CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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OTHER REVIEW(S)

Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo

Date:	October 17, 2023
Reviewer:	Sally Peprah, PhD, MSPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD, MS Division of Epidemiology I
Associate Division Director:	Wei Hua, MD, PhD, MHS, MS Division of Epidemiology I
Subject:	ARIA Sufficiency Memo for Pregnancy Safety Concerns
Drug Name:	Bimekizumab
Application Type/Number:	BLA 761151
Sponsor:	UCB, Inc.
OSE RCM #:	2020-1495

Expedited ARIA Sufficiency Template for Pregnancy Safety Concerns

1. BACKGROUND INFORMATION

1.1. Medical Product

Bimzelx (bimekizumab) injection, for subcutaneous use, is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[1] Bimekizumab is a humanized immunoglobulin IgG1/κ monoclonal antibody, with two identical antigen binding regions that selectively bind to human interleukin 17A (IL-17A), interleukin 17F (IL-17F), and interleukin 17-AF cytokines, and inhibits their interaction with the IL-17RA/IL-17RC receptor complex. IL-17A and IL-17F are naturally occurring cytokines that are involved in normal inflammatory and immune responses. Levels of IL-17A and IL-17F are elevated in several immune mediated inflammatory diseases and drive chronic inflammation and damage across multiple tissues. Bimekizumab inhibits the release of proinflammatory cytokines.[1]

1.2. Describe the Safety Concern

The Division of Dermatology and Dentistry (DDD) requested that the Division of Epidemiology-I (DEPI-I) assess the sufficiency of ARIA for evaluating the safety risk among women exposed to bimekizumab during pregnancy.

Safety due to drug exposure during pregnancy is a concern for women who are pregnant or of childbearing potential. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.[2] The estimated risks of birth defects (0.8%) and miscarriage (14%) are similar among women with moderate-to-severe plaque psoriasis.[3]

There are limited data on bimekizumab use in pregnant women to inform any drug associated risks. Human IgG is known to cross the placental barrier; therefore, bimekizumab may be transmitted from the mother to the developing fetus.[1]

Pregnant women were excluded from bimekizumab trials. However, a total of 11 bimekizumab exposed pregnancies have been reported to the UCB Global Safety Database as of the 120-Day Safety Update clinical cutoff date of April 15, 2020.[3] Per protocol, study medication was stopped as soon as the pregnancy was discovered. Thus, bimekizumab exposure was limited to a maximum of one dose during the first trimester. Pregnancy outcomes (n=11 total) included:

- 6 normal livebirths (gestational age at delivery not reported)
- 2 spontaneous abortions (both occurred in the first trimester)
- 1 induced abortion (due to unintended pregnancy)
- 2 unknown outcomes (lost to follow-up).

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[1] UCB, Inc. Proposed labeling for BLA 761151, submitted July 16, 2020.
[2] Dinatale M. Division of Pediatric and Maternal Health, FDA. The pregnancy and lactation labeling rule (PLLR), Pediatric Advisory Committee Meeting. https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/PediatricAdvisoryCommittee/UCM520454.pdf. Accessed March 17, 2021.
[3] Kimball AB, Guenther L, Kalia S, et al. Pregnancy Outcomes in Women with Moderate-to-Severe Psoriasis from the Psoriasis Longitudinal Assessment and Registry (PSOLAR). JAMA Dermatol. 2021 Mar 1;157(3):301-306.

No congenital anomalies or major maternal complications were reported. One serious treatment emergent adverse event of hemorrhage in pregnancy was reported; however, the outcome was unknown and no further information was available as the patient was lost to follow-up.[4] In the nonclinical studies, an enhanced pre- and postnatal developmental toxicity study was conducted in cynomolgus monkeys, and no maternal toxicity was noted in this study. Based on the animal studies, there were no treatment-related effects on growth and development, malformations, developmental immunotoxicology or neurobehavioral development.[5]

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

Purpose (place an "X" in the appropriate boxes; more than one may be chosen)	
Assess a known serious risk	
Assess signals of serious risk	
Identify unexpected serious risk when available data indicate potential for serious risk	x

2. REVIEW QUESTIONS

2.1. Why is pregnancy safety a safety concern for this product? Check all that apply.

☐ Specific FDA-approved indication in pregnant women exists and exposure is expected

☐ No approved indication, but practitioners may use product off-label in pregnant women

☒ No approved indication, but there is the potential for inadvertent exposure before a pregnancy is recognized

☒ No approved indication, but use in women of childbearing age is a general concern

2.2. Regulatory Goal

☒ *Signal detection* – Nonspecific safety concern with no prerequisite level of statistical precision and certainty

☐ *Signal refinement of specific outcome(s)* – Important safety concern needing moderate level of statistical precision and certainty. †

☐ *Signal evaluation of specific outcome(s)* – Important safety concern needing highest level of statistical precision and certainty (e.g., chart review). †

† ***If checked, please complete General ARIA Sufficiency Template.***

2.3. What type of analysis or study design is being considered or requested along with ARIA? Check all that apply.

[4] Baisden K, Johnson T and Yao L. Pregnancy and Lactating Labeling Review. U.S. Food and Drug Administration, Silver Spring (MD). Submitted to BLA 761151, DARRTS Reference ID: 4741087.
[5] Baisden K and Johnson T. Division of Pediatrics and Maternal Health, Addendum to PLLR Labeling and Pregnancy/Lactation Postmarketing Requirements (PMRs) Review. U.S. Food and Drug Administration, Silver Spring (MD). Submitted to BLA 761151, DARRTS Reference ID: 5163918.

☒ Pregnancy registry with internal comparison group
☐ Pregnancy registry with external comparison group
☐ Enhanced pharmacovigilance (i.e., passive surveillance enhanced by with additional actions)
☐ Electronic database study with chart review
☒ Electronic database study without chart review
☒ Other, please specify: Alternative study designs such as a case-control study design will be considered if there is a need to collect additional information from the mothers through personal interviews, to obtain additional information on infants, to request permission to review medical records, or to perform long-term follow-up of their offspring, and such a study maybe nested within an electronic database study or conducted independent of it.

2.4. Which are the major areas where ARIA not sufficient, and what would be needed to make ARIA sufficient?

☐ Study Population
☐ Exposures
☒ Outcomes
☒ Covariates
☒ Analytical Tools

For any checked boxes above, please describe briefly:

Outcomes: The pregnancy registry being considered requires that an expert clinical gynecologist or dysmorphologist review and classify medical records of all major congenital malformations. However, ARIA lacks access to medical records. Further, the prospective registry requires clinical information from medical records and risk factors that may not be available in claims data. Also, although in a first stage, the study using claims or electronic medical data may be algorithm-based, if it shows an imbalance in any of the outcomes being investigated, FDA may consider requiring outcome validation in the selected database(s) or a chart-confirmed analysis.

Covariates: The pregnancy registry being considered will collect detailed narratives with information on potential covariates such as severity of plaque psoriasis, family history of the disease or outcomes, and lifestyle factors such as prenatal supplements. However, ARIA does not have detailed information on potential confounders for the pregnancy registry.

Analytical tools: ARIA data mining methods have not been fully tested and implemented in post-marketing surveillance of maternal, fetal, and infant outcomes.

2.5. Please include the proposed PMR language in the approval letter.

The Division of Pediatric and Maternal Health recommends two PMRs related to pregnancy outcomes. As of April 7, 2021, the proposed PMR language is:

1. 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, neonatal deaths, and infections, will be assessed through at least the first year of life.

2. 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 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 bimekizumab during pregnancy compared to an unexposed control population.

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/

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Department of Health and Human Services
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Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo

Date:	October 17, 2023
Reviewer:	Sally Peprah, PhD, MSPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD, MS Division of Epidemiology I
Deputy Division Director:	Wei Hua, MD, PhD, MHS, MS Division of Epidemiology I
Subject:	Active Risk Identification Assessment (ARIA) Sufficiency Memo: Risk of immunosuppression-related adverse outcomes associated with bimekizumab treatment in psoriasis patients
Drug Name(s):	Bimekizumab
Application Type/Number:	BLA 761151
Applicant/sponsor:	UCB, Inc.
OSE RCM #:	2020-1495

EXECUTIVE SUMMARY

Memo type	Malignancy	Opportunistic Infections	Reactivation of Hepatitis B	Tuberculosis	Serious Infections	Other Adverse Events*
-Initial						
-Interim						
-Final	X	X	X	X	X	X
Source of safety concern						
-Peri-approval	X	X	X	X	X	X
-Post-approval						
Is ARIA sufficient to help characterize the safety concern?						
-Yes						
-No	X	X	X	X	X	X
If "No", please identify the area(s) of concern.						
-Surveillance or Study Population						
-Exposure						
-Outcome(s) of Interest	X	X	X	X	X	X
-Covariate(s) of Interest						
-Surveillance Design/Analytic Tools						

*** Other adverse events of special interest 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**

1. BACKGROUND INFORMATION

1.1. Medical Product

Bimzelx (bimekizumab) injection, for subcutaneous use, is proposed for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[a] Bimekizumab is a humanized immunoglobulin IgG1/κ monoclonal antibody, with two identical antigen binding regions that selectively bind to human interleukin 17A (IL-17A), interleukin 17F (IL-17F), and interleukin 17-AF cytokines, and inhibits their interaction with the IL-17RA/IL-17RC receptor complex. IL-17A and IL-17F are naturally occurring cytokines that are involved in normal inflammatory and immune responses. Levels of IL-17A and IL-17F are elevated in several immune mediated inflammatory diseases and drive chronic inflammation and damage across multiple tissues. Bimekizumab inhibits the release of proinflammatory cytokines.[b] The proposed recommended dosage is 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.[c]

1.2. Describe the Safety Concern

Bimekizumab poses theoretical risks for malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections based on its immunosuppressive mechanism of action. Further, elevated rates of infections were observed in psoriasis patients treated with bimekizumab compared to psoriasis patients not treated with bimekizumab in a clinical setting.[c]

1.2.1. Malignancy

A theoretical increased risk for malignancies exists based on the immunosuppressive mechanism of action of bimekizumab. However, 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).[c]

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.[c] Some literature suggests that IL-17 may have a role in tumor formation, tumor proliferation, metastasis and chemoresistance;[d,e] 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

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[a] UCB, Inc. Proposed labeling for BLA 761151, submitted July 16, 2020.

[b] Ibid.

[c] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: February 17, 2021.

[d] Yang B, Kang H, Fung A, Zhao H, Wang T, Ma D. The role of interleukin 17 in tumour proliferation, angiogenesis, and metastasis. Mediators of inflammation. 2014 Oct;2014.

[e] Zhao J, Chen X, Herjan T, Li X. The role of interleukin-17 in tumor development and progression. Journal of Experimental Medicine. 2019 Nov 14;217(1):e20190297.

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 cynomolgus monkeys at doses up to 200 mg/kg for 26 weeks followed by a 21-week post-dosing observational period.

The proposed product labeling does not include any warnings or precautions related to potential malignancy risk.

1.2.2. Opportunistic Infections and Serious Infections

Increased susceptibility to infections is regarded as a class effect of psoriasis biologics due to their immunosuppressant effects and is a labeled risk for the class. 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).[f] In addition, serious infections were reported in 1.5% of subjects treated with bimekizumab (EAIR 1.6/100 subject-years). During the development program, opportunistic infections were primarily mucocutaneous fungal infections.[g]

The proposed product labeling includes warnings and precautions for infections:[h]

> Bimekizumab may increase the risk of infections. In clinical studies in patients with plaque psoriasis, infections occurred in 36% of the bimekizumab group compared to 23% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections, oral candidiasis gastroenteritis, tinea pedis, and oral herpes occurred more frequently in the bimekizumab group than in the placebo group. Serious infectious occurred in 0.3% of patients treat with bimekizumab and 0% treated with placebo. (b) (4) .

1.2.3. Reactivation of Hepatitis B

The sponsor excluded patients with hepatitis B infection (HBsAg and/or anti-HBc positive) from their studies. Therefore, reactivation risk could not be assessed as no data are available.[i] However, the first approved monoclonal antibody directed against IL-17A, secukinumab, has been associated with a significant rate of reactivation. Hepatitis B reactivation is an increasingly recognized form of drug-induced liver injury (DILI; indirect DILI) from immunosuppressant medications. This risk was also evaluated by consultants from the Division of Pharmacovigilance I (DPV) and Division of Epidemiology I (DEPI-I).[j] Based on their analyses, consultants from the DILI team, DPV, and DEPI recommended inclusion of a recommendation for pretreatment evaluation for hepatitis B infection in the labeling for bimekizumab. This recommendation was based on findings from the review of postmarketing case series and guidelines from the American Association for the Study of Liver Diseases and the Joint American Academy of Dermatology and National Psoriasis Foundation. There was

[f] See footnote c.

[g] Ibid.

[h] See footnote a.

[i] See footnote c.

[j] Weintraub J, Booth B. Integrated Safety Review (of Hepatitis B Virus Reactivation with Bimekizumab, Secukinumab, Ixekizumab, and Brodalumab). September 8, 2021. BLA 761151, BLA 125504, BLA 125521, BLA 761032. Silver Spring (MD), U.S. Food and Drug Administration. (DARRTS Reference ID: 4853451).

insufficient evidence in the literature to provide labeling recommendations based on epidemiologic findings alone. Because no data are available regarding the potential risk of hepatitis B reactivation from clinical trials, a recommendation for pretreatment evaluation for hepatitis B will not be included in product labeling at this time. However, hepatitis B reactivation will be included as an outcome of interest in an observational, long-term postmarketing safety study.

1.2.4. Tuberculosis

A theoretical risk of tuberculosis exists for bimekizumab based on its immunosuppressive mechanism of action. However, there was insufficient data from the bimekizumab clinical trials. Although subjects with active tuberculosis were excluded from clinical trials, subjects with latent tuberculosis could be enrolled provided they began prophylactic treatment prior to the beginning of the trial.[k] No subjects developed new onset tuberculosis infection during the clinical trials. A total of 14 subjects with latent tuberculosis were enrolled in the phase 3 trials and received prophylactic treatment for tuberculosis. None of these subjects developed active tuberculosis.

The proposed product labeling includes warnings and precautions for tuberculosis:[l]

> Evaluate patients for tuberculosis infection prior to initiating treatment with bimekizumab. Do not administer bimekizumab to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering bimekizumab. Consider anti-tuberculosis therapy prior to initiation of bimekizumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving bimekizumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment. (b) (4)

1.2.5. Other Adverse Events

Hypersensitivity

Hypersensitivity was considered an adverse event of special interest (AESI) in the development program for bimekizumab.[m] In the initial submission, a total of 13/1789 subjects (0.7%, EAIR 0.8/100 subject-years) had treatment emergent adverse events (TEAEs) of urticaria. 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. 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.[n]

[k] See footnote c.

[l] See footnote a.

[m] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: October 10, 2023.

[n] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: October 10, 2023.

Gastrointestinal Events (Including Inflammatory Bowel Disease, Elevated Liver Enzymes/Drug-Induced Liver Injury)

Inflammatory Bowel Disease

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. 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 ulcerative colitis (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 IBD cases (three cases of UC, three cases of Crohn's Disease (CD), and one case of IBD unclassified) in subjects treated with bimekizumab which were adjudicated as "definite IBD" by the IBD-CAC. Based on the clinical narratives and summaries provided by the Applicant, the Division of Gastroenterology (DG) consultant 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."[o]

Elevated Liver Enzymes/Drug-Induced Liver Injury

During the initial BLA review, the review team discovered potential cases of drug-induced liver injury (DILI) associated with treatment with bimekizumab.[p] In addition, the review team identified an imbalance for transaminases > 3x the upper limit of normal (ULN) during the placebo-controlled trials. 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.

Consultants from the Drug-Induced Liver Injury (DILI) team from the Division of Hepatology and Nutrition identified no definite or probable Hy's Law cases but noted two possible cases that the consultants considered to have reasonable alternative diagnoses that were as or more likely than DILI. There were three probable cases of notable bimekizumab liver injury but without jaundice. The DILI consultants concluded that bimekizumab can lead to hepatocellular or mixed liver injury but did not think the risk of severe DILI is high enough to hold up approval if benefit and need are clear for bimekizumab. Nevertheless, the DILI consultants noted that significant DILI may still arise when bimekizumab is given to larger numbers of patients postmarketing, and any labeling should discuss this possibility.[q] 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.

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[o] Nayyar A, Altepeter T, Lee J. Division of Gastroenterology, Review and Comment on the Applicant's Evaluation of Adverse Events of Inflammatory Bowel Disease (IBD) and Inclusion of IBD in Section 5 of the Product Labeling, and Comment on SAE of Hepatic Enzyme Increased (liver injury) in One Patient (Subject# PS0008-(b) (6)). Submitted to BLA 761151 (DARRTS Reference ID: 4766223) on March 22, 2021.

[p] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: October 10, 2023.

[q] Hayashi PH, Avigan M, Toerner J. Division of Hepatology and Nutrition Consult Review, submitted to BLA 761151 (DARRTS Reference ID: 4838201) on August 09, 2021.

Major Adverse Cardiovascular Events (Myocardial Infarction, Stroke, Cardiovascular Death, and Sudden Death)

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.

