PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI and carton/container. Refer to the OPDP reviews by Laurie Buonaccorsi, PharmD dated August 31, 2021 and September 29, 2021. The following table provides the location of the labeling discussion for each section.

Table 74: Location of the Labeling Discussion

Summary of Significant High Level Labeling Changes	
Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1, 8.2.5.3
2 DOSAGE AND ADMINISTRATION	Section 6.2.2
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	Section 8.2.5
6 ADVERSE REACTIONS	Section 8.2.4
7 DRUG INTERACTIONS	Section 6.3.2
8 USE IN SPECIFIC POPULATIONS	Section 5.5.4, 8.2.9, 19.3
12 CLINICAL PHARMACOLOGY	Section 6.2, 6.3
13 NONCLINICAL TOXICOLOGY	Section 19.3
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6, 7 and 14.

Source: Reviewer's Table

11.2. Patient Labeling

The Applicant submitted a proposed Medication Guide (MG) and Instructions for Use (IFU) for BIMZELX (bimekizumab). The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments regarding the MG and IFU. These comments are reflected in final labeling. Refer to the DMPP/OPDP reviews by Shawna Hutchins, MPH, BSN, RN, and Laurie Buonaccorsi, PharmD dated August 31, 2021 and Sharon R. Mills, BSN, RN, CCRP, Susan Redwood, MPH, BSN, RN, and Laurie Buonaccorsi, PharmD dated September 29, 2021. In addition, Lissa C. Owens, PharmD from the the Division of Medication Error Prevention and Analysis (DMEPA) provided comments regarding the proposed IFU and carton and container labels. Refer to the DMEPA reviews dated May 4, 2021, May 27, 2021, and August 19, 2021.

12 Risk Evaluation and Mitigation Strategies (REMS)

Based on the favorable safety profile of this product, risk mitigation measures beyond professional labeling and a Medication Guide are not required at this time. Under 21CFR208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 11.1 (Labeling Recommendations).

13 Postmarketing Requirements

Clinical postmarketing requirements are intended to characterize the risks of bimekizumab use in special populations (pregnancy) and address the long-term safety of this novel biologic product in the target population. Development of final pharmacovigilance plans is ongoing.

The available safety data regarding bimekizumab use during pregnancy are limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, as well as females planning to become pregnant or breastfeed during the trials. Because exposures to bimekizumab during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the Agency will require the applicant to conduct the post-marketing assessments to characterize the drug associated risk.

Analysis of expected adverse reactions based on biologic plausibility and potential class effects did not identify a definitive safety signal. However, based on the mechanism of action, the Agency will require post-marketing safety studies to assess the risk of malignancy and other serious adverse events which may not be identified during clinical trials due to a long latency period or low incidence rate.

Based on review of the data in this submission, proposed postmarketing requirements (PMRs) were conveyed to the Applicant. On January 21, 2022, the Applicant submitted a response to the proposed PMRs. The Agency considered the Applicant's proposed edits reasonable. The final PMR language and milestone dates are as follows:

<u>Postmarketing Requirements under 505(o)</u>

Conduct a prospective, registry based observational exposure cohort study that compares the maternal, fetal, and infant outcomes of women exposed to Bimzelx during pregnancy to an unexposed control population. The registry should be designed to detect and record major and minor congenital malformations, spontaneous abortions, stillbirths, elective terminations, small for gestational age, preterm birth, and any other adverse pregnancy outcomes. These outcomes will be assessed throughout pregnancy. Infant outcomes, including effects on postnatal growth and development, will be assessed through at least the first year of life.

Draft Protocol submission: April 2022
Final Protocol Submission: December 2022
Interim Report: June 2027
Study Completion: October 2032
Final Report Submission: December 2034

Conduct an additional pregnancy study that uses a different design from the pregnancy registry (for example a retrospective cohort study using claims or electronic medical record data with outcome validation or a case control study) to assess major congenital malformations,

spontaneous abortions, stillbirths, and small for gestational age and preterm birth in women exposed to Bimzelx during pregnancy compared to an unexposed control population.

Draft Protocol submission: June 2022
Final Protocol Submission: June 2023
Interim Report: June 2027
Study Completion: June 2033
Final Report Submission: December 2033

Perform a lactation study (milk only) in lactating women who have received therapeutic doses of Bimzelx to assess concentrations of bimekizumab-bkzx in breastmilk using a validated assay and to assess the effects on the breastfed infant.

Draft Protocol submission: June 2022
Final Protocol Submission: June 2023
Study Completion: December 2025
Final Report Submission: June 2026

Long-term safety study: Conduct a prospective observational study to assess the long-term safety of bimekizumab treatment in U.S. adult patients with moderate to severe plaque psoriasis. Fully ascertain and centrally verify malignancy (including lymphoma), opportunistic infections, reactivation of Hepatitis B, tuberculosis, and serious infections. Other outcomes include hypersensitivity, gastrointestinal events (including inflammatory bowel disease, elevated liver enzymes/drug-induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death), hematologic events, and neuropsychiatric (suicidal ideation/behavior) adverse events. For each adverse-event outcome separately, compare incidence in bimekizumab-treated patients against reference rates internally derived from analyses conducted in patients treated with other chronic systemic treatments for moderate-to-severe plaque psoriasis. Regardless of treatment discontinuation or switch to a different treatment for plaque psoriasis, continue following patients for malignancy outcomes and possibly other adverse events with delayed onset. Enroll a sufficient number of patients to describe the frequency of the adverse events in representative U.S. patients who start treatment with bimekizumab for plaque psoriasis in the setting of routine clinical practice. Implement a plan that uses rigorous, transparent, and verifiable methods to ascertain and characterize safety events that occur during and after treatment with bimekizumab. Enroll patients over a 4-year period and plan to follow for a minimum of 8 years from time of enrollment.

Draft Protocol submission: June 2022
Final Protocol Submission: June 2023
Study Completion: October 2035
Final Report Submission: October 2036

REQUIRED PEDIATRIC ASSESSMENTS: Pediatric Research Equity Act (PREA) (21 U.S.C. 355c)

Bimekizumab triggers the Pediatric Research Equity Act (PREA) as a new active ingredient. The following studies in the pediatric population age 6 years to less than 18 years of age were included in the Agreed iPSP and will be deferred:

Conduct a multicenter, open-label trial to assess the PK, safety, and efficacy of bimekizumab in adolescents (12 to <18 years of age) with moderate to severe chronic plaque psoriasis. (Protocol PS0020 and request for advice submitted 8/13/2020; Advice Letter sent 9/29/2020)

Draft Protocol submission: No later than Jul 2020; estimated study initiation no later than Sep 2020 (Protocol PS0020 and request for advice submitted 8/13/2020; Advice Letter sent 9/29/2020)
Final Protocol Submission: December 2021
Study Completion: March 2025
Final Report Submission: December 2025

Conduct a multicenter, randomized, parallel-group, blinded active-controlled trial to assess the efficacy, safety, and PK of bimekizumab in pediatric subjects 6 to <18 years old with moderate to severe chronic plaque psoriasis.

Draft Protocol submission: March 2023
Final Protocol Submission: September 2023
Study Completion: November 2030 (The Applicant proposed an estimated interim data cutoff no later than Nov 2028 and estimated interim report/sBLA submission no later than May 2029.)
Final Report Submission: June 2031

We are waiving the pediatric study requirement for ages 0 to less than 6 years because necessary studies are impossible or highly impracticable. We are deferring submission of pediatric studies for ages 6 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. Refer to Section 8.2.9 of this review for a more detailed discussion of the waiver and deferral of pediatric studies.

14 Division Director (DPT-II) Comments

Not applicable.