As of the 120- day safety update submitted during review of the initial BLA, adjudicated MACE was reported in 14/1798 subjects (0.8%; EAIR 0.6/100 subject-years). In the safety update provided with the resubmission, adjudicated MACE was 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 was reported in 17/1798 subjects (1.0%; EAIR 0.7/100 subject-years). In the safety update provided with the resubmission, extended MACE was 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. The review conducted by the Division of Cardiology and Nephrology (DCN) did not reveal a clinical concern from the cardiovascular perspective and no labeling language was recommended.[r] DCN concluded that that "all cases (MACE deaths) 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."

Hematologic Events

Reduction in neutrophil counts is a potential pharmacodynamic effect of blockade of IL-17A. 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. 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 the resubmitted safety update, results were comparable to those in the original BLA submission and 120-Day safety update. In the resubmitted data, 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 exposure-adjusted incidence rate, the data did not demonstrate an increased treatment-related risk of neutropenia with longer duration of treatment with bimekizumab.

[r] DeConti S, Southworth MR, Stockbridge N. Division of Cardiology and Nephrology, Cardiovascular safety of bimekizumab. Submitted to BLA 761151 (DARRTS Reference ID: 5156429) on April 12, 2023.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

	Malignancy	Opportunistic Infection	Reactivation of Hepatitis B	Tuberculosis	Serious Infection	Other Adverse Events*
Assess a known serious risk						
Assess signals of serious risk						
Identify unexpected serious risk when available data indicate potential for serious risk	X	X	X	X	X	X

*** Other adverse events of special interest 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**

1.4. Statement of Purpose

This memo reflects the discussions, recommendations, and determinations between Division of Epidemiology I (DEPI-I), the Division of Dermatology and Dentistry (DDD), and CDER's Sentinel Team. Under assessment are the risk for malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, serious infections, and other adverse events of special interest including 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. The team considered whether ARIA was sufficient to detect a safety signal or whether to issue a postmarketing requirement (PMR) for an observational study to collect additional data on long-term safety of bimekizumab treatment.

The purpose of this memo is to describe the determination of ARIA's capabilities to assess risk of malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, serious infections, and other adverse events of special interest when, in some instances, clinical data did not identify a safety signal, but theoretical concerns indicate the potential for a serious risk. The regulatory goal of ARIA in this assessment is signal detection (i.e., postmarketing surveillance) for malignancies, reactivation of hepatitis B, tuberculosis, serious and opportunistic infections as well as other adverse events of special interest including 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. The anticipated regulatory impact is to further characterize the risk of malignancies, opportunistic

infections, reactivation of hepatitis B, tuberculosis, serious infections and the other adverse events of special interest, to inform labeling decisions. Because the events of interest are rare, they may have long-term latency periods (particularly for malignancies), and because multiple products are available for treatment of the underlying disease (plaque psoriasis), the sufficiency determination primarily rests upon the need for a large sample size, the availability of long-term follow-up (particularly for malignancies), the availability of relevant covariates, and on the ensuing market uptake of bimekizumab.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The regulatory goal for evaluating the risk of malignancies, reactivation of hepatitis B, tuberculosis, serious and opportunistic infections as well as the other adverse events of special interest in ARIA is for signal detection (i.e., postmarketing surveillance), rather than a hypothesis-driven study.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Bimekizumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. All patients identified as having a psoriasis diagnosis or received a dispensing of a medication indicated exclusively for plaque psoriasis in Sentinel could be considered in the study population for postmarket surveillance. Reference rates could come from a comparator population that includes patients who have received a dispensing of other psoriasis biologics. To evaluate a class-effect (IL-17 antagonists), reference rates could come from a population of patients receiving non-biologic systemic medications for psoriasis.

2.2 Is ARIA sufficient to assess the intended population?

The underlying indication of psoriasis is needed to target this study population, which can be screened for using the ICD-10 code of L40.XX (psoriasis).

Few studies have been published that aimed to validate ICD-10 diagnostic codes for estimating the prevalence of psoriasis. A Swedish, population-based, validation study demonstrated observed positive predictive values (PPV) of ICD-10 codes ranging from 81%-100% with a post-validation prevalence of 1.23% (95% CI = 1.21-1.25) for psoriasis.[s] Another validation study using the Danish National Patient Register observed a PPV of 97.1% (95% CI = 95.5-98.1).[t] To date, no studies have validated the ICD-10 codes for estimating prevalence of psoriasis in a U.S. population. However, several studies in the United States have aimed to validated ICD-9 diagnostic codes for psoriasis. These studies reported PPVs that aligned with the abovementioned study.[uv] Taken together, findings from these studies suggest that

[s] Löfvendahl S, Theander E, Svensson A, et al. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in Southern Sweden – a population-based registry study. Plos One. 2014; 9(5).
[t] Loft ND, Andersen CH, Halling-Overgaard A-S, et al. Validation of psoriasis diagnoses in the Danish National Patient Register. Acta Derm Venereol. 2019; 99:1037-1038.
[u] Asgari MM, Wu JJ, Gelfand JM, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996-2009. Pharmacoepidemiol Drg Saf. 2013; 22(8):842-849.
[v] Icen M, Crowson CS, McEvoy MT, Gabriel SE, Maradit Kremers H. Potential misclassification of patients with psoriasis in electronic databases. J Am Acad Dermatol. 2008; 59:981-985.

performance of the ICD-10 codes (L40.XX) to identify psoriasis patients for surveillance purposes in the United States would be adequate.

ARIA is sufficient to identify the indicated population for this analysis and is not a limiting factor of concern.

EXPOSURES

3.1 Treatment Exposure(s)

Patients with pharmacy benefits who receive at least one dispensing of bimekizumab can be identified in health care claims data.

3.2 Comparator Exposure(s)

The regulatory goal of this ARIA assessment is signal detection. However, to help interpret the observed incidence rates of malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections among psoriasis patients treated with bimekizumab, reference rates from two comparator populations may be used: 1) patients using other psoriasis biologic medications and 2) patients using non-biologic systemic medications (to establish a class-effect). Both comparator populations could be identified through the Sentinel health care claims data.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify dispensing of both bimekizumab and comparator biologics and non-biologic systemic medications through corresponding National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) codes, and therefore is not a limiting factor. However, with several treatment options available to patients, market uptake of bimekizumab will affect whether enough users are available to further characterize risk of rare outcomes. The extent of market uptake can only be evaluated post-approval.

4. OUTCOME(S)

4.1 Outcomes of Interest

4.1.1 Malignancy

Malignancy outcomes include: 1) lymphoma and 2) all malignancies.
A workgroup[w] supporting Mini-Sentinel development reviewed the literature to identify algorithms that could be used in electronic claims-based data to identify cohorts of vulnerable groups, including persons with selected cancers of interest.

The Workgroup cautioned that:

> "Cancers are not typically studied as a homogenous group, given differences in the histological type and primary site of lesion – each that often has its distinct risk factors, screening requirements, pathology, clinical manifestations, diagnostic testing, differential diagnoses, staging, treatment and prognosis, as examples. Therefore, studies examining algorithms for identifying persons with any-type of cancer are scant."[x]

[w] Leonard C, Freeman C, Razzaghi H, et al. Mini-Sentinel methods: 15 cohorts of interest for surveillance preparedness. https://www.sentinelinitiative.org/sites/default/files/Methods/Mini-Sentinel_Methods_15-Cohorts-of-Interest-for-Surveillance-Preparedness_0.pdf. Accessed March 1, 2021.
[x] Ibid.

Thus, in the absence of cancer registry data, the Workgroup recommended against studying cohorts with an outcome of any cancer, but rather focusing on subcohorts with specific cancers. The Workgroup recommended that primary consideration should be given to the identification of persons with hematopoietic cancers such as leukemias, lymphomas, and myelomas.

As part of the Workgroup's deliverable, the Workgroup specified an algorithm for lymphoma that involved: two or more diagnoses of cancer (ICD-9 codes) within two months (algorithm 2); this algorithm performed with a PPV of 63% and a sensitivity of 80%. Another validation study for lymphoma was conducted among four Sentinel data partners using ICD-10-CM codes.[y] Their three component algorithm required: two diagnosis codes for Non-Hodgkin lymphoma and/or Hodgkin lymphoma on different dates within a 183-day window, at least one procedure code indicating a relevant diagnostic procedure (e.g., biopsy, flow cytometry) within 90 days before or after the first lymphoma diagnostic code, and at least one procedure code indicating a relevant imaging study within 90 days before or after the index date.[z] The study found an overall lymphoma (Hodgkin and non-Hodgkin combined) PPV of 77% (95% CI = 69%-84%).

4.1.2 Opportunistic Infections and Serious Infections

Opportunistic and serious infections outcomes include: 1) opportunistic infections broadly defined, 2) serious infections broadly defined, 3) reactivation of hepatitis B, and 4) tuberculosis.

Serious infection is defined as an infection that is a serious adverse event; an operational definition for the purpose of this ARIA assessment is an infection that requires hospitalization. A subset of serious infections are serious opportunistic infections, caused by pathogens to which immunosuppressed patients are especially vulnerable. The validity of an algorithm to identify serious infections was evaluated in 223 patients with a serious infection of any type in the Sentinel Distributed Database.[aa] Specific infections were bacteremia, pneumonia, skin/soft tissue infection, gastrointestinal infection, acute osteomyelitis, acute pyelonephritis, and acute meningitis. After weighting by the prevalence of the types of infection, authors found an overall PPV of 80.2% (95% CI = 75.3%-84.7%) using an ICD-10-CM based algorithm. Specific infection PPVs ranged from 68.6% (95% CI = 50.7%-83.1%) for acute pyelonephritis to 84.1% (95% CI = 74.8%-91.0%) for bacteremia. A systematic review of the validity of serious infection diagnostic codes in healthcare claims data found mixed results for the performance of case definition algorithms across 24 studies.[bb]

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[y] Epstein MM, Dutcher SK, Maro JC, et al. Validation of an electronic algorithm for Hodgkin and non-Hodgkin lymphoma in ICD-10-CM. Pharmacoepidemiol Drug Saf 2021;30:910-7.

[z] Index date was the first lymphoma diagnosis code where the patient was enrolled in the health plan with medical and drug coverage for 365 days prior and had no lymphoma-specific diagnosis codes in the pre-index period.

[aa] Lo Re V, 3rd, Carbonari DM, Jacob J, et al. Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies. Pharmacoepidemiol Drug Saf 2021;30:899-909.

[bb] Barber, C, D Lacaille, PR Fortin, 2013, Systematic Review of Validation Studies of the Use of Administrative Data
to Identify Serious Infections, Arthritis Care Res, 65:1343-1357.

4.2 Is ARIA sufficient to assess the outcome of interest?

ARIA is not sufficient, based on the proposed PMR language to fully ascertain and centrally verify outcomes because ARIA does not include chart review or other forms of adjudication. This applies to all outcomes, including malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections. For study outcomes with low incidence (such as malignancies in the psoriasis patient population), recent FDA Guidance for Real-World Data (e.g., Sentinel) stressed the importance of identifying outcomes with both high specificity and high sensitivity.[cc] Adequate verification of adverse events typically requires standardized clinical review of primary patient records stored in paper or electronic medical records systems. An example of verification is an electronic healthcare data source linked to a suitable cancer registry to accurately identify patients with a newly recognized malignancy. Currently, ARIA does not include (1) clinical review of primary patient records for outcome verification and (2) Sentinel linkage to population-based cancer registries. In the regulatory context presented by bimekizumab (BLA 761151), sufficient postmarket assessment of ultra-rare and heterogenous outcomes (such as lymphoma) requires access to primary patient records for detailed characterization and accurate classification. Poor patient retention in claims data, including Sentinel, also limits the usefulness of ARIA for long latency outcomes (such as malignancy, described further in Section 4.2.1).

To address the regulatory purpose presented by bimekizumab for psoriasis, ARIA is insufficient in the outcomes domain. Sufficiency requires particularly rigorous methods for ascertaining and characterizing the outcomes of concern (malignancy, serious infections, opportunistic infections, reactivation of hepatitis B, and tuberculosis). Further outcome specific ARIA considerations are described in subsequent subsections.

4.2.1 Malignancy

Based on the findings and recommendations from the Workgroup (as described above in Section 4.1.1), ARIA is more capable of identifying lymphoma as an outcome compared to grouping all malignancies together when studying safety in the postmarket setting among bimekizumab users. However, ARIA is not sufficient to fully ascertain and centrally verify lymphomas or malignancies.

In addition to the limitation of validating overall malignancy outcomes of any type (i.e., variable PPV), long-term follow-up in Sentinel may not be sufficient. As described in Table 1 below, roughly 3.1%, 6.6%, and 9.5% of the Sentinel patient population in age groups, 18-30, 31-64, and 65+ years, respectively would have at least 8 years of follow-up, as is required for the proposed PMR observational study for bimekizumab (see Section 7).

[cc] Food and Drug Administration, September 2021, Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance for Industry, accessed at https://www.fda.gov/media/152503/download on February 1, 2022, p19.

Table 1. Proportion of Patients with Follow-Up Time for Patients Diagnosed with Psoriasis in the Sentinel Distributed Database[dd]

Age Group (Years)	Percentage of Patients by Years of Follow-Up Time						
	<3	3+	4+	5+	6+	7+	8+
18-30	75.0%	25.0%	16.7%	11.2%	7.4%	4.9%	3.1%
31-64	66.1%	33.9%	24.6%	18.1%	13.2%	9.7%	6.6%
65+	56.9%	43.1%	32.8%	24.8%	18.6%	13.7%	9.5%

Note: Table 1 includes data from 16 individual data partners. The start and end dates for data collection from these partners range from as early as January 1, 2000, through March 31, 2017.

4.2.2 Opportunistic Infections and Serious Infections

ARIA is more capable of assessing serious infections broadly defined than it is for assessing serious opportunistic infections specifically as the results vary by type of infection.[ee] Accordingly, an association with one specific type of serious or opportunistic infection could be missed. ARIA would be of uncertain utility for assessing hepatitis B reactivation and tuberculosis due to an absence of well validated algorithms in claims data. ARIA is not sufficient to fully ascertain and centrally verify serious infections, opportunistic infections, tuberculosis, or hepatitis B reactivation.

4.2.3 Other Adverse Events

ARIA is capable of assessing the other adverse events of special interest including hypersensitivity, gastrointestinal events (including inflammatory bowel disease), and hematologic events. However, complete capture of Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death) requires a method for identifying cardiovascular, and sudden deaths that occur in settings outside the healthcare system and ARIA's capabilities currently do not capture these deaths.[ff] Although non-fatal myocardial infarctions and strokes maybe captured by ARIA, sufficient assessment of MACE as a composite requires a uniform approach that assesses each of the MACE components with comparable rigor.

ARIA has been previously determined by DEPI to be incapable of assessing gastrointestinal events that involve elevated liver enzymes/drug-induced liver injury.[gg] DEPI determined that access to laboratory data (either directly or indirectly through chart review) is a necessary condition for sufficient assessment of DILI risk.[hh]

[dd] Source: Michael D. Nguyen, MD. FDA Sentinel Program Lead. Modular Program Report (cder_mpl1p_wp006_nsdp_v01). https://sentinelinitiative.org/studies/drugs/individual-drug-queries/length-follow-time-new-users-immunosuppressive-drugs. Accessed February 14, 2022.

[ee] See footnote r and footnote s.

[ff] Weissfeld JL, Zhang M, and Sandhu SK. Division of Epidemiology I, ARIA Sufficiency Memorandum for Cibinqo (abrocitinib). U.S. Food and Drug Administration, Silver Spring (MD). Submitted to NDA 213871 (S-002) , DARRTS Reference ID: 4919286.

[gg] Weissfeld JL, Booth B, and Sandhu SK. Division of Epidemiology I, ARIA Sufficiency Memorandum for Skyrizi (risankizumab-rzaa). U.S. Food and Drug Administration, Silver Spring (MD). Submitted to BLAs 761262 & 761105 (S-016), DARRTS Reference ID: 4998707.

[hh] Ibid.

ARIA's Sentinel Common Data Model (SCDM) captures laboratory data in a Laboratory Result data table.[ii] Minimum requirements for initial screening include complete outpatient laboratory values for alanine transferase (ALT) and alkaline phosphatase (ALP),[jj] both of which are included in the SCDM. However, Sentinel Data Partners populate the Laboratory Result data table for a subset of individuals, and completeness of laboratory data for these individuals is unknown.

Sentinel permits access to medical charts for retrieval of missing patient information (e.g., laboratory data). However, medical chart review is not considered part of the ARIA system.

5. COVARIATES

5.1 Covariates of Interest

The covariates of interest that may confound the association between bimekizumab and the safety outcomes of interest include demographic (e.g., age, sex, calendar year, and geographic region), lifestyle (e.g., smoking status, alcohol use), medical history (e.g., family history of malignancy), and clinical (e.g., comorbidities and concomitant medications) characteristics.

Specific covariates of interest that may confound the observed association are noted below:

- Malignancy: history of malignancy, family history of malignancy, BMI, and smoking status
- Lymphoma: infection with HIV, and hepatitis C
- Infections: history of infection

5.2 Is ARIA sufficient to assess the covariates of interest?

Demographic and certain clinical characteristics could be assessed in ARIA. Additional characteristics such as smoking or personal or family history of cancer may not be obtained reliably. Duration and severity of psoriasis also may not be available in claims data. However, covariate information would be important for subsequent study analyses that assess risk factors for adverse outcomes and for assessing systematic differences when comparing incidence rates between bimekizumab users and other biologics users. Therefore, covariate information not available through ARIA is not critical for the regulatory purpose of signal detection (malignancy, reactivation of hepatitis B, and tuberculosis). Covariate information not available through ARIA may be needed for the regulatory purpose of signal refinement (serious and opportunistic infections).