15 Division Director (OCP) Comments

Not applicable.

16 Division Director (OB) Comments

Not applicable.

17 Division Director (Clinical) Comments

I concur with the review team's recommendation for a Complete Response action. The available safety and efficacy data support approval of BIMZELX (bimekizumab-bkzx) injection for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy, However, because of Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 3003909356), the application cannot be approved at this time. Refer to Section 4.2 (Product Quality) of this review for more detailed information regarding the deficiencies identified and steps needed to correct the deficiencies.

Bimekizumab is a humanized IgG1 monoclonal antibody that binds to and inhibits interleukin-17A and F. BIMZELX (bimekizumab-bkzx) injection is a sterile, preservative-free, clear to slightly opalescent and pale brownish-yellow solution for subcutaneous use; each BIMZELX (bimekizumab-bkzx) prefilled syringe or prefilled autoinjector delivers 1 mL containing 160 mg bimekizumab-bkzx. The proposed dose is 320 mg (two 160 mg injections) administered by subcutaneous injection (SC) at Weeks 0, 4, 8, 12 and 16, then every 8 weeks thereafter. For some patients, a dose of 320 mg every 4 weeks after week 16 may be considered.

Two placebo-controlled 16 week trials (PS0009 and PS0013) provided evidence of effectiveness of bimekizumab in adults with moderate to severe plaque psoriasis. Both trials randomized subjects to either bimekizumab 320 mg or placebo SC every four weeks; study PS0009 included a third ustekinumab arm. These two pivotal trials assessed the co-primary endpoints:

- Proportion of subjects achieving Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from Baseline to Week 16

- Proportion of subjects achieving ≥90% improvement in the Psoriasis Area and Severity Index (PASI) from Baseline to Week 16 (PASI90)

Bimekizumab was statistically superior to placebo (p-values < 0.001) for both co-primary efficacy endpoints in both trials. Results of key secondary endpoints (e.g., PASI-100, IGA 0, Scalp IGA 0/1 at Week 16; and PASI-75 at Week 4) were consistent with bimekizumab's treatment effect. In trial PS0013, responders entered a randomized placebo-controlled 48 week withdrawal period and results further supported bimekizumab's efficacy and durability of effect (whether administered every 4 weeks or every 8 weeks) with a median time to loss of PASI-90 of 24 weeks in subjects withdrawn to placebo; the median time to loss of IGA 0, also 24 weeks, was consistent with the PASI-90 results.

The overall safety appears to be adequately characterized. Similar to other IL 17A-antagonists, infections were reported more frequently in subjects treated with bimekizumab than placebo. The most commonly reported infections were upper respiratory infections, Candida infections, Tinea infections, and Herpes simplex infections.

Transaminase elevations > 3 times the upper limit of normal were observed in 1.0% of subjects treated with bimekizumab and 0.6% of subjects treated with placebo and these cases were evaluated by the review team, in consultation with the DILI Team. I concur with the recommendation to communicate risks and provide guidance in labeling and further assess risk via a prospective longer-term study.

Approval of bimekizumab will include postmarketing requirements to study pediatric (6 to < 18 years) psoriasis patients and a prospective observational long-term safety study to provide additional long-term data concerning hepatic risk, infectious disease and malignancy risks.

18 Office Director Comments

I concur with the recommendation of the Division of Dermatology and Dentistry to withhold approval of BLA 761151 for bimekizumab-bkzx injection for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. Deficiencies identified on inspection of the drug product manufacturing site preclude approval at this time. Satisfactory resolution of the identified deficiencies is required before the application may be approved.

Bimekizumab, an original biologic product, is an interleukin-17A and F antagonist that inhibits the release of proinflammatory cytokines and chemokines that have been implicated in the pathogenesis of psoriasis. The recommended dose is 320 mg administered by subcutaneous injection at weeks 0, 4, 8, 12 and 16, then every 8 weeks (Q8W) thereafter. For patients weighing ≥ 120 kg, a dose of 320 mg Q4W after week 16 may be considered.

The efficacy of bimekizumab was demonstrated in two randomized controlled trials conducted in adult patients with moderate-to-severe plaque psoriasis. Bimekizumab response was statistically superior to placebo in both trials at week 16 for the co-primary efficacy endpoints of: 1) proportion of subjects achieving Investigator's Global Assessment (IGA) score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from baseline, and 2) proportion of subjects achieving ≥ 90% improvement from baseline in the Psoriasis Area and Severity Index (PASI 90).

In one trial, the majority of week 16 bimekizumab responders maintained their response at week 56 following re-randomization to either bimekizumab Q4W or Q8W maintenance regimens. For PASI 90 responders at week 16 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of PASI 90 response was approximately 24 weeks. Evaluation of subjects with a higher body weight (i.e., ≥ 120 kg) led to a recommendation that the Q4W maintenance regimen be considered to provide comparable exposures and clinical responses as the Q8W regimen in subjects weighing < 120 kg.

Bimekizumab treatment was generally well tolerated. In placebo-controlled clinical trials, oral candidiasis was reported in 9% of bimekizumab-treated subjects vs. 0% in placebo-treated subjects. Elevations of liver serum transaminases > 3xULN were reported more frequently in bimekizumab-treated subjects as compared to placebo-treated subjects (1% vs. 0.6%). Elevations resolved with continued treatment or following discontinuation of bimekizumab. Product labeling will recommend that bimekizumab use be avoided in patients with acute liver disease or cirrhosis. A prospective, observational study will be required to further assess the long-term safety of bimekizumab use, including the potential risks of drug-induced liver injury, malignancy (including lymphoma), opportunistic infections, reactivation of Hepatitis B, tuberculosis, and serious infections.

19 Appendices

19.1. References

Blauvelt, A and B Ehst, 2015, Pathophysiology of Psoriasis, accessed July 1, 2020, http://www.UptoDate.com.

Feldman, S, 2015, Epidemiology, Clinical Manifestations, and Diagnosis of Psoriasis, accessed July 1, 2020, http://www.UptoDate.com.

Fleming, C, C Ganslandt, L Guenther, A Johannesson, C Buckley, J Simon, H Stegmann, and L Vestergaard Tingleff, 2010, Calcipotriol plus betamethasone dipropionate gel compared with its active components in the same vehicle and the vehicle alone in the treatment of psoriasis vulgaris: a randomised, parallel group, double-blind, exploratory study, Eur J Dermatol, 20(4):465-471.

Korman, N, 2017, Comorbid Disease in Psoriasis, accessed July 1, 2020, http://www.UptoDate.com.

Menter, A, L Gold, M Bukhalo, S Grekin, S Kempers, B Boyce, C Ganslandt, J Villumsen, and M Lebwohl, 2013, Calcipotriene plus betamethasone dipropionate topical suspension for the treatment of mild to moderate psoriasis vulgaris on the body: a randomized, double-blind, vehicle-controlled trial, J Drugs Dermatol, 12(1):92-98.

19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical studies for bimekizumab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The covered clinical studies as defined in 21 CFR 54.2(e) were, phase 3 Trials PS0008, PS0009, and PS0013, as well as phase 2 Trials PS0010 and PS0016, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1.1 for the trial designs.

A total of 2 investigators from Trial PS0008, 3 investigators from Trial PS0009, and 3 investigators from Trial PS0013 had disclosable financial interests and arrangements and are listed in the table below. No investigators from Trial PS0010 or PS0016 had disclosable

financial interests or arrangements. Financial disclosure forms for Trials PS0008, PS0009, PS0013, PS0010, and PS0016 are also displayed below.