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The regulatory goal of ARIA for this assessment is signal detection (i.e., postmarketing surveillance) for malignancy, reactivation of hepatitis B, tuberculosis, serious and opportunistic infections as well as other adverse events of special interest. As such, the study design involves identifying the incidence of malignancies, opportunistic infections, serious infections, reactivation of hepatitis B, tuberculosis and the other adverse events of special interest in patients exposed to bimekizumab. The incidence of these outcomes is to be

[ii] See, Sentinel, SCDM: Laboratory Result Table Structure, accessed at https://dev.sentinelsystem.org/projects/SCDM/repos/sentinel_common_data_model/browse/files/file2610_clinical_lab_result.md on October 03, 2023.

[jj] Cheetham TC, Lee J, Hunt CM, et al. An automated causality assessment algorithm to detect drug-induced liver injury in electronic medical record data. Pharmacoepidemiol Drug Saf. 2014;23(6):601-608.

compared against reference rates from patients treated with other chronic systemic treatments for moderate-to-severe plaque psoriasis.

The analytic tools to conduct a surveillance study, including the potential for an inferential assessment, are available through ARIA.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The analytic tools in ARIA are not a major limiting factor to feasibility and ARIA offers the tools needed to both describe the incidence of the adverse outcomes of interest (malignancies, lymphoma, serious infections, opportunistic infections, reactivation of hepatitis B, tuberculosis as well as other adverse events of special interest including inflammatory bowel disease, elevated liver enzymes/drug-induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death) and can possibly conduct an inferential assessment comparing incidence rates to other psoriasis biologic medications and non-biologic systemic medications.

7. NEXT STEPS

A virtual signal assessment meeting was held on January 18, 2022, to determine ARIA's sufficiency with respect to outcomes related to immunosuppression (malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections) from bimekizumab. DEPI, DDD, and the Sentinel Core Team agreed that ARIA is not sufficient to identify the risk of malignancy (including lymphoma), opportunistic infections, reactivation of hepatitis B, tuberculosis, serious infections and other adverse events of special interest including inflammatory bowel disease, elevated liver enzymes/drug-induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death associated with bimekizumab treatment in psoriasis patients. Outcome assessment is the principal factor limiting ARIA.

ARIA was deemed insufficient for studying immunosuppression related outcomes among bimekizumab users due to the inability of ARIA to fully ascertain and centrally validate outcomes. ARIA is further limited for malignancy outcomes by short length of follow-up in Sentinel and variable validation characteristics and sensitivity by malignancy type. ARIA was also deemed insufficient for studying specific opportunistic infections such as tuberculosis and serious infections such as reactivation of hepatitis B. Specific infections may not be well captured in claims data in addition ARIA is insufficient for fully ascertaining and centrally validating the other adverse events of special interest. Contingent on approval, the FDA will issue a PMR to the Sponsor to evaluate malignancy (including lymphoma), opportunistic infections, reactivation of Hepatitis B, tuberculosis, serious infections and other adverse events of special interest including 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 following bimekizumab exposure.

The PMR language for bimekizumab is modeled after the PMR language of previously approved JAK inhibitors (tofacitinib, abrocitinib and baricitinib), which have a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. The primary outcomes listed in the proposed PMR language are considered to be related to a similar mechanism (patients immunocompromised due to treatment). The proposed PMR language is as follows:

"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 adverse events of special interest 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 of special interest 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 follow each patient for at least 8 years from time of enrollment."

The finalized PMR language will be issued upon approval.

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/

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Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research | Office of Surveillance and Epidemiology (OSE)
Epidemiology: ARIA Sufficiency Memo

Date:	October 17, 2023
Reviewer:	Sally Peprah, PhD, MSPH Division of Epidemiology I
Team Leader:	Benjamin J. Booth, PhD, MS Division of Epidemiology I
Deputy Division Director:	Wei Hua, MD, PhD, MHS, MS Division of Epidemiology I
Subject:	Active Risk Identification Assessment (ARIA) Sufficiency Memo: Risk of immunosuppression-related adverse outcomes associated with bimekizumab treatment in psoriasis patients
Drug Name(s):	Bimekizumab
Application Type/Number:	BLA 761151
Applicant/sponsor:	UCB, Inc.
OSE RCM #:	2020-1495

EXECUTIVE SUMMARY

Memo type	Malignancy	Opportunistic Infections	Reactivation of Hepatitis B	Tuberculosis	Serious Infections	Other Adverse Events*
-Initial						
-Interim						
-Final	X	X	X	X	X	X
Source of safety concern						
-Peri-approval	X	X	X	X	X	X
-Post-approval						
Is ARIA sufficient to help characterize the safety concern?						
-Yes						
-No	X	X	X	X	X	X
If "No", please identify the area(s) of concern.						
-Surveillance or Study Population						
-Exposure						
-Outcome(s) of Interest	X	X	X	X	X	X
-Covariate(s) of Interest						
-Surveillance Design/Analytic Tools						

*** Other adverse events of special interest 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**

1. BACKGROUND INFORMATION

1.1. Medical Product

Bimzelx (bimekizumab) injection, for subcutaneous use, is proposed for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.[a] Bimekizumab is a humanized immunoglobulin IgG1/κ monoclonal antibody, with two identical antigen binding regions that selectively bind to human interleukin 17A (IL-17A), interleukin 17F (IL-17F), and interleukin 17-AF cytokines, and inhibits their interaction with the IL-17RA/IL-17RC receptor complex. IL-17A and IL-17F are naturally occurring cytokines that are involved in normal inflammatory and immune responses. Levels of IL-17A and IL-17F are elevated in several immune mediated inflammatory diseases and drive chronic inflammation and damage across multiple tissues. Bimekizumab inhibits the release of proinflammatory cytokines.[b] The proposed recommended dosage is 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.[c]

1.2. Describe the Safety Concern

Bimekizumab poses theoretical risks for malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections based on its immunosuppressive mechanism of action. Further, elevated rates of infections were observed in psoriasis patients treated with bimekizumab compared to psoriasis patients not treated with bimekizumab in a clinical setting.[c]

1.2.1. Malignancy

A theoretical increased risk for malignancies exists based on the immunosuppressive mechanism of action of bimekizumab. However, 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).[c]

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.[c] Some literature suggests that IL-17 may have a role in tumor formation, tumor proliferation, metastasis and chemoresistance;[d,e] 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

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[a] UCB, Inc. Proposed labeling for BLA 761151, submitted July 16, 2020.

[b] Ibid.

[c] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: February 17, 2021.

[d] Yang B, Kang H, Fung A, Zhao H, Wang T, Ma D. The role of interleukin 17 in tumour proliferation, angiogenesis, and metastasis. Mediators of inflammation. 2014 Oct;2014.

[e] Zhao J, Chen X, Herjan T, Li X. The role of interleukin-17 in tumor development and progression. Journal of Experimental Medicine. 2019 Nov 14;217(1):e20190297.

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 cynomolgus monkeys at doses up to 200 mg/kg for 26 weeks followed by a 21-week post-dosing observational period.

The proposed product labeling does not include any warnings or precautions related to potential malignancy risk.

1.2.2. Opportunistic Infections and Serious Infections

Increased susceptibility to infections is regarded as a class effect of psoriasis biologics due to their immunosuppressant effects and is a labeled risk for the class. 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).[f] In addition, serious infections were reported in 1.5% of subjects treated with bimekizumab (EAIR 1.6/100 subject-years). During the development program, opportunistic infections were primarily mucocutaneous fungal infections.[g]

The proposed product labeling includes warnings and precautions for infections:[h]

> Bimekizumab may increase the risk of infections. In clinical studies in patients with plaque psoriasis, infections occurred in 36% of the bimekizumab group compared to 23% of the placebo group through 16 weeks of treatment. Upper respiratory tract infections, oral candidiasis gastroenteritis, tinea pedis, and oral herpes occurred more frequently in the bimekizumab group than in the placebo group. Serious infectious occurred in 0.3% of patients treat with bimekizumab and 0% treated with placebo. (b) (4)

1.2.3. Reactivation of Hepatitis B

The sponsor excluded patients with hepatitis B infection (HBsAg and/or anti-HBc positive) from their studies. Therefore, reactivation risk could not be assessed as no data are available.[i] However, the first approved monoclonal antibody directed against IL-17A, secukinumab, has been associated with a significant rate of reactivation. Hepatitis B reactivation is an increasingly recognized form of drug-induced liver injury (DILI; indirect DILI) from immunosuppressant medications. This risk was also evaluated by consultants from the Division of Pharmacovigilance I (DPV) and Division of Epidemiology I (DEPI-I).[j] Based on their analyses, consultants from the DILI team, DPV, and DEPI recommended inclusion of a recommendation for pretreatment evaluation for hepatitis B infection in the labeling for bimekizumab. This recommendation was based on findings from the review of postmarketing case series and guidelines from the American Association for the Study of Liver Diseases and the Joint American Academy of Dermatology and National Psoriasis Foundation. There was

[f] See footnote c.

[g] Ibid.

[h] See footnote a.

[i] See footnote c.

[j] Weintraub J, Booth B. Integrated Safety Review (of Hepatitis B Virus Reactivation with Bimekizumab, Secukinumab, Ixekizumab, and Brodalumab). September 8, 2021. BLA 761151, BLA 125504, BLA 125521, BLA 761032. Silver Spring (MD), U.S. Food and Drug Administration. (DARRTS Reference ID: 4853451).

insufficient evidence in the literature to provide labeling recommendations based on epidemiologic findings alone. Because no data are available regarding the potential risk of hepatitis B reactivation from clinical trials, a recommendation for pretreatment evaluation for hepatitis B will not be included in product labeling at this time. However, hepatitis B reactivation will be included as an outcome of interest in an observational, long-term postmarketing safety study.

1.2.4. Tuberculosis

A theoretical risk of tuberculosis exists for bimekizumab based on its immunosuppressive mechanism of action. However, there was insufficient data from the bimekizumab clinical trials. Although subjects with active tuberculosis were excluded from clinical trials, subjects with latent tuberculosis could be enrolled provided they began prophylactic treatment prior to the beginning of the trial.[k] No subjects developed new onset tuberculosis infection during the clinical trials. A total of 14 subjects with latent tuberculosis were enrolled in the phase 3 trials and received prophylactic treatment for tuberculosis. None of these subjects developed active tuberculosis.

The proposed product labeling includes warnings and precautions for tuberculosis:[l]

> Evaluate patients for tuberculosis infection prior to initiating treatment with bimekizumab. Do not administer bimekizumab to patients with active tuberculosis infection. Initiate treatment of latent tuberculosis prior to administering bimekizumab. Consider anti-tuberculosis therapy prior to initiation of bimekizumab in patients with a past history of latent or active tuberculosis in whom an adequate course of treatment cannot be confirmed. Patients receiving bimekizumab should be monitored closely for signs and symptoms of active tuberculosis during and after treatment. (b) (4)

1.2.5. Other Adverse Events

Hypersensitivity

Hypersensitivity was considered an adverse event of special interest (AESI) in the development program for bimekizumab.[m] In the initial submission, a total of 13/1789 subjects (0.7%, EAIR 0.8/100 subject-years) had treatment emergent adverse events (TEAEs) of urticaria. 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. 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.[n]

Gastrointestinal Events (Including Inflammatory Bowel Disease, Elevated Liver Enzymes/Drug-Induced Liver Injury)

Inflammatory Bowel Disease

[k] See footnote c.

[l] See footnote a.

[m] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: October 10, 2023.

[n] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: October 10, 2023.

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. 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 ulcerative colitis (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 IBD cases (three cases of UC, three cases of Crohn's Disease (CD), and one case of IBD unclassified) in subjects treated with bimekizumab which were adjudicated as "definite IBD" by the IBD-CAC. Based on the clinical narratives and summaries provided by the Applicant, the Division of Gastroenterology (DG) consultant 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."[o]

Elevated Liver Enzymes/Drug-Induced Liver Injury

During the initial BLA review, the review team discovered potential cases of drug-induced liver injury (DILI) associated with treatment with bimekizumab.[p] In addition, the review team identified an imbalance for transaminases > 3x the upper limit of normal (ULN) during the placebo-controlled trials. 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.

Consultants from the Drug-Induced Liver Injury (DILI) team from the Division of Hepatology and Nutrition identified no definite or probable Hy's Law cases but noted two possible cases that the consultants considered to have reasonable alternative diagnoses that were as or more likely than DILI. There were three probable cases of notable bimekizumab liver injury but without jaundice. The DILI consultants concluded that bimekizumab can lead to hepatocellular or mixed liver injury but did not think the risk of severe DILI is high enough to hold up approval if benefit and need are clear for bimekizumab. Nevertheless, the DILI consultants noted that significant DILI may still arise when bimekizumab is given to larger numbers of patients postmarketing, and any labeling should discuss this possibility.[q] 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.

<u>Major Adverse Cardiovascular Events (Myocardial Infarction, Stroke, Cardiovascular Death, and Sudden Death)</u>

In view of the epidemiologic associations between psoriasis and cardiovascular (CV) comorbidities, and the potential association between anti-cytokine therapies used in the

[o] Nayyar A, Altepeter T, Lee J. Division of Gastroenterology, Review and Comment on the Applicant's Evaluation of Adverse Events of Inflammatory Bowel Disease (IBD) and Inclusion of IBD in Section 5 of the Product Labeling, and Comment on SAE of Hepatic Enzyme Increased (liver injury) in One Patient (Subject# PS0008-(b) (6)). Submitted to BLA 761151 (DARRTS Reference ID: 4766223) on March 22, 2021.

[p] BLA 761151 Multi-disciplinary review and evaluation, bimekizumab. Version date: October 10, 2023.

[q] Hayashi PH, Avigan M, Toerner J. Division of Hepatology and Nutrition Consult Review, submitted to BLA 761151 (DARRTS Reference ID: 4838201) on August 09, 2021.

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.

As of the 120- day safety update submitted during review of the initial BLA, adjudicated MACE was reported in 14/1798 subjects (0.8%; EAIR 0.6/100 subject-years). In the safety update provided with the resubmission, adjudicated MACE was 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 was reported in 17/1798 subjects (1.0%; EAIR 0.7/100 subject-years). In the safety update provided with the resubmission, extended MACE was 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. The review conducted by the Division of Cardiology and Nephrology (DCN) did not reveal a clinical concern from the cardiovascular perspective and no labeling language was recommended.[r] DCN concluded that that "all cases (MACE deaths) 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."

Hematologic Events

Reduction in neutrophil counts is a potential pharmacodynamic effect of blockade of IL-17A. 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. 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 the resubmitted safety update, results were comparable to those in the original BLA submission and 120-Day safety update. In the resubmitted data, 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 exposure-adjusted incidence rate, the data did not demonstrate an increased treatment-related risk of neutropenia with longer duration of treatment with bimekizumab.

[r] DeConti S, Southworth MR, Stockbridge N. Division of Cardiology and Nephrology, Cardiovascular safety of bimekizumab. Submitted to BLA 761151 (DARRTS Reference ID: 5156429) on April 12, 2023.

1.3. FDAAA Purpose (per Section 505(o)(3)(B))

	Malignancy	Opportunistic Infection	Reactivation of Hepatitis B	Tuberculosis	Serious Infection	Other Adverse Events*
Assess a known serious risk						
Assess signals of serious risk						
Identify unexpected serious risk when available data indicate potential for serious risk	X	X	X	X	X	

*** Other adverse events of special interest 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**

1.4. Statement of Purpose

This memo reflects the discussions, recommendations, and determinations between Division of Epidemiology I (DEPI-I), the Division of Dermatology and Dentistry (DDD), and CDER's Sentinel Team. Under assessment are the risk for malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, serious infections, and other adverse events of special interest including 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. The team considered whether ARIA was sufficient to detect a safety signal or whether to issue a postmarketing requirement (PMR) for an observational study to collect additional data on long-term safety of bimekizumab treatment.

The purpose of this memo is to describe the determination of ARIA's capabilities to assess risk of malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, serious infections, and other adverse events of special interest when, in some instances, clinical data did not identify a safety signal, but theoretical concerns indicate the potential for a serious risk. The regulatory goal of ARIA in this assessment is signal detection (i.e., postmarketing surveillance) for malignancies, reactivation of hepatitis B, tuberculosis, serious and opportunistic infections as well as other adverse events of special interest including 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. The anticipated regulatory impact is to further characterize the risk of malignancies, opportunistic

infections, reactivation of hepatitis B, tuberculosis, serious infections and the other adverse events of special interest, to inform labeling decisions. Because the events of interest are rare, they may have long-term latency periods (particularly for malignancies), and because multiple products are available for treatment of the underlying disease (plaque psoriasis), the sufficiency determination primarily rests upon the need for a large sample size, the availability of long-term follow-up (particularly for malignancies), the availability of relevant covariates, and on the ensuing market uptake of bimekizumab.

1.5. Effect Size of Interest or Estimated Sample Size Desired

The regulatory goal for evaluating the risk of malignancies, reactivation of hepatitis B, tuberculosis, serious and opportunistic infections as well as the other adverse events of special interest in ARIA is for signal detection (i.e., postmarketing surveillance), rather than a hypothesis-driven study.

2. SURVEILLANCE OR DESIRED STUDY POPULATION

2.1 Population

Bimekizumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. All patients identified as having a psoriasis diagnosis or received a dispensing of a medication indicated exclusively for plaque psoriasis in Sentinel could be considered in the study population for postmarket surveillance. Reference rates could come from a comparator population that includes patients who have received a dispensing of other psoriasis biologics. To evaluate a class-effect (IL-17 antagonists), reference rates could come from a population of patients receiving non-biologic systemic medications for psoriasis.

2.2 Is ARIA sufficient to assess the intended population?

The underlying indication of psoriasis is needed to target this study population, which can be screened for using the ICD-10 code of L40.XX (psoriasis).

Few studies have been published that aimed to validate ICD-10 diagnostic codes for estimating the prevalence of psoriasis. A Swedish, population-based, validation study demonstrated observed positive predictive values (PPV) of ICD-10 codes ranging from 81%-100% with a post-validation prevalence of 1.23% (95% CI = 1.21-1.25) for psoriasis.[s] Another validation study using the Danish National Patient Register observed a PPV of 97.1% (95% CI = 95.5-98.1).[t] To date, no studies have validated the ICD-10 codes for estimating prevalence of psoriasis in a U.S. population. However, several studies in the United States have aimed to validated ICD-9 diagnostic codes for psoriasis. These studies reported PPVs that aligned with the abovementioned study.[uv] Taken together, findings from these studies suggest that

[s] Löfvendahl S, Theander E, Svensson A, et al. Validity of diagnostic codes and prevalence of physician-diagnosed psoriasis and psoriatic arthritis in Southern Sweden – a population-based registry study. Plos One. 2014; 9(5).
[t] Loft ND, Andersen CH, Halling-Overgaard A-S, et al. Validation of psoriasis diagnoses in the Danish National Patient Register. Acta Derm Venereol. 2019; 99:1037-1038.
[u] Asgari MM, Wu JJ, Gelfand JM, et al. Validity of diagnostic codes and prevalence of psoriasis and psoriatic arthritis in a managed care population, 1996-2009. Pharmacoepidemiol Drg Saf. 2013; 22(8):842-849.
[v] Icen M, Crowson CS, McEvoy MT, Gabriel SE, Maradit Kremers H. Potential misclassification of patients with psoriasis in electronic databases. J Am Acad Dermatol. 2008; 59:981-985.

performance of the ICD-10 codes (L40.XX) to identify psoriasis patients for surveillance purposes in the United States would be adequate.

ARIA is sufficient to identify the indicated population for this analysis and is not a limiting factor of concern.

EXPOSURES

3.1 Treatment Exposure(s)

Patients with pharmacy benefits who receive at least one dispensing of bimekizumab can be identified in health care claims data.

3.2 Comparator Exposure(s)

The regulatory goal of this ARIA assessment is signal detection. However, to help interpret the observed incidence rates of malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections among psoriasis patients treated with bimekizumab, reference rates from two comparator populations may be used: 1) patients using other psoriasis biologic medications and 2) patients using non-biologic systemic medications (to establish a class-effect). Both comparator populations could be identified through the Sentinel health care claims data.

3.3 Is ARIA sufficient to identify the exposure of interest?

ARIA is sufficient to identify dispensing of both bimekizumab and comparator biologics and non-biologic systemic medications through corresponding National Drug Codes (NDCs) and Healthcare Common Procedure Coding System (HCPCS) codes, and therefore is not a limiting factor. However, with several treatment options available to patients, market uptake of bimekizumab will affect whether enough users are available to further characterize risk of rare outcomes. The extent of market uptake can only be evaluated post-approval.

4. OUTCOME(S)

4.1 Outcomes of Interest

4.1.1 Malignancy

Malignancy outcomes include: 1) lymphoma and 2) all malignancies.
A workgroup[w] supporting Mini-Sentinel development reviewed the literature to identify algorithms that could be used in electronic claims-based data to identify cohorts of vulnerable groups, including persons with selected cancers of interest.

The Workgroup cautioned that:

> "Cancers are not typically studied as a homogenous group, given differences in the histological type and primary site of lesion – each that often has its distinct risk factors, screening requirements, pathology, clinical manifestations, diagnostic testing, differential diagnoses, staging, treatment and prognosis, as examples. Therefore, studies examining algorithms for identifying persons with any-type of cancer are scant."[x]

[w] Leonard C, Freeman C, Razzaghi H, et al. Mini-Sentinel methods: 15 cohorts of interest for surveillance preparedness. https://www.sentinelinitiative.org/sites/default/files/Methods/Mini-Sentinel_Methods_15-Cohorts-of-Interest-for-Surveillance-Preparedness_0.pdf. Accessed March 1, 2021.
[x] Ibid.

Thus, in the absence of cancer registry data, the Workgroup recommended against studying cohorts with an outcome of any cancer, but rather focusing on subcohorts with specific cancers. The Workgroup recommended that primary consideration should be given to the identification of persons with hematopoietic cancers such as leukemias, lymphomas, and myelomas.

As part of the Workgroup's deliverable, the Workgroup specified an algorithm for lymphoma that involved: two or more diagnoses of cancer (ICD-9 codes) within two months (algorithm 2); this algorithm performed with a PPV of 63% and a sensitivity of 80%. Another validation study for lymphoma was conducted among four Sentinel data partners using ICD-10-CM codes.[y] Their three component algorithm required: two diagnosis codes for Non-Hodgkin lymphoma and/or Hodgkin lymphoma on different dates within a 183-day window, at least one procedure code indicating a relevant diagnostic procedure (e.g., biopsy, flow cytometry) within 90 days before or after the first lymphoma diagnostic code, and at least one procedure code indicating a relevant imaging study within 90 days before or after the index date.[z] The study found an overall lymphoma (Hodgkin and non-Hodgkin combined) PPV of 77% (95% CI = 69%-84%).

4.1.2 Opportunistic Infections and Serious Infections

Opportunistic and serious infections outcomes include: 1) opportunistic infections broadly defined, 2) serious infections broadly defined, 3) reactivation of hepatitis B, and 4) tuberculosis.

Serious infection is defined as an infection that is a serious adverse event; an operational definition for the purpose of this ARIA assessment is an infection that requires hospitalization. A subset of serious infections are serious opportunistic infections, caused by pathogens to which immunosuppressed patients are especially vulnerable. The validity of an algorithm to identify serious infections was evaluated in 223 patients with a serious infection of any type in the Sentinel Distributed Database.[aa] Specific infections were bacteremia, pneumonia, skin/soft tissue infection, gastrointestinal infection, acute osteomyelitis, acute pyelonephritis, and acute meningitis. After weighting by the prevalence of the types of infection, authors found an overall PPV of 80.2% (95% CI = 75.3%-84.7%) using an ICD-10-CM based algorithm. Specific infection PPVs ranged from 68.6% (95% CI = 50.7%-83.1%) for acute pyelonephritis to 84.1% (95% CI = 74.8%-91.0%) for bacteremia. A systematic review of the validity of serious infection diagnostic codes in healthcare claims data found mixed results for the performance of case definition algorithms across 24 studies.[bb]

4.2 Is ARIA sufficient to assess the outcome of interest?

[y] Epstein MM, Dutcher SK, Maro JC, et al. Validation of an electronic algorithm for Hodgkin and non-Hodgkin lymphoma in ICD-10-CM. Pharmacoepidemiol Drug Saf 2021;30:910-7.

[z] Index date was the first lymphoma diagnosis code where the patient was enrolled in the health plan with medical and drug coverage for 365 days prior and had no lymphoma-specific diagnosis codes in the pre-index period.

[aa] Lo Re V, 3rd, Carbonari DM, Jacob J, et al. Validity of ICD-10-CM diagnoses to identify hospitalizations for serious infections among patients treated with biologic therapies. Pharmacoepidemiol Drug Saf 2021;30:899-909.

[bb] Barber, C, D Lacaille, PR Fortin, 2013, Systematic Review of Validation Studies of the Use of Administrative Data
to Identify Serious Infections, Arthritis Care Res, 65:1343-1357.

ARIA is not sufficient, based on the proposed PMR language to fully ascertain and centrally verify outcomes because ARIA does not include chart review or other forms of adjudication. This applies to all outcomes, including malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections. For study outcomes with low incidence (such as malignancies in the psoriasis patient population), recent FDA Guidance for Real-World Data (e.g., Sentinel) stressed the importance of identifying outcomes with both high specificity and high sensitivity.[cc] Adequate verification of adverse events typically requires standardized clinical review of primary patient records stored in paper or electronic medical records systems. An example of verification is an electronic healthcare data source linked to a suitable cancer registry to accurately identify patients with a newly recognized malignancy. Currently, ARIA does not include (1) clinical review of primary patient records for outcome verification and (2) Sentinel linkage to population-based cancer registries. In the regulatory context presented by bimekizumab (BLA 761151), sufficient postmarket assessment of ultra-rare and heterogenous outcomes (such as lymphoma) requires access to primary patient records for detailed characterization and accurate classification. Poor patient retention in claims data, including Sentinel, also limits the usefulness of ARIA for long latency outcomes (such as malignancy, described further in Section 4.2.1).

To address the regulatory purpose presented by bimekizumab for psoriasis, ARIA is insufficient in the outcomes domain. Sufficiency requires particularly rigorous methods for ascertaining and characterizing the outcomes of concern (malignancy, serious infections, opportunistic infections, reactivation of hepatitis B, and tuberculosis). Further outcome specific ARIA considerations are described in subsequent subsections.

4.2.1 Malignancy

Based on the findings and recommendations from the Workgroup (as described above in Section 4.1.1), ARIA is more capable of identifying lymphoma as an outcome compared to grouping all malignancies together when studying safety in the postmarket setting among bimekizumab users. However, ARIA is not sufficient to fully ascertain and centrally verify lymphomas or malignancies.

In addition to the limitation of validating overall malignancy outcomes of any type (i.e., variable PPV), long-term follow-up in Sentinel may not be sufficient. As described in Table 1 below, roughly 3.1%, 6.6%, and 9.5% of the Sentinel patient population in age groups, 18-30, 31-64, and 65+ years, respectively would have at least 8 years of follow-up, as is required for the proposed PMR observational study for bimekizumab (see Section 7).

[cc] Food and Drug Administration, September 2021, Real-World Data: Assessing Electronic Health Records and Medical Claims Data to Support Regulatory Decision-Making for Drug and Biological Products, Draft Guidance for Industry, accessed at https://www.fda.gov/media/152503/download on February 1, 2022, p19.

Table 1. Proportion of Patients with Follow-Up Time for Patients Diagnosed with Psoriasis in the Sentinel Distributed Database[dd]

Age Group (Years)	Percentage of Patients by Years of Follow-Up Time						
	<3	3+	4+	5+	6+	7+	8+
18-30	75.0%	25.0%	16.7%	11.2%	7.4%	4.9%	3.1%
31-64	66.1%	33.9%	24.6%	18.1%	13.2%	9.7%	6.6%
65+	56.9%	43.1%	32.8%	24.8%	18.6%	13.7%	9.5%

Note: Table 1 includes data from 16 individual data partners. The start and end dates for data collection from these partners range from as early as January 1, 2000, through March 31, 2017.

4.2.2 Opportunistic Infections and Serious Infections

ARIA is more capable of assessing serious infections broadly defined than it is for assessing serious opportunistic infections specifically as the results vary by type of infection.[ee] Accordingly, an association with one specific type of serious or opportunistic infection could be missed. ARIA would be of uncertain utility for assessing hepatitis B reactivation and tuberculosis due to an absence of well validated algorithms in claims data. ARIA is not sufficient to fully ascertain and centrally verify serious infections, opportunistic infections, tuberculosis, or hepatitis B reactivation.

4.2.3 Other Adverse Events

ARIA is capable of assessing the other adverse events of special interest including hypersensitivity, gastrointestinal events (including inflammatory bowel disease), and hematologic events. However, complete capture of Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death) requires a method for identifying cardiovascular, and sudden deaths that occur in settings outside the healthcare system and ARIA's capabilities currently do not capture these deaths.[ff] Although non-fatal myocardial infarctions and strokes maybe captured by ARIA, sufficient assessment of MACE as a composite requires a uniform approach that assesses each of the MACE components with comparable rigor.

ARIA has been previously determined by DEPI to be incapable of assessing gastrointestinal events that involve elevated liver enzymes/drug-induced liver injury.[gg] DEPI determined that access to laboratory data (either directly or indirectly through chart review) is a necessary condition for sufficient assessment of DILI risk.[hh]

[dd] Source: Michael D. Nguyen, MD. FDA Sentinel Program Lead. Modular Program Report (cder_mpl1p_wp006_nsdp_v01). https://sentinelinitiative.org/studies/drugs/individual-drug-queries/length-follow-time-new-users-immunosuppressive-drugs. Accessed February 14, 2022.

[ee] See footnote r and footnote s.

[ff] Weissfeld JL, Zhang M, and Sandhu SK. Division of Epidemiology I, ARIA Sufficiency Memorandum for Cibinqo (abrocitinib). U.S. Food and Drug Administration, Silver Spring (MD). Submitted to NDA 213871 (S-002) , DARRTS Reference ID: 4919286.

[gg] Weissfeld JL, Booth B, and Sandhu SK. Division of Epidemiology I, ARIA Sufficiency Memorandum for Skyrizi (risankizumab-rzaa). U.S. Food and Drug Administration, Silver Spring (MD). Submitted to BLAs 761262 & 761105 (S-016), DARRTS Reference ID: 4998707.

[hh] Ibid.

ARIA's Sentinel Common Data Model (SCDM) captures laboratory data in a Laboratory Result data table.[ii] Minimum requirements for initial screening include complete outpatient laboratory values for alanine transferase (ALT) and alkaline phosphatase (ALP),[jj] both of which are included in the SCDM. However, Sentinel Data Partners populate the Laboratory Result data table for a subset of individuals, and completeness of laboratory data for these individuals is unknown.

Sentinel permits access to medical charts for retrieval of missing patient information (e.g., laboratory data). However, medical chart review is not considered part of the ARIA system.

5. COVARIATES

5.1 Covariates of Interest

The covariates of interest that may confound the association between bimekizumab and the safety outcomes of interest include demographic (e.g., age, sex, calendar year, and geographic region), lifestyle (e.g., smoking status, alcohol use), medical history (e.g., family history of malignancy), and clinical (e.g., comorbidities and concomitant medications) characteristics.

Specific covariates of interest that may confound the observed association are noted below:

- Malignancy: history of malignancy, family history of malignancy, BMI, and smoking status
- Lymphoma: infection with HIV, and hepatitis C
- Infections: history of infection

5.2 Is ARIA sufficient to assess the covariates of interest?

Demographic and certain clinical characteristics could be assessed in ARIA. Additional characteristics such as smoking or personal or family history of cancer may not be obtained reliably. Duration and severity of psoriasis also may not be available in claims data. However, covariate information would be important for subsequent study analyses that assess risk factors for adverse outcomes and for assessing systematic differences when comparing incidence rates between bimekizumab users and other biologics users. Therefore, covariate information not available through ARIA is not critical for the regulatory purpose of signal detection (malignancy, reactivation of hepatitis B, and tuberculosis). Covariate information not available through ARIA may be needed for the regulatory purpose of signal refinement (serious and opportunistic infections).

6. SURVEILLANCE DESIGN / ANALYTIC TOOLS

6.1 Surveillance or Study Design

The regulatory goal of ARIA for this assessment is signal detection (i.e., postmarketing surveillance) for malignancy, reactivation of hepatitis B, tuberculosis, serious and opportunistic infections as well as other adverse events of special interest. As such, the study design involves identifying the incidence of malignancies, opportunistic infections, serious infections, reactivation of hepatitis B, tuberculosis and the other adverse events of special interest in patients exposed to bimekizumab. The incidence of these outcomes is to be

[ii] See, Sentinel, SCDM: Laboratory Result Table Structure, accessed at https://dev.sentinelsystem.org/projects/SCDM/repos/sentinel_common_data_model/browse/files/file2610_clinical_lab_result.md on October 03, 2023.

[jj] Cheetham TC, Lee J, Hunt CM, et al. An automated causality assessment algorithm to detect drug-induced liver injury in electronic medical record data. Pharmacoepidemiol Drug Saf. 2014;23(6):601-608.

compared against reference rates from patients treated with other chronic systemic treatments for moderate-to-severe plaque psoriasis.

The analytic tools to conduct a surveillance study, including the potential for an inferential assessment, are available through ARIA.

6.2 Is ARIA sufficient with respect to the design/analytic tools available to assess the question of interest?

The analytic tools in ARIA are not a major limiting factor to feasibility and ARIA offers the tools needed to both describe the incidence of the adverse outcomes of interest (malignancies, lymphoma, serious infections, opportunistic infections, reactivation of hepatitis B, tuberculosis as well as other adverse events of special interest including inflammatory bowel disease, elevated liver enzymes/drug-induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death) and can possibly conduct an inferential assessment comparing incidence rates to other psoriasis biologic medications and non-biologic systemic medications. However, ARIA is insufficient to conduct a prospective observational study with full ascertainment and central verification of adverse outcomes.

7. NEXT STEPS

A virtual signal assessment meeting was held on January 18, 2022, to determine ARIA's sufficiency with respect to outcomes related to immunosuppression (malignancies, opportunistic infections, reactivation of hepatitis B, tuberculosis, and serious infections) from bimekizumab. DEPI, DDD, and the Sentinel Core Team agreed that ARIA is not sufficient to identify the risk of malignancy (including lymphoma), opportunistic infections, reactivation of hepatitis B, tuberculosis, serious infections and other adverse events of special interest including inflammatory bowel disease, elevated liver enzymes/drug-induced liver injury), Major Adverse Cardiovascular Events (myocardial infarction, stroke, cardiovascular death, and sudden death associated with bimekizumab treatment in psoriasis patients. Outcome assessment is the principal factor limiting ARIA.