The Applicant adequately disclosed financial interests involving clinical investigators. Because the number of investigators with financial disclosures was limited and assessments were blinded, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Table 75: Investigators with Financial Disclosure Forms 3455 for Trials PS0008, PS0009, and PS0013

Investigator	Trial/Site	Country	# Subjects Randomized	Description of Disclosure
(b) (6)			PS0008- 3 PS0013- 5	Significant Payments of Other Sorts: The investigator accepted $75,578.18 in speaker's fees from the Applicant
			PS0009- 12 PS0013- 6	Significant Payments of Other Sorts: The investigator accepted $42,018.63 in speaker's fees from the Applicant
			5	Significant Payments of Other Sorts: The investigator accepted $66,599.09 in speaker's and consulting fees from the Applicant
			4	The investigator (b) (4)
			PS0008- 4 PS0009- 0	The sub-investigator's (b) (6)

Source: Compiled by Reviewer from Applicant's submission

Table 76: Covered Clinical Study (Name and/or Number): PS0008

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 77		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0		

Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Table 77: Covered Clinical Study (Name and/or Number): PS0009

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 105		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		

Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Table 78: Covered Clinical Study (Name and/or Number): PS0013

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 77		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 3		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Table 79: Covered Clinical Study (Name and/or Number): PS0010

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 40		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455):		

0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NA Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____ Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) NA
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) NA
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

Table 80: Covered Clinical Study (Name and/or Number): PS0016

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 7		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 0		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): NA Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: _____ Significant payments of other sorts: _____		

Proprietary interest in the product tested held by investigator: _____ Significant equity interest held by investigator in S Sponsor of covered study: _____		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☐	No ☐ (Request details from Applicant) NA
Is a description of the steps taken to minimize potential bias provided:	Yes ☐	No ☐ (Request information from Applicant) NA
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason:	Yes ☐	No ☐ (Request explanation from Applicant) NA

19.3. Nonclinical Pharmacology/Toxicology

Multiple of Human Exposure Calculations

The multiples of human exposure based on a mg/kg basis comparison between the NOAELs identified in pivotal toxicology studies and the proposed maximum recommended human dose (MRHD) are provided in the following table.

Table 81: Multiples of Human Exposure for NOAELs Identified in Pivotal Toxicology Studies Contained in Labeling

Study	Route	NOAEL (mg/kg)	Multiples of human exposure[a] (based on mg/kg comparison)
Enhanced pre- and post-natal development study	SC	50	38
Male, female fertility as assessed during the 26-week repeat-dose toxicity study	SC	200	150

[a] Compared with the maximum recommended human dose (MRHD) of 320 mg, or 1.33 mg/kg on a mg/kg basis.

Recommended revisions to the nonclinical portions of labeling

Revisions to the sponsor's proposed wording for the nonclinical and related sections of the label are provided below. Reviewer proposed deletions are annotated as ~~strikeout~~ text and reviewer proposed additions are annotated as underlined text.

HIGHLIGHTS OF PRESCRIBING INFORMATION
INDICATIONS AND USAGE

1 Page of Draft Labeling has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Population PK Analysis

PKPD Model:
Study Design:
UP0008: first-in-human study on intravenous (IV) administration
UP0031: relative bioavailability study of two SC formulations
UP0042: PK study of SC administration in Japanese and Caucasian
RA0124: absolute bioavailability study on SC and IV administration

Methods:
The bimekizumab plasma-concentration-time data were graphically explored and analysed using the nonlinear mixed effects modelling approach within the software NONMEM. The base PK model for the analysis was the final PK model from RA0124. All the fixed and random effects parameters and respective standard errors were estimated. Body size (body weight, body surface area and body mass index), sex and race of study participants and formulation and manufacturing process of bimekizumab were tested as potential covariates on clearance, volume of distribution of central compartment, sc bioavailability and SC absorption rate.

Number of Study Participants: n=104
Test Product, Dose and Mode of Administration:
Bimekizumab: 8mg IV, 40mg IV, 80mg SC, 160mg IV, 160mg SC, 320mg SC, 480mg IV, and 640mg IV. Single dose administration

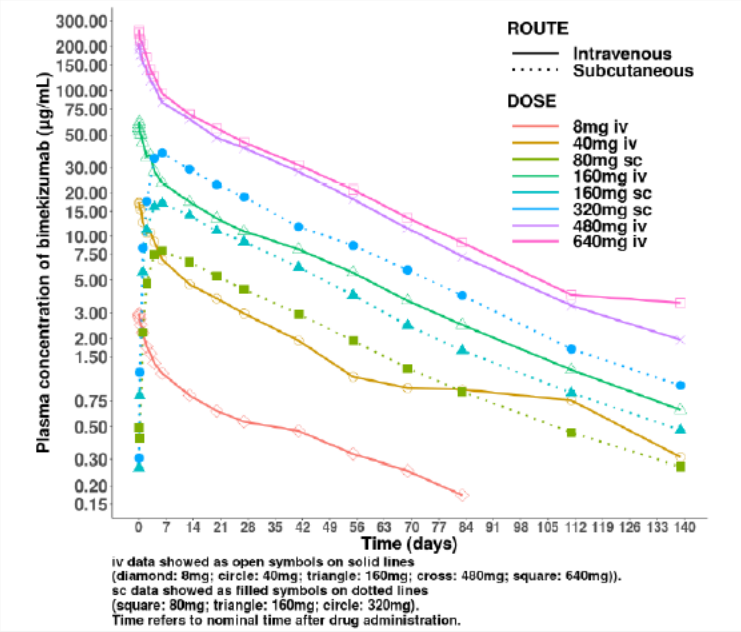
Table 82: Summary of Plasma Concentration Records

Dose (mg)	Route	Number of study participants	Total number of observations [a]	Number of observations above lower limit of quantification (percentage) [a]	Number of observations below lower limit of quantification (percentage) [a]	Number of post-dose observations below lower limit of quantification (percentage) [b]
8	iv	4	74	61 (82%)	13 (18%)	9 (13%)
40	iv	4	76	66 (87%)	10 (13%)	6 (8%)
80	sc	22	346	278 (80%)	68 (20%)	46 (14%)
160	iv	16	289	269 (93%)	20 (7%)	4 (1%)
160	sc	34	508	453 (89%)	55 (11%)	22 (5%)
320	sc	12	192	172 (90%)	20 (10%)	8 (4%)
480	iv	6	116	109 (94%)	7 (6%)	1 (1%)
640	iv	6	120	112 (93%)	8 (7%)	2 (2%)
		Total	1721	1520 (88%) [c]	201 (12%)	98 (6%)

Source: table 5-1 of PK analysis report.

Mean concentrations versus time are shown in Figure 20.

Figure 20: Semi-Log Plot of Mean Plasma Concentration Versus Time- Iv And SC Bimekizumab Administration



Source: Figure 5-3 of pk analysis report.

Population PK parameter estimates of the final model is listed in Table 83:

Table 83: 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

Source; Table 5-4 of pk analysis report.

Summary of Result:

- PK: A two-compartment model, with body weight as covariate on clearance and on volume of central compartment, was found to adequately describe the bimekizumab plasma concentration after IV and SC administration.

- The estimated parameters (and the respective inter-individual variability in parenthesis, if any) were as follows: elimination clearance 0.179 L/day (21.4%), inter-compartment clearance was 0.296 L/day, volume of central compartment was 3.03 L (23.9%), volume of peripheral compartment was 2.13 L, and the sc absorption rate was 0.172 /day (25.5%).
- The absolute bioavailability of sc administration was estimated to be 70.1% (45.9%). The residual error model took proportional plus additive form and the estimated values were 0.13 and 0.173 µg/ml, respectively.
- Body weight was identified as a covariate on both elimination clearance and volume of central compartment, and the estimated exponent values were 0.54 and 0.60 respectively.
- Different drug formulations [redacted] (b) (4) formulations) and manufacturing processes (processes [redacted] (b) (4) did not result in different bioavailability or absorption rate of sc administration.