ARIA was deemed insufficient for studying immunosuppression related outcomes among bimekizumab users due to the inability of ARIA to fully ascertain and centrally validate outcomes. ARIA is further limited for malignancy outcomes by short length of follow-up in Sentinel and variable validation characteristics and sensitivity by malignancy type. ARIA was also deemed insufficient for studying specific opportunistic infections such as tuberculosis and serious infections such as reactivation of hepatitis B. Specific infections may not be well captured in claims data in addition ARIA is insufficient for fully ascertaining and centrally validating the other adverse events of special interest. Contingent on approval, the FDA will issue a PMR to the Sponsor to evaluate malignancy (including lymphoma), opportunistic infections, reactivation of Hepatitis B, tuberculosis, serious infections and other adverse events of special interest including 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 following bimekizumab exposure.

The PMR language for bimekizumab is modeled after the PMR language of previously approved JAK inhibitors (tofacitinib, abrocitinib and baricitinib), which have a boxed warning for serious infections, mortality, malignancy, major adverse cardiovascular events (MACE), and thrombosis. The primary outcomes listed in the proposed PMR language are considered to be

related to a similar mechanism (patients immunocompromised due to treatment). The proposed PMR language is as follows:

> "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 adverse events of special interest 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 of special interest 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 follow each patient for at least 8 years from time of enrollment."

The finalized PMR language will be issued upon approval.

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/

SALLY A PEPRAH
10/17/2023 12:51:58 PM

BENJAMIN J BOOTH
10/17/2023 01:03:55 PM

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JUDITH W ZANDER
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SARAH K DUTCHER
10/17/2023 02:53:53 PM

ROBERT BALL
10/17/2023 02:55:52 PM

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 29, 2023
To:	Strother Dixon, PharmD Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** David Foss, PharmD **Regulatory Review Officer** **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and Instructions for Use (IFUs)
Drug Name (established name):	BIMZELX (bimekizumab-bkzx)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761151
Applicant:	UCB, Inc.

1 INTRODUCTION

On November 21, 2022, UCB, Inc., submitted for the Agency's review a complete response to the Agency's Complete Response Letter dated May 12, 2022, for Biologics for License Application (BLA) 761151 for BIMZELX (bimekizumab-bkzx) injection. The proposed indication for BIMZELX (bimekizumab-bkzx) is for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to requests by the Division of Dermatology and Dentistry (DDD) on December 29, 2022, for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for BIMZELX (bimekizumab-bkzx), injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU will be forthcoming.

2 MATERIAL REVIEWED

- Draft BIMZELX (bimekizumab-bkzx) injection MG received on November 21, 2022, and July 10, 2023, respectively, and received by DMPP and OPDP on September 18, 2023.
- Draft BIMZELX (bimekizumab-bkzx) injection, single-dose prefilled syringe IFU received on November 21, 2022, and July 10, 2023, respectively, and received by DMPP and OPDP on September 21, 2023.
- Draft BIMZELX (bimekizumab-bkzx) injection, single-dose autoinjector IFU received on November 21, 2022, and July 10, 2023, respectively, and received by DMPP and OPDP on September 21, 2023.
- Draft BIMZELX (bimekizumab-bkzx) injection Prescribing Information (PI) received on November 21, 2022, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 19, 2023.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible
- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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/s/

SUSAN W REDWOOD
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JAMES S DVORSKY
09/29/2023 11:54:55 AM
on behalf of David Foss

BARBARA A FULLER
09/29/2023 11:56:31 AM

LASHAWN M GRIFFITHS
09/29/2023 12:55:07 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 25, 2023

To: Strother Dixon, Regulatory Project Manager, Division of Dermatology and Dentistry (DDD)

Kevin Clark, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Jim Dvorsky, Team Leader, OPDP

Subject: OPDP Labeling Comments for BIMZELX® (bimekizumab-bkzx) injection, for subcutaneous use

BLA: 0761151

Background:
In response to DDD's consult request dated December 29, 2022, OPDP has reviewed the proposed Prescribing Information (PI), Medication Guide/Instructions for Use (IFU), and carton and container labeling for the original BLA submission for Bimzelx.

PI/Medication Guide/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 19, 2023, and our comments are below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed for the proposed Medication Guide/IFU, and comments will be sent under separate cover.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on January 27, 2023, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Center for Drug Evaluation and Research
Office of New Drugs
Division of Pediatrics and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
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M E M O R A N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

John J. Alexander, MD, MPH, Deputy Director
DPMH, ORPURM, OND

To: Division of Dermatology and Dentistry (DDD)
Office of Immunology and Inflammation (OII)

Subject: Feasibility, Ethical Acceptability, and Clinical Utility of Data from Post Marketing Requirement (PMR) to Evaluate Placental Transfer of Bimekizumab in Infants Born to Women Who Received the Drug During Pregnancy.

Applicant: UCB, Inc

Application number: BLA 761151

Drug: Bimekizumab

Drug Class: Psoriasis Agents

Approved Indication: None

Proposed Indication: Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy

Proposed Dosage: 320 mg (given as 2 subcutaneous injections of 160 mg each) at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter.

Route of administration: Subcutaneous Injection

Dosage Form: Solution for injection

Dosage Strengths: 160 mg

Materials Reviewed:

Documents entered in DARRTS

Under BLA761151

- DPMH-Maternal Health Consult Request Form on March 9, 2023
- DPMH-Pediatrics Consult Request Form on May 1, 2023

- Final DPMH PLLR Review Bimekizumab.on February 5, 2021
- Final Addendum DPMH PLLR and PMR Review.on April 26, 2023

Under sBLA 125309

- DPMH PLLR ReviewIlaris(canakinumab).on June 5, 2020

Documents submitted to DocuBridge

Agreed iPSP - Initial Agreement submitted to IND 128707 on July 19, 2018

Consult Request:

DDD consulted the DPMH Pediatrics Team to address the feasibility, ethical acceptability, and clinical utility of data which would be generated from a post marketing requirement (PMR) being proposed by the DPMH Maternal Health Team (MHT) to inform maternal dosing and placental transfer of this biologic if administered during pregnancy.

I. Brief Overview of Interleukin 17 (IL-17) Family Cytokines

The interleukin 17 (IL-17) cytokine family consists of six members; IL-17A (commonly referred to as IL-17), IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25) and IL-17F[1]. The biological function and regulation of IL-17A and IL-17F are better understood than the other four members. IL-17A and IL-17F mediate pro-inflammatory responses, with some differences depending on the type and site of inflammation.The IL-17 family of cytokines mediates biological functions via surface receptors on target cells.[1] IL-17R is expressed in multiple cell lines, including mesothelial cells, epithelial cells, fibroblasts, keratinocytes, and leukocytes. IL-17A and IL-17F play protective roles at epithelial and mucosal barriers in host defense against certain pathogens such as certain bacterial and fungal infections. People with defective IL-17A/F production due to a genetic mutation suffer from high susceptibility to *Staphylococcus aureus*, *Streptococcus pneumoniae* and *Candida albicans* infection, highlighting the role IL-17A and IL-17F play in the immune defense against these pathogens[1].

II. Brief Overview of Monoclonal Antibody Use During Pregnancy

Biologics such as monoclonal antibodies (mAbs) are increasingly being used across therapeutic areas in pregnant individuals to treat a variety of conditions. In these individuals, continuing treatment during pregnancy may be critical to reduce the risk of disease flare and resultant pregnancy complications. Achieving clinical remission is the best predictor of favorable pregnancy outcomes, resulting in an increased use of biologics before conception, during pregnancy and postpartum, with treat-to-target objectives varying for each disease.[2]

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[1] Jin, W. and C. Dong (2013). "IL-17 cytokines in immunity and inflammation." Emerging Microbes & Infections 2(1): 1-5.

[2] Pham-Huy A, Top KA, Constantinescu C, Seow CH, El-Chaâr D. The use and impact of monoclonal antibody biologics during pregnancy. CMAJ. 2021 Jul 26;193(29):E1129-E1136. doi: 10.1503/cmaj.202391. PMID: 34312166; PMCID: PMC8321301.

Most monoclonal antibodies readily cross the placenta, although the extent varies widely among different monoclonal antibodies and the trimester the exposure occurs. This transfer across placenta has led to concerns regarding their use during pregnancy and their impact on the fetus and infant.[2]

Available data are currently limited to inform the extent to which a given biologic crosses the placenta during pregnancy and the risk of in utero exposure to the biologic in the fetus and newborn through the first year of life. Clinical trials for biologics in development historically excluded pregnant individuals or withdrew trial subjects once they become pregnant. Pregnant individuals who were discontinued from the trial were followed for pregnancy outcomes, but these individuals were typically not routinely studied to determine the extent of placental transfer of the biologic. Though the FDA asks pregnancy registries for biologics at approval to follow babies born to individuals receiving these biologics for upto one year for any general safety signals such as hospitalization for serious infections, there has not been a systematic assessment conducted to determine if in utero exposure to the biologic led to adverse functional impacts on the child's developing immunologic system. DPMH-MHT labeling review[3] references the 2020 Joint American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) Guidelines of Care for the Management and Treatment of Psoriasis with Biologics guideline acknowledgement that these data gaps exist; noting "that the safety of other newer biological products (including IL-12, IL-17, and IL-23 inhibitors) during pregnancy and lactation is unknown" and that for IL-17 inhibitors, "there are no studies in human pregnancies and the presence of IL-17 inhibitors in excreted human milk has not been studied."[3]

III. Regulatory Background of Bimekizumab

Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) that binds to IL-17A and IL-17F, and is expressed in a genetically engineered Chinese Hamster Ovary cell line. Therefore, it is an IL-17 A and F antagonist.

UCB, Inc. submitted the first biologic liscense application (BLA) for bimekizumab on July 15, 2020 for which a complete response (CR) was issued on May 12, 2022 due to deficiencies at a manufacturing facility[4]. UCB, Inc. resubmitted the BLA on November 21, 2022. The application is seeking an approval for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. This application is subject to PREA requirements because the product represents a new active ingredient. The BLA includes an Agreed iPSP dated July 19, 2018 in which the Agency agreed to a plan to request a waiver in patients from birth to less than 6 years of age, because studes are impossible or highly impracticable as the disease rarely occurs in this pediatric age range, and to defer the assessment in those 6 years and older until results from adult phase 3 trials and the population

[3] Final DPMH PLLR Review Bimekizumab on February 5, 2021

[4] DPMH-Pediatrics Consult Request Form on May 1, 2023

pharmacokinetic (PopPK) and PopPK pharmacodynamic (PD) analysis were submitted and reviewed.[5]

IV. DPMH Discussion of Consult Request

DDD consulted the DPMH-MHT to assist with compliance with the Pregnancy and Lactation Labling Rule (PLLR). In their consult review, the MHT concluded the following: [6]

- There are no available human data on placental transfer, concentrations at birth in exposed infants, or duration of persistence of bimekizumab in infant serum.
- Placental transfer is presumed based on other monoclonal antibodies.
- Placental transfer varies widely among different monoclonal antibodies and the half-life in adults may not correlate with the half-life in infants.
- The duration of PD effects in prenatally exposed infants may not be easily predicted by what is known in adults.
- Labeling considerations due to lack of bimekizumab data should mirror other monoclonals and recommended a risk assessment prior to giving live vaccines to the exposed infants.

The MHT recommended the following language be added to labeling[6]:

Under Section 8.1: Pregnancy, subsection Clinical considerations,

- Fetal/Neonatal Adverse Reactions
    - Because bimekizumab-bkzx may interfere with immune response to infections, the 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.

Under 8.2 Lactation

- Risk Summary
    - 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.

The Advisory Committee on Immunization Practices (ACIP) recommends administration of the following four live vaccines as part of the routine immunization schedule to the pediatric population in the United States: measles, mumps and rubella (MMR), chickenpox (varicella), rotavirus, and intranasal influenza vaccine[7]. Of the four live vaccines, only the rotavirus vaccine is to be given the first year of life, starting from two months of age. The risk of delaying rotavirus

[5] Agreed iPSP on July 19, 2018

[6] Final Addendum DPMH PLLR and PMR Review.on April 26, 2023

[7] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/prinvac.pdf

vaccination to infants born to pregnant individuals treated with bimekizumab must be balanced with the risk of these infants developing rotavirus infection and associated complications. The first dose of the rotavirus vaccine must be given before 15 weeks of life[8]. Rotavirus infection prior to implementation of routine vaccination caused severe watery diarrhea, fever and vomiting, which led to severe dehydration, hospitalization and even death in some cases[9].

ACIP recommends additional non-routine live vaccines that are to be given in certain circumstances. These live vaccines include adenovirus vaccine (used by the military), typhoid vaccine (Ty21a) and yellow fever (recommended for those travelling to areas endemic for these diseases, and Bacille Calmette-Guerin (BCG)[10] given for the prevention of tuberculosis (TB). BCG, which may be given to infants as young as 28 days old, is not routinely given as a vaccine in the United States[11].

Recommended Routine Live Vaccinations in the US

Timing of Dose								
Vaccine	**Birth**	**1 mos**	**2 mos**	**4 mos**	**6 mos**	**9 mos**	**12 mos**	**15 mos**
Rotavirus (RV)* RV1 (2-dose series); RV5** (3-dose series)			1st dose	2nd dose	3rd dose (RV5)			
MMR							1st dose	
Varicella							1st dose	

Created by Reviewer
*RV – Rotarix approved 2008
** RV5 – RotaTeq Rotavirus Vaccine approved 2006
Note: Intranasal Influenza vaccine is not recommended for patients less than 2 years of age.

The MHT further recommended that DDD consider issuing a PMR under the Food and Drug Administration Amendment Act (FDAAA) (505(o)(3)), for a pregnancy PK and placental transfer study and proposed the following PMR language:

> "Evaluate the clinical pharmacokinetics of bimekizumab in maternal plasma during pregnancy and at delivery, in cord blood at the time of delivery, and post-delivery in

[8] https://www.cdc.gov/vaccines/hcp/vis/vis-statements/rotavirus.html#why-vaccinate

[9] https://www.cdc.gov/vaccines/hcp/vis/vis-statements/rotavirus.html#why-vaccinate

[10] Bacille Calmette-Guerin (BCG) vaccination should only be considered for children who test negative for TB, but are continually exposed and, either can not be separated from adults who are untreated or ineffectively treated for TB or can not be given long-term preventative treatment for TB infection; Are continuously exposed to persons with TB who have bacilli resistant to isoniazid and rifampin; tuberculin-negative infants and children in groups in which the rate of new infections exceeds 1% per year and for whom the usual surveillance and treatment programs have been attempted but are not operationally feasible.

[11] https://www.cdc.gov/vaccines/pubs/pinkbook/downloads/prinvac.pdf

plasma of infants exposed to bimekizumab in utero. These assessments may be conducted as a sub-study of the pregnancy registry."

DDD and the DPMH MHT and DPMH Pediatrics Team met on May 3, 2023, to discuss the utility of issuing this PMR. The following key points were discussed:

- The DPMH MHT discussed the importance of understanding the extent of placental transfer of this biologic at birth to help inform the risk to the fetus and newborn.
- The DPMH Pediatrics Team noted that the clinical significance of the PK data alone, even if collected in infants exposed to bimekizumab in utero as part of a substudy, would not be sufficient to inform the risk to the newborn unless PD measures, based on the mechanism of action of the product, are incorporated in the study to assess the product's impact on the function of the newborn's developing immune system in the first year of life. The DPMH Pediatric Team informed DDD that DPMH had begun having broader discussions with relevant internal subject matter experts to help inform consistent advice across OND on how to conduct these assessments and had also begun planning a public workshop to be held in the Spring of 2024.

DDD expressed their preference to not issue the PMR proposed by the MHT at this time given the lack of a PD component and the uncertainty with what PD measures to incorporate into the study as part of the newborn assessment that would be considered clinically meaningful. DDD agreed that further discussions already initiated by DPMH would be helpful to inform OND's internal policy so consistent advice can be given on how to assess the risk of in utero exposure for individual biologcs in development. Evaluating an investigation in newborns exposed to bimekizumab in utero would be permissible under 21CFR 50.53 as long as the investigation poses no more than a minor risk to the neonate.[12] According to this regulation, interventions or procedures in clinical investigations without prospect of direct benefit that present a minor increase over minimal risk are permissible if children either with or at risk for the disorder or condition are enrolled and not healthy children and the results are likely to yield generalizable knowledge about the disorder. For this program, studying newborns exposed in utero to bimekizumab would be permissible under 21CFR 50.53 if only those babies at risk for immunosuppression would be studied and the results would inform product use across the broader population of pregnant individuals who require bimekizumab treatment.

V. Conclusion

There are no available data to inform the extent to which bimekizumab undergoes placental tranfer during pregnancy, the timeframe over which levels are detectable in the newborn, and the clinical implications of detectable levels in the newborn through the first year of life. Although these data are needed to inform specific labeling recommendations about risks to exposed fetuses, a PK substudy alone in infants exposed to bimekizumab in utero would not be sufficient to generate such data.

[12] Email conversation between DPMH and Dr. Donna Snyder, Office of Pediatric Therapeutics

VI. Recommendation

DPMH recommends DDD not include an infant substudy as part of a PMR for a pregnancy registry at this time. There should be consensus, first, on the most appropriate PD measures to be included in such a study, 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.