Reviewer's comments: The Applicant's analysis seems reasonable. The absolute bioavailability of sc administration was estimated to be 70.1% (45.9%). Body weight was identified as a covariate on both elimination clearance and volume of central compartment, and the estimated exponent values were 0.54 and 0.60 respectively. Different drug formulations ([redacted] (b) (4) formulations) and manufacturing processes (processes [redacted] (b) (4)) did not result in different bioavailability or absorption rate of SC administration.

19.4.2. Overall PKPD Models of Bimekizumab for IGA and PASI

Data:
The data for the PK and pharmacokinetic-pharmacodynamic (PKPD) model development originated fromthree Phase 2 studies (PS0010, PS0011, and PS0016), and interim data from two Phase 3 studies (PS0008 and PS0009). Interim data from PS0013 were used for external validation of the PK and PKPD models. Bimekizumab and placebo (PBO) doses were administered via SC injections in these studies.

PK analysis data set included 9183 PK observations from 999 study participants, PASI analysis data set included 15865 PASI observations from 1013 study participants, and IGA analysis data set included 15864 IGA observations from 1013 study participants.

Method:
Bimekizumab doses were administered subcutaneously, on a monthly basis for most study participants (64 to 480mg every 4 weeks [Q4W]). Other dosing regimens were 320mg every 8 weeks (Q8W) from Week 16, 320mg loading dose followed by 160mg Q4W, 320mg at baseline, Week 4 and Week 16). Duration of bimekizumab treatment differed between studies and ranged from 2 to 13 months.

Result and Conclusion:

PASI model: The final population PKPD model for PASI was a bounded integer (BI) model with a placebo effect model, described with maximum placebo effect (PL_{max}), and a treatment effect maximum effect (Emax) model of bimekizumab average concentration (Cav) over the dosing intervals added on the placebo effect. The time course of both effects was described by a mono exponential time-dependent effect parameter (time to reach half maximum effect (EF_{half})). Covariates were tested on the population PKPD model for PASI model if indicated by η versus covariate plots in the base model. Covariates in the model were baseline WT, baseline PASI score and region on Emax, and baseline age and region on EF_{half}. Study participants with higher baseline WT had a smaller reduction in PASI score than study participants with lower baseline WT. Study participants who were not from Central/Eastern European region had a smaller reduction in PASI score and faster onset of treatment effect than the study participants who were from Central/Eastern European region.

The base population PKPD model for PASI included base and SP parameters. The placebo response was described with a mono-exponential placebo effect using PL_{max} and EF_{half} parameters. The bimekizumab treatment effect was characterized with an Emax type effect added to PL_{max}. Normally distributed IIV was included on the base parameter, PLmax and Emax parameters, while SP, EF_{half} and EC50 were assumed to be log-normally distributed between individuals. Covariance terms were included between EF_{half}, Emax and EC50. The parameter estimates of the base bimekizumab population PKPD model for PASI are presented in Table 84.

Table 84: Parameter estimates of the base bimekizumab population PKPD model for PASI

	Run 170 (Condition number = 77.3)		
	Unit	Value	RSE (%)
Scaling parameter (SP)		0.196	2.10
BASE		-0.633	1.52
PL_{max}		-0.280	20.5
EF_{half}	Week	4.14	3.61
E_{max}		-2.02	2.29
EC_{50}	µg/mL	0.155	16.5
IIV SP	CV	0.463	5.07
IIV BASE	SD	0.209	4.72
IIV PL_{max}	SD	0.515	14.7
IIV EF_{half}	CV	0.880	3.69
Corr EF_{half}-E_{max}	Corr.	-0.600	7.37
IIV E_{max}	SD	0.715	6.13
Corr EF_{half}-EC_{50}	Corr.	0.158	56.0
Corr E_{max}-EC_{50}	Corr.	-0.573	12.9
IIV EC_{50}	CV	2.22	6.44

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.
EF_{half}: time to reach half maximum effect
IIV: interindividual variability
PL_{max}: maximum placebo effect
SD: standard deviation CV: coefficient of variation
Corr: Correlation

Source: Table 20 of PKPD report.

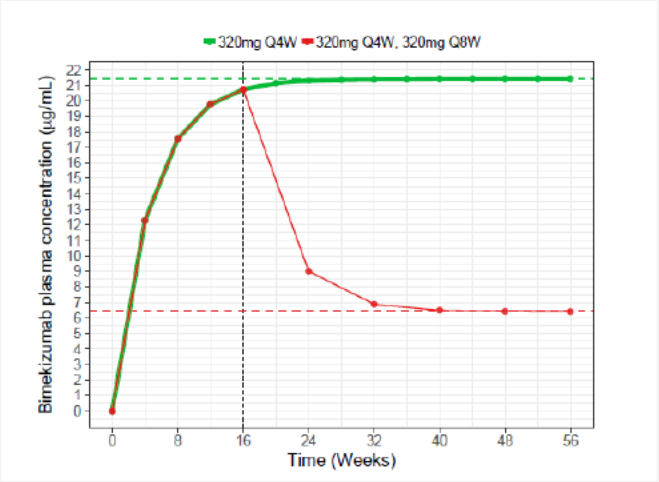
Study participants with higher baseline PASI had a larger reduction in PASI score than study participants with lower baseline PASI score. Younger study participants had a faster onset of treatment effect than the older study participants.

IGA model: The final population PKPD model for IGA was a BI model with a mono-exponential time-dependent placebo effect described by PLmax and time to reach half maximum placebo effect (PLhalf). Bimekizumab exposure response for IGA score 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. The final population PKPD model for IGA also included a Markov element describing the influence of the previous IGA score on the probability of the IGA score at the current visit. Covariates were tested on the population PKPD model for IGA model if indicated by η versus covariate plots in the base model. 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). Study participants with higher baseline IGA had a smaller Kout of the indirect treatment effect on IGA score than study participants with lower baseline IGA score. Study participants with higher baseline WT had a slower development of treatment effect on IGA score than study participants with lower baseline WT.
Reviewer's comments: The Applicant's analysis seems reasonable.

19.4.3. Covariate Effects for Final Bimekizumab Population PK model

A plot showing simulated bimekizumab concentrations from the final bimekizumab population PK model for a subject receiving either 320mg bimekizumab Q4W or 320mg bimekizumab Q4W until Week 16 followed by 320mg bimekizumab Q8W is presented in Figure 21. At Week 16, the concentration of the 320mg Q4W regimen is 97% of the concentration at Week 56 under the same regimen, indicating that steady state is reached shortly after. At Week 32 the concentration of the 320 Q8W regimen is 107% of the concentration at Week 56 under the same regimen, indicating that a new SS will be reached shortly after that time. The mean accumulation ratio (AR) for Q4W dosing in the typical non-Asian male subject with 90kg WT and negative ADAb status was 1.74.

Figure 21: Simulated Bimekizumab Concentration from Final Model.