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CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT # 11958

Consultant Reviewer:	Jennifer Reid, MD, Clinical Reviewer Bernard Fischer, MD, Deputy Director Division of Psychiatry
Consultation Requestor:	Strother D. Dixon, RPM Kevin Clark, MD, Clinical Reviewer Division of Dermatology and Dentistry
Subject of Request:	BLA 761151 / IND 128707 Bimekizumab subcutaneous injection for psoriasis
Date of Request:	March 9, 2023
Date Received:	March 9, 2023
Desired Completion Date:	April 6, 2023

I. Executive Summary, Conclusions, and Recommendations

The applicant, UCB Inc., has resubmitted a biological licensing application (BLA) for bimekizumab for the indication of treatment of moderate to severe plaque psoriasis in adults. The resubmission is currently under review by the Division of Dermatology and Dentistry (DDD).

During evaluation of the initial submission (July 15, 2020), a consult was completed by the Division of Psychiatry (DP) to review the program's data and provide input on mitigating possible psychiatric adverse effects associated with bimekizumab. The prior DP consult pooled clinical trial data from two phase 2 studies (PS0010 and PS0016) and three randomized, placebo-controlled phase 3 studies (PS0008, PS0009, PS0013) to evaluate psychiatric adverse events (AEs), suicidal ideation and behavior (SI/B), and depression and anxiety. Data available from open-label long-term extension safety studies were analyzed separately (PS0011, PS0018, and the ongoing PS0014). Based on the data evaluated from the Applicant's initial submission, DP did not find a clinically meaningful signal for bimekizumab-associated psychiatric AEs, SI/B, or symptoms of depression and anxiety. DP did not recommend specific psychiatric warning language for bimekizumab's label.

The Applicant has re-submitted the BLA for bimekizumab. The resubmission contains safety data from study PS0015, a phase 3b study comparing bimekizumab to secukinumab followed by open-label bimekizumab, and additional data from study PS0014. There was one completed suicide from a subject with no prior psychiatric history 718 days after starting bimekizumab. There were two ambiguous deaths while subjects were on bimekizumab (one subject died at home alone from unknown cause, one subject was a pedestrian killed in a motor vehicle accident). There were five and nine cases of serious neuropsychiatric AEs in patients exposed to bimekizumab in PS0015 and PS0014, respectively. These cases included worsening PHQ-9 scores and SI/B—although all cases were confounded by past psychiatric history and/or situational stressors. Notably, a re-review of controlled SI/B data collected using the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) found nearly threefold more SI/B in a pooled bimekizumab group compared to pooled placebo (mostly passive wish to be dead, 1.7% versus 0.6%).

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.[1] 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—especially given that another drug affecting IL-17 has a labeled risk of SI/B (i.e., brodalumab). 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.

Based on our review of the bimekizumab resubmission, DP recommends the bimekizumab label reflect a potential association with SI/B. DP does not believe that a risk evaluation and mitigation strategy (REMS) would mitigate the risk beyond what labeling would accomplish. However, we defer to DDD whether the precedent with brodalumab and dermatologists' lack of familiarity with SI/B risk may warrant consideration of a brodalumab-type REMS (which requires education of patients and providers). 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.

We propose the following language for section 5 (with the language for the boxed warning based on this warning):

> **5.X Suicidal Ideation and Behavior**
> Suicidal ideation and behavior, including one completed suicide, occurred in subjects treated with TRADENAME in the psoriasis clinical trials. The completed suicide was not during the placebo-controlled trials. A causal association between treatment with TRADENAME and increased risk of suicidal ideation and behavior has not been established. Prescribers should weigh the potential risks and benefits before using TRADENAME in patients with a history of depression or suicidality. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate. Advise patients and caregivers to seek medical attention for manifestations of suicidal ideation and behavior, new onset or worsening depression, anxiety, or other mood changes. Prescribers should also re-evaluate the risks and benefits of continuing treatment with TRADENAME if such events occur.

We propose the following language for section 6:

> Suicidal Ideation and Behavior
> Based on a pooled analysis of the first 16 weeks of controlled clinical trials, 17 of the 976 subjects in the TRADENAME group (1.7%) endorsed new-onset wish to be dead/suicidal ideation on the Columbia-Suicide Severity Rating Scale compared to 1 of 169 subjects in the placebo group (0.6%).

[1] 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.

During open-label TRADENAME treatment, there was 1 completed suicide in a subject without a past psychiatric history. There were also 3 suicide attempts; 2 of these subjects had a history of prior suicide attempts [see Warnings and Precautions (5.X)].

II. Background

Bimekizumab is a humanized, monoclonal antibody of the immunoglobulin G1 (IgG1) subclass that selectively binds and neutralizes human interleukin-17A (IL-17A) and interleukin-17F (IL-17F). The Applicant, UCB Inc., is developing bimekizumab for the treatment of moderate to severe plaque psoriasis in adults. The Applicant proposes to administer bimekizumab subcutaneously with a dosing regimen of 320 mg every 4 weeks for 16 weeks, followed by a maintenance dose of 320 mg every 8 weeks.

Patients with psoriasis are at a higher risk for depression and suicide than the general public. It is unclear if the higher rate is due to an immune-mediated cause, psychosocial burden of the illness, or a combination of factors. In a population-based cohort study of 8 million people in the United Kingdom, Kurd and colleagues found the excess risk of "suicidality" (defined as a diagnosis of suicidal ideation, suicide attempts, or suicide) in patients with psoriasis to be one case per 2,500 patients.[1]

There has also been concern for increased depression and suicidal behaviors in response to IL-17 mediated treatments. The relationship is unclear, and SI/B risk appears to vary across IL-17 agents, but brodalumab carries a boxed warning for SI/B and has required a risk evaluation and mitigation strategy (REMS) for safe use.

III. Review

A. Trial Descriptions

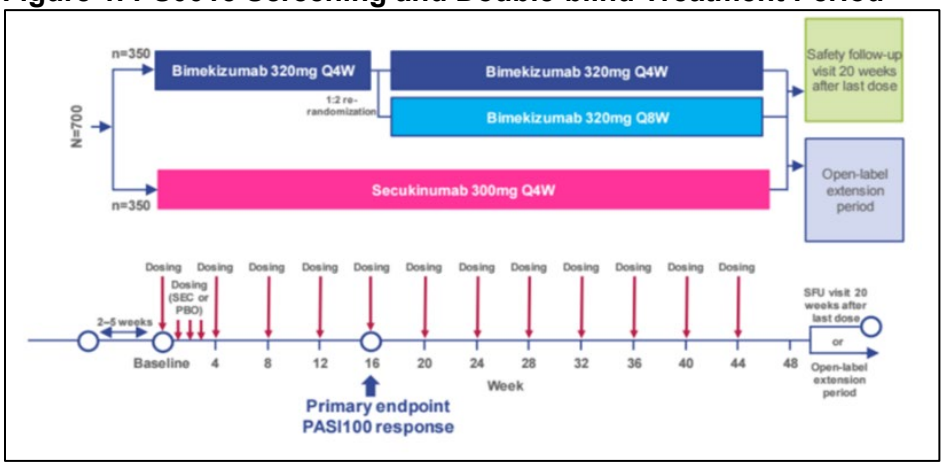
PS0015

An ongoing phase 3b, multicenter, randomized, double-blind, active comparator-controlled, parallel-group study designed to compare the efficacy and safety of bimekizumab to secukinumab in adult subjects with moderate to severe plaque psoriasis. The blinded phase of the study was ongoing at the time of the clinical cutoff dates for the initial submission and the 120-Day Safety Update.

This study consists of a 48-week treatment period, a 96-week open-label extension period, and a 20-week safety follow-up period. In the United States and Canada, an additional 48-week open-label extension treatment period was added during which eligible subjects could continue or re-initiate bimekizumab treatment for 40 weeks followed by a second 20-week safety follow-up period.

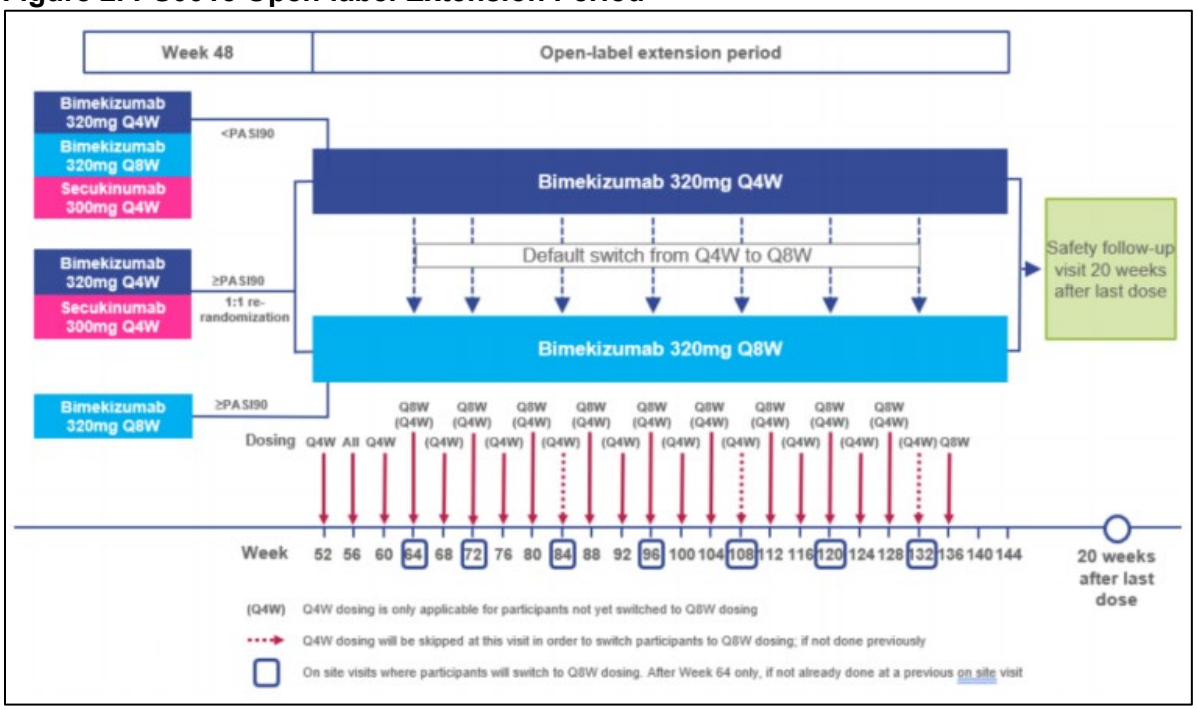
See Figure 1 and Figure 2 for the study design and treatment period details. The second open-label extension period for subjects in the United States and Canada is ongoing and no data from this period are included in the resubmission. Data from 691 individuals was included in the resubmission.

Figure 1. PS0015 Screening and Double-blind Treatment Period



Source: Applicant's safety update resubmission, Figure 1-3.

Figure 2. PS0015 Open-label Extension Period



Source: Applicant's safety update resubmission, Figure 1-4.

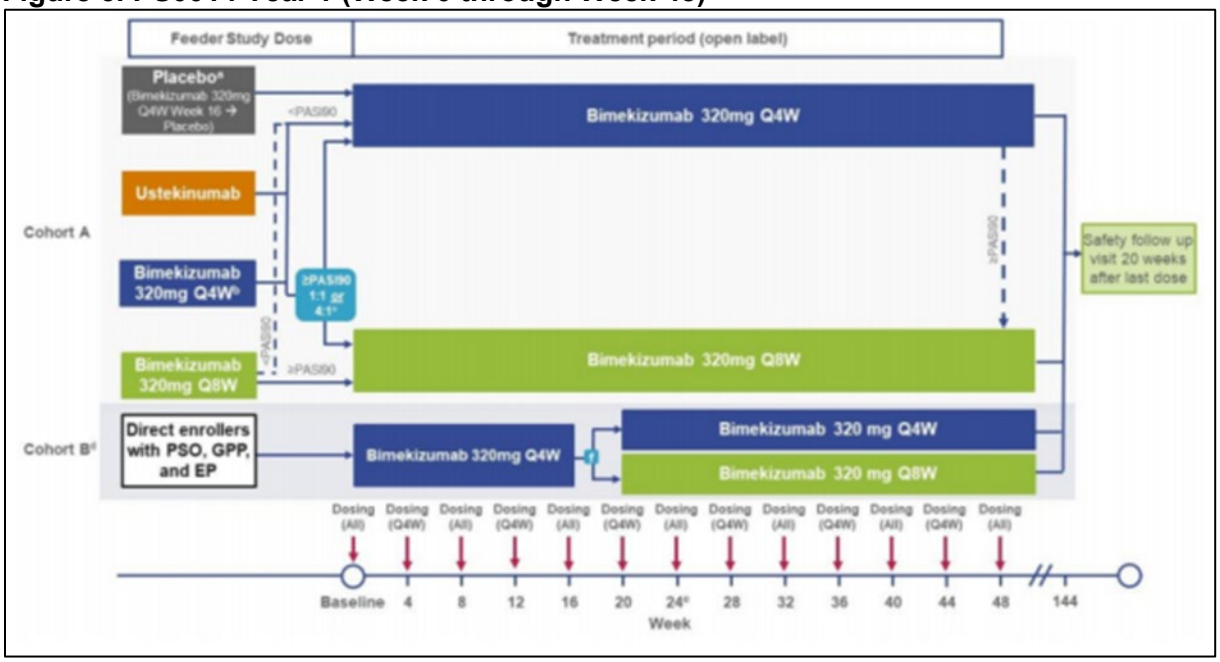
PS0014

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 chronic plaque psoriasis who completed one of the phase 3 feeder studies (PS0008, PS0009, or PS0013). Subjects must have achieved ≥50% improvement from baseline in the Psoriasis Area Severity Index (PASI) score in the feeder study to be eligible. This study also includes an open-label cohort in Japan to allow direct enrollment of subjects with moderate to severe plaque psoriasis, generalized pustular psoriasis, and erythrodermic psoriasis.

The treatment period of this study is 144 weeks followed by a 20-week safety follow-up period. In the United States and Canada, an additional 48-week open-label treatment period was added during which eligible subjects could continue or re-initiate bimekizumab treatment for 40 weeks followed by a second 20-week safety follow-up period.

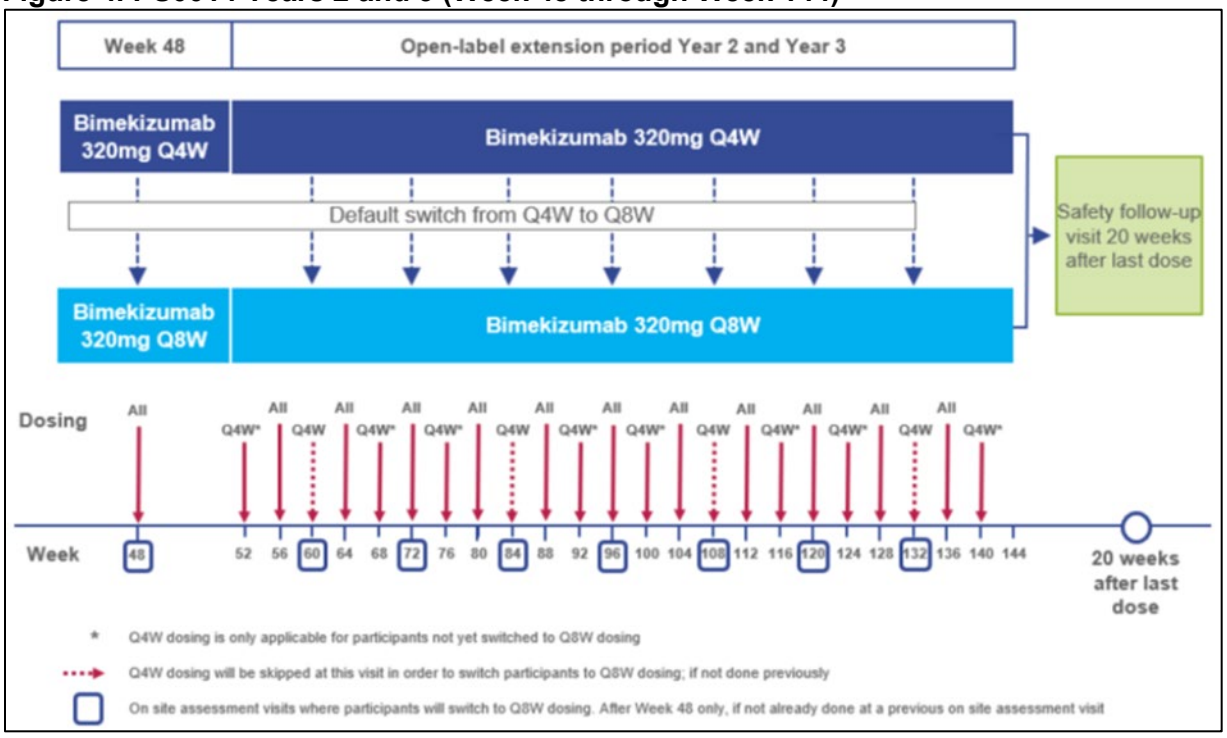
See Figure 3 and Figure 4 for the study design and treatment period details. The second open-label extension period for subjects in the United States and Canada is ongoing and no data from this period are included in the resubmission. Data from 1,353 subjects was included in the resubmission.