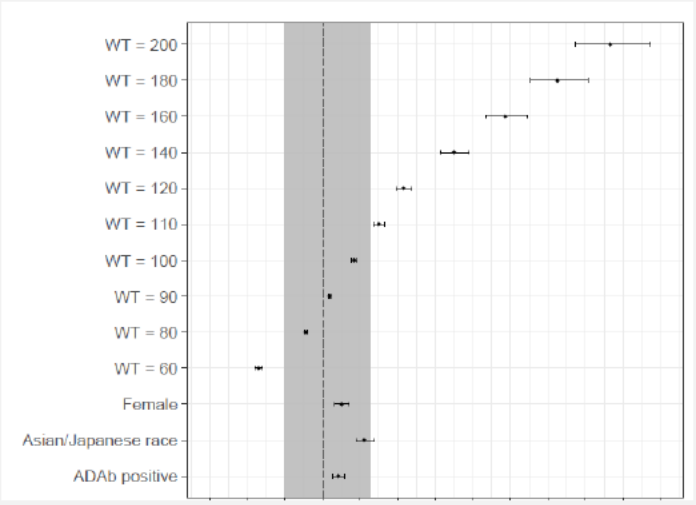


Source: Figure 19 of PKPD report. Simulated bimekizumab concentrations from the final bimekizumab population PK model for a typical non- Asian male subject with a baseline body weight of 90kg and negative ADAb status receiving either 320mg bimekizumab Q4W (green line and points) or 320mg bimekizumab Q4W until Week 16 (indicated by dashed vertical line) followed by 320mg bimekizumab Q8W (red line and points). The horizontal dashed lines indicate the concentrations at Week 56 for the corresponding treatment regimens.

Covariate Effect on PK Parameters

A Forest plot showing the covariate-parameter relationships of the final bimekizumab population PK model is presented in Figure 22 to Figure 23, for CL/F, V/F and exposure metrics, respectively. The plots are based on 200 bootstrap samples. Six bootstrap samples terminated unsuccessfully due to rounding errors (NONMEM error code = 134) but were retained in all calculations. The plots indicate that WT seems to be the most clinically significant covariate on CL/F and V/F.

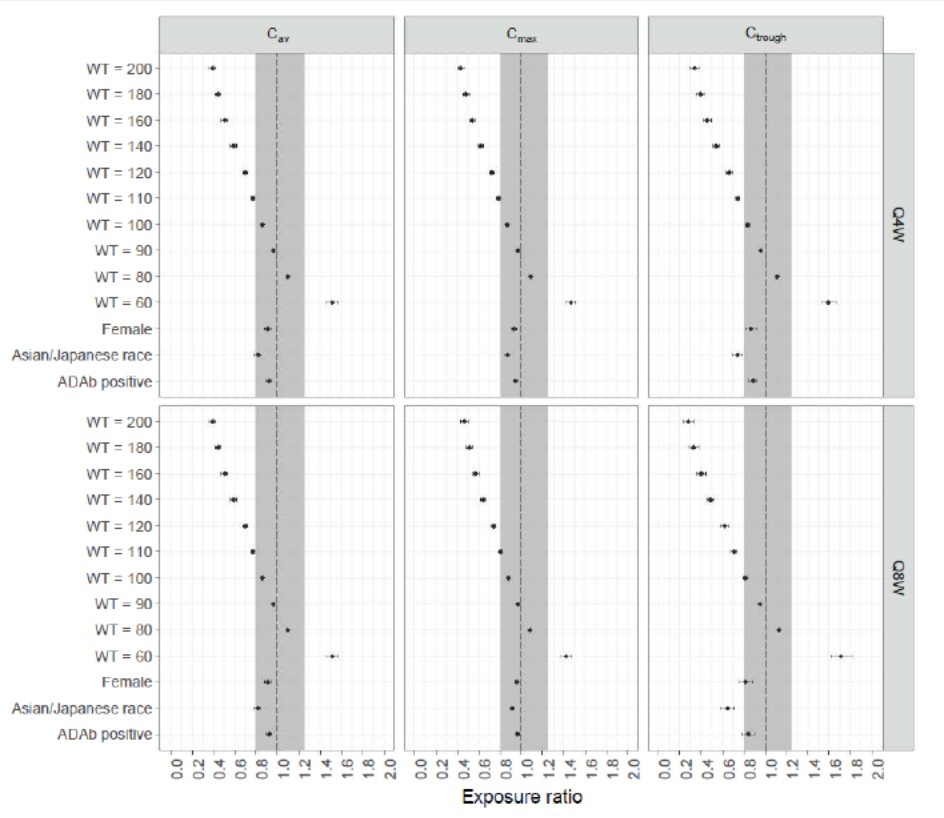
Figure 22: Forest Plot of The Final Bimekizumab Population PK Model Illustrating the Ratio Of CL/F for The Statistically Significant Covariates



Source: Figure 20 of PKPD report. Forest plot of the final bimekizumab population PK model illustrating the ratio of CL/F for the statistically significant covariates with respect to the reference group, based on 200 bootstrap samples. The points and the horizontal error bars represent the median and 95% CI of the relative CL/F for different covariate groups. The vertical dashed

line indicates a ratio of 1. The vertical grey shaded area shows the range from x=0.8 to x=1.25. Six bootstrap samples failed due to rounding errors (NONMEM error code = 134) but were retained in the calculations. CL/F: apparent clearance; CI: confidence interval; WT: body weight; ADAb: anti-drug-antibody.

Figure 23: Forest Plot of The Final Bimekizumab Population PK Model Illustrating the Ratio of Exposure Metrics



Source: Figure 22 of PKPD Report. Forest plot of the final bimekizumab population PK model illustrating the ratio of exposure metrics (Cav, Cmax and Ctrough) for the statistically significant covariates with respect to the reference group, based on 200 bootstra p samples, stratified by 320mg Q4W and 320mg Q8W regimens. The points and the horizontal error bars represent the median and 95% CI of the exposure metric ratio for different covariate groups. The vertical dashed line indicates a ratio of 1. The vertical grey shaded area shows the range from x=0.8 to x=1.25. Six bootstrap samples failed due to rounding errors (NONMEM error code = 134) but were retained in the calculations. Cav: average concentration; Cmax: maximum concentration; Ctrough: trough concentration; CI: confidence interval; Q4W: every 4 weeks; Q8W: every 8 weeks.

Covariate Effect on PASI Score

Body Weight Effect on PASI:

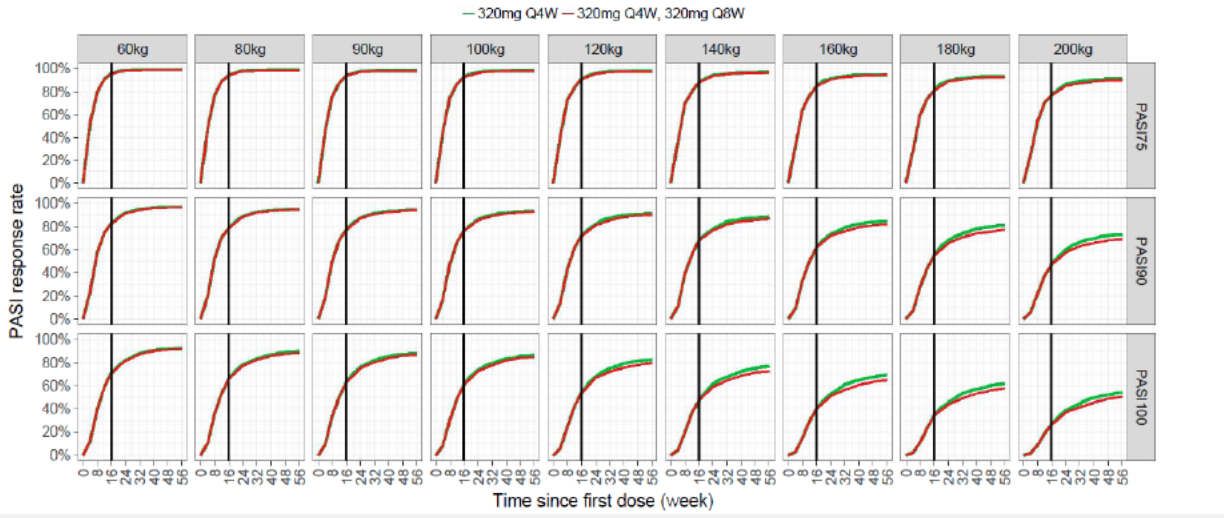
Simulated subpopulations for PASI response included all combinations of the following covariate values (resulting in 432 unique subpopulations):

- Weight: 60, 80, 90, 100, 120, 140, 160, 180 or 200 kg.
- Dosage regimen: 320mg Q4W from 0 to 56 weeks or 320mg Q4W from 0 to 12 weeks with a switch to320mg Q8W at week 16.
- ADAb status: ADAb negative or ADAb positive

All study participants were assumed to have the same baseline PASI (18.5) and the region was assumed to be Eastern/Central Europe.

Figure 24 presents the results for non-Asian male trial participants from Central/Eastern Europe with different baseline WT categories, stratified by the baseline WT categories. Boxplots showing the response in these individuals at Week 56 are presented in Figure 26 presents the mean differences in PASI response rates at Week 56 between Q4W and Q8W dosing for different body weights and the cumulative differences for different body-weight cut-off points. In this plot, for the 100kg weight cut-off point, the differences between Q4W and Q8W response are summed for all included weight categories 100kg. For the 120kg weight cut-off point, the difference between Q4W and Q8W response are summed for all included weight categories _ 120kg, and so forth. Figure 26 suggests that using 120kg as body weight cut off, the additive benefit in response for transitioning from a Q8W to a Q4W regimen is closer to the maximum value, while there is little benefit at a lower weight cut off. Conversely, setting the cut off at a higher weight would result in fewer proportion of patients with this benefit. Among the study participants with a given body weight, the percentage of study participants that would benefit from continuing on a Q4W regimen after Week 16 is shown in the solid bars. While the transparent bars show the percentage of study participants that would benefit on Q4W regimen with a body weight a given body weight group. The plots show that 2% additional study participants would benefit if the body weight cut was 100kg instead of a 120kg on a PASI100 endpoint.

Figure 24: PASI Response Rate Versus Time for Different Weight Categories

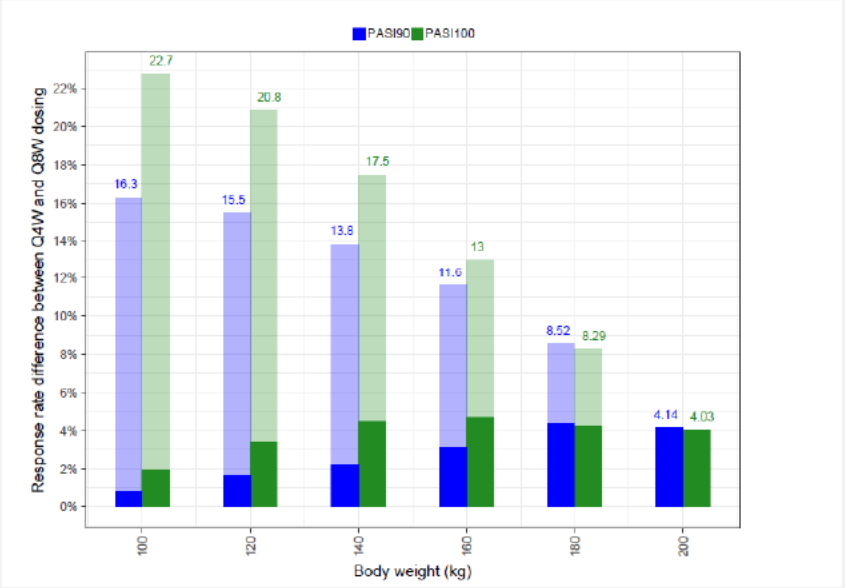


Source: figure 34 of PKPD report. PASI response rate versus time for different weight categories for a 65 year old non-Asian male study participant from Central/Eastern Europe, ADAb negative status and a baseline PASI of 18.5, based on the final exposure response model for PASI, colored by the treatment 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;

Figure 25: Boxplots of the simulated PASI response rate versus WT categories at Week 56

Source: figure 35 of PKPD report. Boxplots of the simulated PASI response rate versus WT categories at Week 56, based on the final exposure response model for PASI, colored by the treatment groups and stratified by PASI response variable type. In the box plots, the line corresponds to the median, the upper and lower hinges correspond to the 97.5th and 2.5th percentiles. The y-axis has been truncated between 40 and 100%.

Figure 26: Difference in Response (Solid Bars) At Week 56 Between Q4W And Q8W Regimens Versus Body Weight Colored by PASI Response Category.



Source: Figure 36 of PKPD report. Difference in response (solid bars) at Week 56 between Q4W and Q8W regimens versus body weight colored by PASI response category. The shaded bars are the cumulative differences (also indicated by numbers) for the corresponding weight and weight categories above that. For the 100 kg weight cut-off, the difference in response rate between Q4W and Q8W dosing are summed for weight categories equal to or greater than 100 kg. For the 120 kg weight cut-off, the difference in response rate between Q4W and Q8W dosing are summed for weight categories equal to or greater than 120 kg, and so forth.

Summary of Simulated PASI responder rate at week 56 for a typical 65 year old, non-Asian male study participant from central/eastern Europe with baseline PASI of 18.5 and negative ADAb status was shown in Table 85.

Table 85: Summary of simulated PASI Responder Rate at Week 56

Body weight / Treatment group	Response rate at Week 56		
	PASI75	PASI90	PASI100
320mg Q4W			
60kg	99.0	97.0	92.0
80kg	98.8	94.7	89.6
90kg	98.4	94.4	88.1
100kg	98.2	93.2	86.4
120kg	97.8	91.2	82.7
140kg	96.7	88.4	76.9
160kg	94.5	84.6	69.6
180kg	93.2	80.9	62.0
200kg	91.3	73.2	54.3
320mg Q4W, 320mg Q8W[a]			
60kg	98.8	96.5	91.8
80kg	98.3	94.5	88.5
90kg	97.9	94.2	87.0
100kg	97.7	92.9	84.8
120kg	97.4	90.1	79.6
140kg	96.5	86.7	72.8
160kg	94.4	81.8	65.0
180kg	92.8	77.3	58.0
200kg	90.1	69.1	50.7

[a] 320 mg Q4W, 320 mg Q8W: 320mg Q4W followed by 320mg Q8W from week 16 onwards.
Q4W: every 4 weeks; Q8W: every 8 weeks; ADAb: anti-drug-antibody; 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; WT: body weight

Source: Table 24 of PKPD report.

Reviewer's comments: Body weight seems to have a significant impact on PK and efficacy. For some patients (patients with body weight ≥120kg), continued dosing with 320mg Q4W after Week 16 may be considered. Body weight was found to be an intrinsic factor that could impact clinical response. Patients with a higher body weight may have a lower clinical response due to lower plasma concentrations with the same dose compared to a lower body weight patient. Therefore, Q4W interval is recommended for dosing regimen in body weight $\geq$ 120 kg PSO adult patients.

19.4.4. Bioanalytical Method Report

There were three PK methods used to analyze the samples from phase 1 to phase 3 studies for Bimekizumab of BLA 761151. PK method 2 was used for samples analysis of all three phase 3 studies and PK comparison for to-be-market presentations (UP0033), therefore method validation and in-study report of PK method 2 for bimekizumab analysis was listed below.