Figure 3. PS0014 Year 1 (Week 0 through Week 48)



Source: Applicant's safety update resubmission, Figure 1-1.

Figure 4. PS0014 Years 2 and 3 (Week 48 through Week 144)



Source: Applicant's safety update resubmission, Figure 1-2.

B. Safety Monitoring

The Patient Health Questionnaire (PHQ-9) is a 9-item multipurpose instrument for measuring the severity of depression. The Applicant used the PHQ-9 in studies PS0015 and PS0014. Scores range from 0 to 27 with higher scores indicating a worse state. A score of 5 to 9 indicates minimal symptoms of depression. A score of 10 to 14 indicates minor depression, dysthymia, or mild major depression. A score of 15 to 19 indicates moderately severe major depression and a score ≥20 indicates severe major depression.

The eC-SSRS was used to monitor for suicidal ideation and behavior during the studies.

In both PS0015 and PS0014, subjects were referred to a mental healthcare professional and could be withdrawn from the study based upon the Investigator's judgment of benefit/risk for a "yes" to Question 4 of the "Since Last Visit" version of the eC-SSRS or for a PHQ-9 score of 15 to 19 (if representing an increase of 3 points compared to the previous visit). Subjects were required to be withdrawn from the study for a "yes" to Question 5 of the "Since Last Visit" version of the eC-SSRS, any suicidal behavior since the previous visit, or a PHQ-9 score ≥20.

A Neuropsychiatric Adjudication Committee, composed of three independent adjudicators, provided independent medical review of potential neuropsychiatric adverse events and evaluated elevated PHQ-9 scores and positive eC-SSRS screenings. For adjudication of potential SI/B events, the review was blinded to treatment and utilized pre-specified C-CASA endpoint criteria. Any event that met eC-SSRS, HADS, or PHQ-9 criteria for withdrawal and all fatal treatment-emergent AEs were automatically sent to the Committee for adjudication.

Additionally, programmatically identified AEs were sent to the Committee Chair for review and potential consideration by the entire Committee.

C. Review of Data

Previous DP consult

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 (which focused on the controlled trials) did not recommend SI/B language for the label. However, in the context of a completed suicide, DP conducted a re-review of the data examined in the previous consult.

In a pool of patients from the initial treatment period of the placebo-controlled phase 3 studies, 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, see Table 1). Of these, 17 positive responses were in bimekizumab-treated patients (1.7%) while only 1 was in placebo-treated patients (0.6%). Of the 17 positive responses in bimekizumab-treated patients, only 4 were in patients with a previous psychiatric history.

Table 1. Incidence of SI/B as Measured by the eC-SSRS during an Initial Treatment Period of Studies 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
Source: Reviewer's table.

In a pool of patients from the open-label maintenance period of the phase 3 studies, 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, see Table 2). Of the 16 positive responses in bimekizumab-treated patients, only 2 were in patients with a previous psychiatric history.

Table 2. Incidence of SI/B as Measured by the eC-SSRS during the Maintenance Period of Studies 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: Reviewer's table.

Reviewer Comments: The pooling strategy for this analysis pooled the bimekizumab and placebo arms from Studies PS0008, PS0009, and PS0013. PS0008 included two bimekizumab arms, while PS009 and PS0013 only included one bimekizumab arm. Pooling studies with different randomization ratios can potentially result in differing trends compared to examining the data without pooling (sometimes referred to as Simpson's paradox). However, in the case of rare events (such as SI/B), statistical adjustment for pooling studies with different randomization ratios is generally not required (because it has a very small effect on observed differences). Additionally, I note that Study PS0008 did not include a placebo arm and was not used in pooling for most of the safety data in the DDD bimekizumab review. However, given the designs of all three of these studies was similar (including the population enrolled), the bimekizumab patients from Study PS0008 can be considered exchangeable with the other bimekizumab patients in the pool. In summary, to capture rare events such as SI/B, it is appropriate to include PS0008 in the pooling.

In DP's previous consult, the data comparing bimekizumab to active controls was not examined. In Study PS0008, eight patients randomized to bimekizumab (n=319, 2.6%) reported positive responses to the eC-SSRS (one patient with non-specific active suicidal thoughts, seven with passive wish to be dead) compared to three patients receiving adalimumab (n=159, 1.9%, one patient with non-specific active suicidal thoughts, two with passive wish to be dead). In Study PS0009, three patients randomized to bimekizumab (n=321, 0.9%, all three with passive wish to be dead) and three patients receiving ustekinumab (n=163, 1.8%, one patient with non-specific active suicidal thoughts, two with passive wish to be dead) reported positive responses to the eC-SSRS.

Reviewer Comments: The comparison between bimekizumab and active controls from Studies PS0008 and PS0009 appears mixed. Neither adalimumab nor ustekinumab have a labeled risk of SI/B, but bimekizumab demonstrated numerically increased and decreased eC-SSRS positive responses compared with these controls, respectively. However, a re-review of the data from the previous DP consult shows a three-fold increase in positive eC-SSRS responses in bimekizumab compared to placebo during the controlled portion of Studies PS0008, PS0009, and PS0013. This is despite the fact that both arms had a similar lifetime prevalence of positive eC-SSRS responses during screening (7.5% in the bimekizumab group, 7.1% in the placebo group). Additionally, only 22% of the eC-SSRS positive responses were in patients with a past psychiatric history. During the open-label maintenance periods of these studies, there were

additional positive eC-SSRS responses—the majority of which were also in patients without a prior psychiatric history. In the context of the completed suicide, this data appears to support an association between positive eC-SSRS responses and bimekizumab.

Case of 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) (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, eC-SSRS screenings had been negative, drug screens (including alcohol) had been negative throughout the study, and the subject had achieved complete skin clearance by Week 28. The subject had unspecified "financial issues."

The site Investigator informed the Applicant that they were not contacted regarding the subject's suicide. Rather, after missing a study visit and not responding to multiple phone calls, the site contacted the subject's wife (his emergency contact) who, during a brief phone call, revealed only that the subject committed suicide and that no psychiatric issues were diagnosed. She was not willing to speak further or provide additional details. The Applicant was not able to obtain a death certificate or identify an obituary for this subject. Of note, the study site attempted to ascertain additional information via internet queries and discussions with other study participants. However, these efforts did not yield additional information.

Concomitant Medications

At the time of the suicide, the subject was prescribed pantoprazole, the beta blocker nebivolol and a combination of amlodipine, indapamide, and perindopril. The U.S. prescribing information for pantoprazole includes depression as a psychiatric adverse reaction and hallucination, confusion, and insomnia as postmarketing reports. The U.S. prescribing information for nebivolol includes insomnia as a psychiatric adverse reaction. The U.S. prescribing information for amlodipine includes postmarketing reports of insomnia, depression, and anxiety. The U.S. prescribing information for indapamide includes adverse reactions of insomnia and depression. The U.S. prescribing information for perindopril does not include psychiatric adverse reactions. None of these drugs has a labeled association with SI/B. 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.

Reviewer Comments: 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.*

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 PS0015

See Table 1 for a listing and discussion of psychiatric cases from PS0015.

Table 3. Psychiatric Case Summaries from Study 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 (b) (6) 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)	Poss ble 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: Reviewer-created.

<u>Reviewer Comments:</u> 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 (b) (6) reporting low mood coinciding with starting bimekizumab with the subject ultimately attempting suicide and Subject (b) (6), 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 PS0014

See Table 2 for a listing and discussion of psychiatric cases from PS0014.

Table 4. Psychiatric Case Summaries from Study 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.
(b) (6)	Elevated PHQ-9	60 year-old female. Received BZK (b) (6) until early termination for skin rash (b) (6). At (b) (6) 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 attr bution of increased score to frustration with increased itchiness.
(b) (6)	Elevated PHQ-9	33 year-old male. Received BKZ (b) (6) until early termination for elevated liver enzymes (b) (6). On (b) (6), pt scored 27 on PHQ-9. Pt reported it was due to termination from the study	Unlikely due to having discontinued BKZ several months previously and pt's

		and increased psoriasis symptoms. Previous PHQ-9 scores were 0 to 1. Pt refused mental health referral and was lost to follow-up.	attribution of increased score to increased symptoms of psoriasis.
(b) (6)	Elevated PHQ-9	47 year-old male. Started BKZ (b) (6). PHQ-9 score 20 on (b) (6). BKZ interrupted and pt referred to mental health. Pt reported low mood due to death in the family. Subsequent PHQ-9 (b) (6)) 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.
(b) (6)	Elevated PHQ-9	35 year-old male. On unknown treatment in Study PS0009 (BKZ vs. placebo/ ustekinumab) starting (b) (6), started open-label BKZ (b) (6). Elevated PHQ-9 of 20 on (b) (6) and pt removed from study. Diagnosed with "acclimatization disfunction (depressive)" (similar to DSM diagnosis of adjustment disorder); reported as resolved (b) (6), 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: Reviewer-created.

Reviewer Comments: As with Study PS0015, the above cases do not demonstrate a clear signal of SI/B risk associated with bimekizumab. Again, most case 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.

Cases with Ambiguous Causes of Death

- Subject (b) (6), a 42 year-old white male with no known psychiatric history, was participating in PS0014 at the time of his death. The cause of death was not reported, and it was unknown whether an autopsy was performed. He had lack of contact with family. Per Sponsor assessment, the subject had risk factors for cardiac disease including hypertension and morbid obesity.

  Reviewer Comments: Without further details, there cannot be certainty that this death was non-psychiatric in nature. The case was adjudicated by the Applicant's cardiovascular committee; the cause of death was undetermined. There was no adjudication by the Neuropsychiatric Adjudication Committee.

- Subject (b) (6), a 72-year-old white male with a past psychiatric history of ADHD and depression (taking venlafaxine and mixed amphetamine salts), was participating in PS0015 at the time of his death. He was randomized to bimekizumab. He was a pedestrian in a motor vehicle accident and was pronounced dead at the scene. An autopsy was performed, and the cause of death was reported as multiple blunt force traumatic injuries. The Investigator considered the accident not related. This was reportedly adjudicated as non-suicidal; however, a report from the Neuropsychiatric Adjudication Committee could not be located by the Applicant.

  Reviewer Comments: Without further details, there cannot be certainty that this death was non-psychiatric in nature.

Postmarketing Data from Other Countries

The Applicant reports no signal for completed suicides or suicide attempts from postmarketing data where bimekizumab is currently marketed.

Reviewer Comments: 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.

Risk in Other Conditions

Hidradenitis Suppurativa

The Applicant's phase 2/3 hidradenitis suppurativa program included 1041 subjects with a total time at risk of 1296.8 subject-years. Per the Applicant, there were two suicide attempts, which gives an exposure-adjusted incidence rate of 0.15/100 PY, or 1.5/1000 PY.

Axial Spondyloarthritis and Ankylosing Spondylitis

Per the FDA's Division of Rheumatology and Transplant Medicine (DRTM), interim clinical study reports for ongoing Study AS0010 (non-radiographic axial spondyloarthritis) and Study AS0011 (ankylosing spondylitis), there were no deaths and no subjects reported SI/B. In Study AS0011, during the maintenance period, one subject (0.3%) in the bimekizumab 160 mg weekly group had SI which led to study discontinuation.

Psoriatic Arthritis

Per DRTM, in the two studies for psoriatic arthritis, there is a final clinical study report available for Study PA0011 and an interim study report for Study PA0010. There were no deaths due to suicide and "abnormal eC-SSRS scores indicating suicidality and PHQ-9 scores indicating depression were infrequent and similar across treatment groups."

Reviewer Comments: 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.

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/

BERNARD A FISCHER on behalf of JENNIFER M REID
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BERNARD A FISCHER
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Dr. Reid started extended leave while preparing the consult and primary review completed by Dr. Fischer.

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Division of Gastroenterology Consult Review

Date:	May 2, 2023
To:	Kevin Clark, MD Clinical Reviewer and Melinda McCord, MD, Clinical Team Leader Division of Dermatology and Dentistry (DDD)
From:	Tara Altepeter, MD, Associate Director for Therapeutic Review, Division of Gastroenterology (DG)
Product:	BLA 761151 Bimzelx (bimekizumab)
Indication:	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.
Subject:	Review of additional adjudicated cases of inflammatory bowel disease in the safety update provided with resubmission, recommendations on labeling.

Product Information:

Bimzelx (bimekizumab) is a humanized, monoclonal IgG1 antibody that binds to interleukins (IL) 17A and 17F. IL17 is a proinflammatory cytokine involved in the pathogenesis of psoriasis and other chronic inflammatory conditions.

Regulatory Background:

BLA 761151 was initially submitted on July 15, 2020. Although the Division of Dermatology and Dentistry (DDD) concluded that the clinical safety and efficacy data supported approval, the application received complete response (CR) on May 12, 2022 due to product quality deficiencies that precluded approval [Good Manufacturing Practice (GMP) deficiencies identified during inspection of the UCB Braine Drug Product Manufacturing Facility (FEI: 300399356).

A Class 2 resubmission was received on November 21, 2022 seeking approval for the treatment of adults with moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy.

Previous Consult Request:

DDD previously requested DG's input during the initial review of the BLA. The initial consult focused on independent evaluation of the data from the phase 3 studies in psoriasis to evaluate whether a risk of inflammatory bowel disease was identified. In brief, DG's review of the available data did not identify a clear signal of new onset IBD within the controlled clinical trials for psoriasis. A single case of ulcerative colitis (UC) was identified in one of the trials. However, some patients who exhibited potential signs/symptoms of IBD did not have a complete evaluation documented to fully exclude the possibility. Additionally, very few patients (n=3) were enrolled with pre-existing stable IBD, so data were not available to inform whether or not bimekizumab may contribute to or cause disease flares in stable IBD patients. Based on other available data in the class, which indicate that IL17 inhibitors are associated with a risk of IBD, a Warning was proposed for inclusion in product labeling. For full details, see the prior consult by Dr. Anil Nayyar, dated March 22, 2021.

New Consult Request:

DDD requested DG's assessment of additional adjudicated cases of IBD that were submitted as part of the sponsor's safety update with the resubmission, and recommendations for any suggested edits to the proposed prescribing information.

DG Response:

In this resubmission, the sponsor provided updates to the previously submitted 120 safety update.

The new safety update includes additional accrued data from study PS0014, which was a phase 3, open-label, long term study conducted in patients who completed one of the phase 3 feeder studies (PS008, PS009, PS0013). The population enrolled in this study included those who achieved at least a 50% improvement from baseline in the Psoriasis Area and Severity Index (PASI) score by the designated timepoint in the individual phase 3 trial. PS0014 also included patients treated in an open-label cohort (Cohort B) in Japan, including those with moderate to severe plaque psoriasis, generalized pustular psoriasis, and erythrodermic psoriasis.

In addition, the safety update provides newly unblinded data from study PS0015, a phase 3b, multicenter, randomized, double-blind, active controlled, parallel-group study evaluating the efficacy and safety of bimekizumab compared with secukinumab in adult patients with moderate to severe plaque psoriasis. This study was still blinded at the time of the initial BLA submission and its related 120 day safety update.

IBD Adjudication Committee:

Since the time of the initial submission, an independent inflammatory bowel disease adjudication committee (IBD-CAC) was established across the bimekizumab clinical program.

The charter for the IBD-CAC was reviewed and appears acceptable. The list of terms preferred terms (PT) used to identify potential cases for adjudication is comprehensive. In addition to terms directly related to colitis (such as colitis, hemorrhagic colitis, etc.) and other features of CD (such as enteritis, fistula, anal abscess, etc.) the search also included the occurrence of diarrhea and abdominal pain if they occurred within 7 days of each other, as well as diarrhea reported for duration of ≥42 days. This approach is important to cast a wider net of cases to review that included potential symptoms of IBD, aside from those which had a definitive diagnosis. The Applicant also clarified that after the IBD-CAC was established, data was reviewed retroactively from the previously completed and ongoing studies in psoriasis. Cases that met any of the PTs were reviewed systematically by 3 independent reviewers and a process was outlined to reach consensus when their initial opinions differed. Details are outlined in the IBD Adjudication Charter, Version 3 (submitted in response to IR, received 3/24/23).

DG's Review of Adjudicated Cases:

In response to information request received 3/24/23, the Applicant provided a listing of all cases of adjudicated IBD, determined by the IBD-CAC to be definite IBD, probable IBD, or possible IBD. There were 26 cases across the updated Pool S2-3b, which included phase 2 and phase 3 studies of bimekizumab in Psoriasis patients. The IBD-CAC identified 7 cases of "Definite IBD" (including 4 cases of UC, 3 cases of CD, and 1 IBD unclassified) in bimekizumab exposed patients. Further, there were 4 cases reported as "Probable IBD".

The following table contains a high level summary of the 7 cases reported as "definite" diagnoses of IBD in patients exposed to bimekizumab in a psoriasis clinical study, and includes comments from the DG reviewer. Note that the independent assessment is based upon the narratives provided in the BLA resubmission, and in some cases data are limited as compared to what was likely provided to 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.
PS009 (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.
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.
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.

In general, based on the clinical summaries/narratives provided by the sponsor, the 7 cases that were adjudicated as "definite IBD" appear reasonably likely to represent IBD. There are some cases where adequate detail was not provided in the summary narrative for this reviewer to have confidence in a definitive diagnosis or sub-type of IBD. However, the IBD-CAC charter appears reasonable, the committee members are well qualified to make these determinations, and the inclusion of 3 reviewers and a process in place to reach consensus on these case determinations appears to be a rigorous process to ensure a thorough review was conducted. It is likely that the committee had access to additional details, medical records, laboratory and pathology reports, etc. that were not provided in the brief narratives that the sponsor provided.