Method	Electrochemiluminescence immunoassay (ECLIA)
Calibration range	0.25-20 µg/mL
Accuracy (LLOQ-ULOQ)	-2.0% to 2.2%
Precision (LLOQ-ULOQ)	<=3.3%
Selectivity	Selectivity determined in 10 individual plasma samples at 250 and 15,000 ng/mL level. 100% of the spiked samples were within 25% (250ng/mL) and 20% (15,000ng/mL) RE. Range of observed bias: 250ng/mL drug, -8.0% to 1.6% for healthy subjects, 3.6% to 10.8% for PSO patients, 15,000ng/mL, -2.7% to 16.7% RE for healthy subjects, -11.3% to 9.3% RE for PSO patients.
Interference and specificity	Interference of IL-17A and IL-17F was tested at target levels of 4 and 8ng/mL in combination with 250ng/mL and 20,000ng/mL drug. Target interference observed at 4 and 8ng/mL target at the 250ng/mL level (bias: -34.4% [4ng/mL target] and -35.6% [8ng/mL target]). No interference observed at the 20,000ng/mL level (bias: -14.0% [4ng/mL target] and -16.0% [8ng/mL target]).
Hemolysis effect	The effect of hemolysis was determined in 5 individual healthy subject plasma samples prepared at 3% hemolyzed plasma and spiked at drug levels of 250ng/mL (LLOQ) and 15,000ng/mL. 100% of the spiked samples were within 25% (250ng/mL) and 20% (15,000ng/mL) RE. Range of observed bias: 250ng/mL drug: -6.8% to 5.6% RE; 15,000ng/mL drug: -5.3% to 4.7% RE.
Lipemic effect	The effect of hyperlipemia was determined in 5 individual healthy subject plasma samples containing approximately 4.00mmol/L of triglycerides and spiked at drug levels of 250ng/mL (LLOQ) and 15,000ng/mL. 100% of the spiked samples were within 25% (250ng/mL) and 20% (15,000ng/mL) RE. Range of observed bias: 250ng/mL drug: -10.8% to 12.0% RE; 15,000ng/mL drug: -10.0% to 5.3% RE.
Dilution linearity and hook effect	Dilution linearity: Demonstrated using a starting dilution of 250µg/mL (2 times the expected Cmax) and 125µg/mL (expected Cmax). Samples were diluted up to a factor of 100 (Cmax) or 200 (2 times Cmax). The observed range of bias for the 250µg/mL level was 0.6% to 3.8% RE

	and for the 125µg/mL level -0.5% to 6.4% RE. Maximum fold dilution (including MRD): 160,000 Hook effect (prozone): The method was not susceptible to hook effect (2 hook effect samples 125µg/mL and 250µg/mL) produced signals above the upper limit of detection).
Stability	Bench-top: 50 hours Six freeze/thaw at -20° and -80°C. Long term stability: -20°C and -80°C up to 351 days
Drug tolerance	Positive control (PC) at 75,000 ng/mL tolerant up to 200 µg/mL of bimekizumab PC at 1,000 ng/mL tolerant up to 200 µg/mL of bimekizumab PC at 100 ng/mL tolerant up to 200 µg/mL of bimekizumab PC at 39.0 ng/mL tolerant up to 100 µg/mL of bimekizumab PC at 16.9 ng/mL tolerant up to 100 µg/mL of bimekizumab
Method validation is acceptable.	
In study bioanalysis results for phase 3 studies (PS0008, 0009 and 0013)	
Assay passing rate	Passing rate 90.3-96.2%
Standard curve performance	Cumulative bias range observed: -1.6 to 1.2% RE; Cumulative precision observed ≤3.5%
QC performance	Cumulative bias range observed: -4.3 to -2.3% RE; Cumulative precision observed ≤13.8% Cumulative %TE observed: ≤13.8%
Incurred sample reanalysis	Incurred sample reanalysis was performed in 6.7% of study samples and 81.0% of samples met the pre-specified criteria
Study sample analysis/stability	From all samples tested, 91.2-97.6% fell within the established stability timeframe
Bioanalytical results are acceptable.	
In study bioanalysis results for to-be-market formulation PK comparison study (UP0033)	
Screening assay performance	39 out of 50 runs acceptable (78%)
Confirmatory assay performance	32 out of 32 runs acceptable (100%)
Screening sample analysis	498 of 1315 samples reported as Positive Screen (38%).
Confirmatory sample analysis	83 of 498 samples reported as Positive Immunodepletion (17%). Confirmatory cut point 18.5%
Low positive control (LPC) failure rate	1/98a runs therefore 1% (rounded).

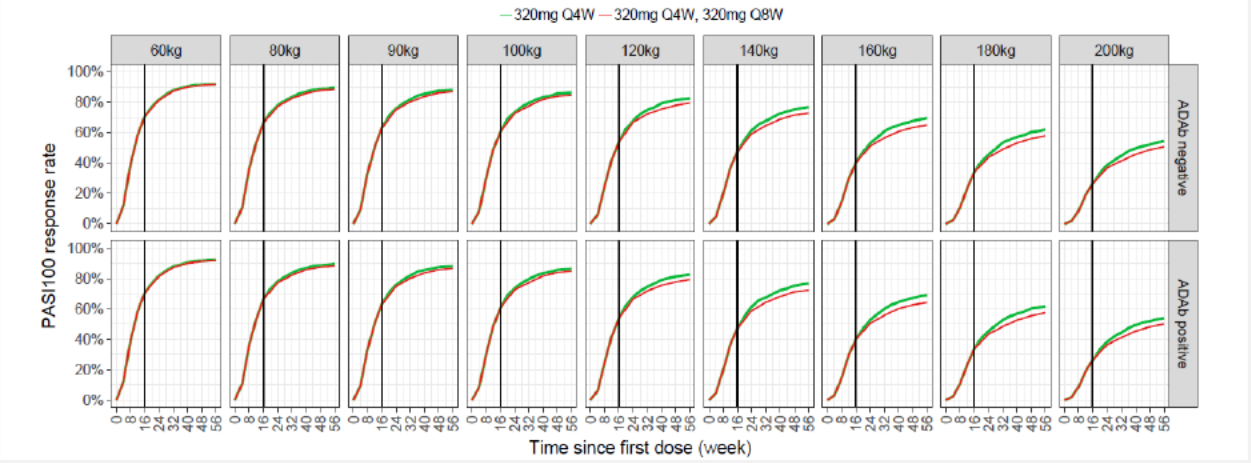
Bioanalytical results are acceptable.

19.4.5. Immunogenicity

Immunogenicity on PK and PD:

Figure 27 presents the similar results for PASI100 response rates, stratified by different baseline WT categories and ADAb status. The figure indicates that the PASI100 response rate for Q4W and Q8W dosing regimens separate at WT of 120kg and above.

Figure 27: PASI100 Response Rate Versus Time for Different Weight and ADAb Status



Source: Figure 41 of PKPD report. PASI100 response rate versus time for different weight and ADAb status categories for a 65 year old non-Asian male study participant from Centra/Eastern Europe with 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; 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.

Revewier's comments: There seems no big differences between the 320mg Q4W and 320mg Q8W dosing regimens within ADA positive or ADA negative subgroups. Thus, no dose change would be recommended based on ADA status.

19.5. Clinical/Biostatistics

Scales Used to Evaluate Efficacy

Table 86: Investigator's Global Assessment (IGA) Scale

Score	Short Descriptor	Detailed Descriptor
0	Clear	No signs of PSO; post-inflammatory hyperpigmentation may be present
1	Almost clear	No thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Clearly distinguishable to moderate thickening; dull to bright red, moderate scaling
4	Severe	Severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

Source: Applicant's Clinical Study Reports for Trial PS008; page 54

Figure 28: Psoriasis Area and Severity Index

The percent area of involvement (BSA%) was estimated across 4 body areas; head, upper extremities, trunk, and lower extremities. Assessors entered the degree of involvement for a given region on a scale of 0 to 6 (0=none; 1=1% to <10% affected, 2=10% to <30% affected, 3=30% to <50% affected, 4=50% to <70% affected, 5=70% to <90% affected, 6=90% to 100% affected) (Table 9–3).

The Investigator assessed the average redness, thickness, and scaliness of lesions in each body area (each on a 5-point scale); 0=none, 1=slight, 2=moderate, 3=marked, and 4=very marked. The PASI score ranges from 0 to 72 with a higher score indicating increased disease severity.

Body areas for calculation of percent BSA for PASI

Body area	Details of area	BSA	Degree of involvement of body area[a]
Head	Face, back of head	10%	0 to 6
Upper extremities	Left, right, upper lower, flexor surface, extensor surface	20%	0 to 6
Trunk	Front, back, groin	30%	0 to 6
Lower extremities	Left, right, upper lower, flexor surface, extensor surface, including buttocks	40%	0 to 6
Total		100%	

BSA=body surface area; PASI=Psoriasis Area and Severity Index
[a] Where 0=none; 1=1% to <10% affected; 2=10% to <30% affected; 3=30% to <50% affected; 4=50% to <70% affected; 5=70% to <90% affected; 6=90% to 100% affected

Source: Applicant's Clinical Study Reports for Trial PS008; page 55

Table 87: Scalp Investigator's Global Assessment (Scalp IGA) Scale

Score	Short Descriptor	Detailed Descriptor
0	Clear	Scalp had no signs of PSO; postinflammatory hyperpigmentation may have been present
1	Almost clear	Scalp had no thickening; normal to pink coloration; no to minimal focal scaling
2	Mild	Scalp had just detectable to mild thickening; pink to light red coloration; predominately fine scaling
3	Moderate	Scalp had clearly distinguishable to moderate thickening; dull to bright red, moderate scaling
4	Severe	Scalp had severe thickening with hard edges; bright to deep dark red coloration; severe/coarse scaling covering almost all or all lesions

PSO=psoriasis; scalp IGA=scalp-specific Investigator's Global Assessment
Source: Applicant's Clinical Study Reports for Trial PS0009; page 58

Table 88: List of Common investigators/Sites Across More than One Trial

SITEID	Trial PS0008	PS0009	PS0013
4	Gebauer Kurt (n=3)	Gebauer Kurt (n=4)	
8	Sinclair Rodney (n=7)		Sinclair Rodney (n=3)
9	Spelman Lynda (n=2)	Spelman Lynda (n=6)	
205	Pauser Sylvia (n=3)	Pauser Sylvia (n=5)	
211	Reich Kristian (n=2)	Reich Kristian (n=8)	
213	Sebastian Michael (n=10)	Sebastian Michael (n=10)	
217	Weber Ridwan (n=4)	Weber Ridwan (n=7)	
220	Klare Andreas (n=2)		Klare Andreas (n=1)
253		Dsa Piroska (n=10)	Dsa Piroska (n=3)
254	Eros Nora (n=5)	Eros Nora(n=4)	
255	Melegh va Patrcia (n=9)	Melegh va Patrcia (n=9)	
350		Ambroziak Marcin (n=13)	Ambroziak Marcin (n=10)
351		Bialo - Wojcicka Ewelina (n=10)	Bialo - Wojcicka Ewelina (n=9)
352	Bielinska - Warezak Dominika (n=6)		Bielinska - Warezak Dominika (n=4)
353	Debniak Tadeusz (n=9)		Debniak Tadeusz (n=5)
354	Galus Ryszard (n=12)		Galus Ryszard (n=3)
355	Janczylo - Jankowska Malgorzata (n=9)		Janczylo - Jankowska Malgorzata (n=8)
356	Juszkiewicz - Borowiec Maria (n=6)		Juszkiewicz - Borowiec Maria (n=6)
357		Klujszo Elzbieta (n=12)	Klujszo Elzbieta (n=4)
358		Kolanko Magdalena (n=13)	Kolanko Magdalena (n=9)
359	Meszynska Elzbieta (n=5)		Meszynska Elzbieta (n=2)
360	Narbutt Joanna (n=8)		Narbutt Joanna (n=4)
362	Poznanska Maria (n=9)	Poznanska Maria (n=15)	
363	Rajzer Lidia (n=8)		Rajzer Lidia (n=13)
365	Szepietowski Jacek (n=16)		Szepietowski Jacek (n=12)
366	Vanaga-Besser Santa (n=3)		Vanaga-Besser Santa (n=5)
367	Weglowska Jolanta (n=5)	Weglowska Jolanta (n=14)	
369		Wilkowska - Trojniel Marta (n=15)	Wilkowska - Trojniel Marta (n=12)
370		Witkowska Dagmara (n=18)	Witkowska Dagmara (n=10)
371	Czaplewski Artur (n=3)	Czaplewski Artur (n=2)	
372	Kaszuba Andrzej (n=9)	Kaszuba Andrzej (n=15)	

374		Adamski Zygmunt (n=16)	Adamski Zygmunt (n=10)
400		Zhukova Olga (n=3)	Zhukova Olga (n=3)
401	Bakulev Andrey (n=9)		Bakulev Andrey (n=3)
402		Molochkov Vladimir (n=4)	Molochkov Vladimir (n=4)
403		Perlamutrov Yuri (n=7)	Perlamutrov Yuri (n=2)
404		Smirnova Yana (n=5)	Smirnova Yana (n=3)
405	Sukharev Alexey (n=2)		Sukharev Alexey (n=2)
406	Yakusevich Vladimir (n=3)		Yakusevich Vladimir (n=4)
555		Warren Richard (n=3)	Warren Richard (n=1)
657	Papp Kim (n=7)	Papp Kim (n=20)	Papp Kim (n=13)
660	Saint-Cyr Proulx Etienne (n=6)		Saint-Cyr Proulx Etienne (n=5)
663	Lomaga Mark (n=15)		Lomaga Mark (n=10)
900	Coggi James (n=7)	Coggi James (n=9)	
901		Jarell Abel (n=12)	Jarell Abel (n=6)
905	McCune Mark (n=6)	McCune Mark (n=9)	
906	Reed Ann (n=3)	Reed Ann (n=3)	
908	Bagel Jerry (n=10)	Bagel Jerry (n=5)	
914		Lee Mark (n=8)	Lee Mark (n=8)
917	Murakawa George (n=5)	Murakawa George (n=1)	
924	Tyring Stephen (n=9)	Tyring Stephen (n=4)	
929	Blauvelt Andrew (n=18)		Blauvelt Andrew (n=20)
940	Greenstein David (n=5)		Greenstein David (n=3)
955	Nahm Walter (n=14)		Nahm Walter (n=2)
967	Yamauchi Paul (n=3)		Yamauchi Paul (n=5)

Source: Statistical Reviewer's Table; adsl.xpt

19.6. Additional Clinical Outcome Assessment Analyses

This section is not applicable.

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

STROTHER D DIXON
05/11/2022 12:39:32 PM

KELLEY A BURRIDGE
05/11/2022 12:44:58 PM

BARBARA A HILL
05/11/2022 12:54:23 PM
Signing on behalf of the primary Nonclinical reviewer (Jill Merrill) and myself

ANDREW C GOODWIN
05/11/2022 12:56:31 PM

SOO HYEON SHIN
05/11/2022 01:50:24 PM

CHINMAY SHUKLA
05/11/2022 01:53:23 PM

YUAN XU
05/11/2022 02:03:30 PM

JIANG LIU
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SURESH DODDAPANENI
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KEVIN L CLARK
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GORDANA DIGLISIC
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SHARI L TARGUM
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MARILENA FLOURI
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MARILENA FLOURI
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MOHAMED A ALOSH
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JULIE G BEITZ
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