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.

Recommendations for labeling:

Section 5:

The previously negotiated Warning related to IBD appears appropriate and no additional revisions are recommended.

"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 new onset or worsening of signs and symptoms occurs."

Section 6:

We recommend DDD update the language in section 6 to reflect the adjudicated cases of IBD.

The previously negotiated language focused on a single case of IBD identified in the clinical trials, as shown below.

"Inflammatory Bowel Disease

We recommend the following updates (revisions in bold):

"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."

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/s/

TARA A ALTEPETER
05/02/2023 03:04:21 PM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Addendum to Division of Pediatrics and Maternal Health Review

Date: April 25, 2023 **Date Consulted:** March 9, 2023

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

To: Strother Dixon, Regulatory Project Manager (RPM)
Division of Dermatology and Dentistry (DDD)

BLA: 761151

Drug: Bimzelx (bimekizumab-bkzx) injection, for subcutaneous use

Proposed Indication: For the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Applicant: UCB, Inc.

Subject: PLLR Labeling and Pregnancy/Lactation Postmarketing Requirements (PMRs)

Materials Reviewed:

- BLA 761151 resubmission on November 21, 2022, including applicant's Summary of Clinical Safety-Safety Update pertaining to use in pregnancy and lactation.
- Prior DPMH Review of Bimzelx (bimekizumab-bkzx) injection BLA 761151 by Kristie Baisden, DO, dated 2/3/21, DARRTs Reference ID: 4741087.

Consult Question: DDD requests DPMH assistance with reviewing the additional pregnancy data in the resubmission, meeting attendance, and updated PLLR labeling recommendations.

PURPOSE

This addendum provides DPMH review of the additional pregnancy data in the resubmission, updated PLLR labeling recommendations, and updated Pregnancy/Lactation PMR language recommendations. For background, refer to the 2021 DPMH Review for Bimzelx (bimekizumab-bkzx) BLA 761151 (as listed in the Materials Review section).

REVIEW

Pregnancy and Lactation

Pregnant and lactating women were excluded from clinical trials with Bimzelx. 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 in the indication of psoriasis (PSO), 4 in the indication of psoriatic arthritis (PsA), and 1 in the indication of axial spondyloarthritis (axSpA). Per protocol, study medication was stopped as soon as the pregnancy was discovered, which generally limits the exposure to the first trimester (see Table 1-1 Appendix A for details). No relevant lactation exposure cases were reported.

Pregnancy outcomes (n=20 total) included:

- 8 normal livebirths (all healthy; although 1 was born preterm at 33wks 1day)
- 1 neonatal death (pregnancy complicated by complication post stenting of urinary stent due to nephrolithiasis, septic shock, placenta abruption, and HELLP syndrome which resulted in 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.”

Reviewer’s Comment
This reviewer agrees with the applicant’s conclusion above. Overall, the available data are limited to a small number of bimekizumab-bkzx exposures early in the 1st trimester followed by immediate discontinuation upon the detection of pregnancy. In addition, there are no available data regarding use in women who continue to take Bimzelx chronically throughout pregnancy.

DISCUSSION and CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with Bimzelx. 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.

There are no available pregnancy pharmacokinetic (PK) data for bimekizumab-bkzx to inform evidence-based dosing recommendations during pregnancy. Although the impact of pregnancy physiology on PK of biologics is understudied, there are published literature that support the need for pregnancy PK data collection and indicate serum concentrations of monoclonal antibodies may be decreased, similar, or increased compared to non-pregnant adults.[1]

There are 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. Considering bimekizumab-bkzx is an IgG1 monoclonal antibody, placental transfer is presumed based on published literature for other monoclonal antibodies.[2] Published literature for other monoclonal antibodies indicate the amount of placental transfer varies widely and the half-life observed in adults may not be predictive of the half-life or the duration of pharmacodynamic effects in the *in utero* exposed infant.[2] Available animal data also indicate bimekizumab-bkzx crossed the placenta in monkeys and concentrations in infant monkeys at birth were comparable to those of mothers. During the prior review cycle, DPMH discussed these findings with the Nonclinical Review Team. The Nonclinical Review Team concluded that the nonclinical studies performed did not demonstrate evidence of immunosuppression in the *in utero* exposed monkeys. However, it is not clear how the available nonclinical data inform the potential risk to the *in utero* exposed human infant.

Given the lack of available human PK and placental transfer data specific to bimekizumab-bkzx use in pregnancy, DPMH recommends including language in subsection 8.1 similar to the Agency's current approach to labeling for other monoclonal antibodies. Pregnancy labeling should include information under Risk Summary and Clinical Considerations about the active transport of monoclonal antibodies across the placenta, the potential for immunosuppression in the *in utero* exposed infant, and the risks and benefits that should be considered prior to administration of live vaccines. The labeling should include a statement that a specific timeframe to delay live virus immunizations in infants exposed in utero is unknown; however a minimum of at least 4 months after birth is recommended (based on the half-life of 23 days x 5-6).

Plaque psoriasis is common in females of reproductive potential, and therefore unintended and intended exposures to bimekizumab-bkzx in pregnancy are likely to occur. The current data are insufficient to inform women regarding bimekizumab-bkzx use during pregnancy. The applicant is planning to perform two postapproval pregnancy studies (both a pregnancy exposure registry and a retrospective cohort study) to evaluate the safety of Bimzelx use during pregnancy. DPMH agrees with the applicant's proposal and recommends these pregnancy safety studies be issued as postmarketing requirements (PMRs). DPMH also recommends including language regarding the planned postapproval pregnancy exposure registry in subsection 8.1 and section 17 of labeling. See below for DPMH suggested PMR language.

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[1] Wiersma TK, et al. The Effect of Pregnancy and Inflammatory Bowel Disease on the Pharmacokinetics of Drugs Related to Inflammatory Bowel Disease-A Systematic Literature Review. Pharmaceutics 2022, 14, 1241.

[2]Soh MC, et al. The Use of Biologics for Autoimmune Rheumatic Diseases in Fertility and Pregnancy. Obstetric Medicine 2020, Vol. 13 (1) 5-13.

In addition, DPMH recommends DDD consider a pregnancy PK and placental transfer PMR study to evaluate the clinical pharmacokinetics of bimekizumab-bkzx in maternal plasma during pregnancy and at delivery, in cord blood at the time of delivery, and post-delivery in plasma of infants exposed to bimekizumab-bkzx *in utero.* On April 21, 2023, DPMH discussed the rationale for a pregnancy PK and placental transfer study with the DDD Clinical and Clinical Pharmacology Review Teams. DDD expressed concerns regarding study design considerations, interpretability, and clinical meaningfulness from a study in a small population. DDD will seek additional input from pediatrics. Input on study design from an immunologist would also be beneficial to evaluate for any potential signal of humoral immunosuppression in infants exposed to bimekizumab-bkzx *in utero*. At this time, DPMH defers to DDD on a final decision regarding such a study for this application.

Lactation

Lactating women were excluded from clinical trials with Bimzelx and no lactation exposures were reported. Overall, there are no available data on the presence of bimekizumab-bkzx in human or animal milk, the effects on the breastfed infant, or the effects on milk production. Considering bimekizumab is an IgG1 monoclonal antibody, DPMH recommends including language in subsection 8.2 of Bimzelx labeling similar to the Agency's current approach to labeling for other monoclonal antibodies. Lactation labeling should include information under Risk Summary that "maternal IgG and monoclonal antibodies are known to be present in human milk" as well as the "the effects of local gastrointestinal exposure and limited systemic exposure in the breastfed infant to bimekizumab are unknown." The following risk/benefit statement should also be included: "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."

Based on the lack of available lactation data and the anticipated use of Bimzelx in females of reproductive potential including lactating women, DPMH recommends issuing a PMR for a milk-only clinical lactation study to inform labeling related to the concentration of bimekizumab-bkzx in human milk and effects on the breastfed infant. If there is evidence that bimekizumab-bkzx is transferred into breastmilk, additional studies (i.e., mother-infant pair study) may be required to further evaluate infant exposure through breast milk. See below for DPMH updated PMR language for monoclonal antibody products.

Females and Males of Reproduction Potential

DPMH recommends omitting subsection 8.3 of Bimzelx labeling. There are no available human data regarding the effects of Bimzelx on male or female fertility. Animal studies do not suggest an adverse effect on fertility. Pregnancy testing and contraception subheadings are not applicable because there are no available data to suggest Bimzelx use is associated with embryo-fetal toxicity.

RECOMMENDATIONS

Postmarketing Requirements (PMRs)

DPMH recommends updating the PMR language for the pregnancy registry and lactation study (see underline below for new language). DPMH defers to the DDD Review Team for final decisions on a pregnancy PK and placental transfer PMR study. See proposed language below.

1. DPMH recommends issuing a PMR for the applicant to conduct a pregnancy exposure registry in order to inform the pregnancy section of labeling. The following PMR language is suggested:

> 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, neonatal deaths, and infections, will be assessed through at least the first year of life.

2. DPMH recommends issuing a PMR for a pregnancy PK study in order to inform maternal dosing and placental transfer. The following PMR language is suggested:

> Evaluate the clinical pharmacokinetics of bimekizumab in maternal plasma during pregnancy and at delivery, in cord blood at the time of delivery, and post-delivery in plasma of infants exposed to bimekizumab in utero. These assessments may be conducted as a sub-study of the pregnancy registry.

Reviewer's Comment
DPMH discussed the pregnancy PK and placental transfer study rationale with the DDD Clinical and Clinical Pharmacology Review Teams at the internal meeting on April 21, 2023. The DDD Clinical Team plans to consult the DPMH Pediatric Team for additional input regarding these considerations. DPMH defers to the DDD Review Team for final PMR decisions.

3. DPMH recommends issuing a PMR for the applicant to conduct a retrospective cohort study in order to inform the pregnancy section of labeling. The following PMR language is suggested:

> 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.

4. DPMH recommends issuing a PMR for the applicant to conduct a lactation study in order to inform the lactation subsection of labeling. The following PMR language is suggested:

> 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. A mother-infant pair study may be required in the future depending on the results of this milk-only study.

5. DPMH updated labeling recommendations for subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR (see underline and ~~strikethrough~~ below). DPMH discussed the below labeling recommendations with DDD at the labeling meeting on April 14, 2023. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Bimzelx (bimekizumab-bkzx) Pregnancy and Lactation Labeling
FULL PRESCRIBING INFORMATION

8.1 Pregnancy

Pregnancy Exposure Registry

There (b) (4) 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 ~~estimated~~ 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)].

APPENDIX A

Table 1-1: Details of maternal bimekizumab exposure pregnancies during the clinical development program

Study participant narrative	LMP date	BKZ dose at pregnancy/ Last BKZ dose date	Reported pregnancy complications / adverse events / maternal outcomes	Pregnancy outcome	Infant / fetal outcomes
PS0011- (b) (6) (b) (6)	(b) (6)	160mg Q4W/ (b) (6)	C-Section due to breech presentation No complications	Live birth	Healthy baby (male) No abnormalities reported Apgar score: 9 (at min 1) / 10 (at min 5)
PS0008- (b) (6) (b) (6)		320mg Q4W/ (b) (6)	Pregnancy with contraceptive device (condom) No complications	Spontaneous abortion (5 weeks 3 days of gestation)	Not applicable
PS0008- (b) (6) (b) (6)		320mg Q4W/ (b) (6)	None reported	Live birth	Healthy baby (gender unk) No abnormalities reported Apgar score: unk
PS0008- (b) (6) (b) (6)		320mg Q4W/ (b) (6)	None reported	Unk - Lost to follow up	None reported
PS0009 (b) (6) (b) (6)		320mg Q4W/ (b) (6)	None reported	Live birth	Healthy baby (female) No abnormalities reported Apgar score: 9 (no further details)
PS0009- (b) (6) (b) (6)		320mg Q4W/ (b) (6)	Pregnancy on contraceptive (unspecified) Hospitalized due to bleeding during pregnancy (no further information)	Live birth	Healthy baby (gender unk) No abnormalities reported Apgar score: unk
PS0009- (b) (6) (b) (6)		320mg Q4W/ (b) (6)	No complications	Live birth	Healthy baby (female) No abnormalities reported Apgar score: unk

Table 1-1: Details of maternal bimekizumab exposure pregnancies during the clinical development program

Study participant narrative	LMP date	BKZ dose at pregnancy/ Last BKZ dose date	Reported pregnancy complications / adverse events / maternal outcomes	Pregnancy outcome	Infant / fetal outcomes
PS0014- (b) (6) (b) (6)	(b) (6)	320mg Q8W/ (b) (6)	No complications	Live birth	Healthy baby (female) No abnormalities reported Apgar score: unk
PS0014 (b) (6) (b) (6)	unk[a]	320mg Q4W/ (b) (6)	Concurrent viral infection with fever was reported as possible risk factor No complications reported	Spontaneous abortion (8 weeks of gestation)	Not applicable
PS0014 (b) (6) (b) (6)	unk[b]	320mg Q4W/ (b) (6)	Unintended pregnancy on oral contraceptive None reported	Induced abortion	Not applicable
PS0014 (b) (6) (b) (6)	(b) (6)	320mg Q4W/ (b) (6)	None reported	Live birth	Healthy baby (male) No abnormalities reported Apgar score: unk
PS0014 (b) (6) (b) (6)	unk	320mg Q8W/ (b) (6)	None reported	Unk	None reported
PS0014 (b) (6) (b) (6)	(b) (6)	320mg Q8W/ (b) (6)	None reported	Unk	None reported
PS0015- (b) (6) (b) (6)		320mg Q8W/ (b) (6)	Pregnancy on contraceptive (ring type contraceptive) None reported	Live birth	Premature but healthy baby (male; gestational age of 33 weeks and 1 day) No abnormalities reported Apgar score: unk
PS0015- (b) (6) (b) (6)		320mg Q8W/ (b) (6)	None reported	Induced abortion (due to personal choice)	None reported
PA0009- (b) (6) (b) (6)	unk [c]	160mg Q4W/ (b) (6)	Pregnancy on contraceptive (oral) None reported	Unk	None reported

Table 1-1: Details of maternal bimekizumab exposure pregnancies during the clinical development program

Study participant narrative	LMP date	BKZ dose at pregnancy/ Last BKZ dose date	Reported pregnancy complications / adverse events / maternal outcomes	Pregnancy outcome	Infant / fetal outcomes
PA0011 (b) (6) (b) (6)	(b) (6)	160mg Q4W/ (b) (6)	Complication post stenting of urinary tract due to nephrolithiasis (septic shock, premature separation of placenta, HELLP syndrome). Emergency C-section Depression and Gestational diabetes	Live birth (neonatal death)	Premature baby (female; gestational age 25 weeks and 5 days) Failure to thrive with no developmental delay or congenital abnormality Apgar score: unk Neonatal death (<1day): resuscitation measures failed
PA0012 (b) (6) (b) (6)		160mg Q4W/ (b) (6)	Pregnancy with contraceptive device (barrier) None reported	Ongoing	None reported
PA0012 (b) (6) (b) (6)		160mg Q4W/ (b) (6)	Pregnancy on oral contraceptive None reported	Ongoing	None reported
AS0014 (b) (6) (b) (6)		160mg Q4W/ (b) (6)	Pregnancy on contraceptive (barrier) None reported	Ongoing	None reported

BKZ=bimekizumab; LMP=last menstruation period; unk=unknown; Q4W=every 4 weeks; Q8W=every 8 weeks; SFU=Safety Follow-Up

[a] First positive serum pregnancy test results: (b) (6)

[b] First pregnancy test positive at home (b) (6)

[c] First urine pregnancy test positive on (b) (6)

Source: UCB Global Safety Database

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/s/

KRISTIE W BAISDEN
04/25/2023 05:27:31 PM

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04/26/2023 10:23:29 AM

Drug-Induced Liver Injury Team Clinical Review Memorandum

Division of Hepatology and Nutrition
Office of New Drugs
Center for Drug Evaluation and Research

BLA	761151
Drug name	Bimekizumab (BKZ)
Sponsor	UCB, Inc.
Review item	Three cases of liver injury
Requesting Division	Division of Dermatology and Dentistry (DDD)
Primary Reviewer	Paul H. Hayashi, MD, MPH
Date	Apr 18, 2023

I. OVERALL ASSESSMENT AND RECOMMENDATION(S)

The three additional subjects with liver injury do not change our prior assessment and recommendations. None of the three were probable DILI due to bimekizumab (BKZ).

II. BACKGROUND

Bimekizumab (BKZ) is a humanized monoclonal antibody that binds IL-17A and 17F. In this BLA, it is used for the treatment of plaque psoriasis (PSO). In 2021, the Division of Dermatology and Dentistry (DDD) identified subjects with liver injury potentially due to BKZ and asked the Drug-Induced Liver Injury (DILI) Team to help with risk assessment. The DILI Team did not see a DILI risk that would hold up approval,[1] but the BLA got a complete response on May 12, 2022, due to deficiencies at a manufacturing facility.

The resubmission on Nov 21, 2022, had three additional subjects with potential DILI, and DDD requested our review of those subjects and any updates to our prior recommendations.

III. SIGNIFICANT REVIEW FINDINGS

Two of the three subjects had unlikely DILI due to BKZ. The third subject had possible DILI due to BKZ, and the liver injury was mild without hyperbilirubinemia. (**Table**) Also, this subject remained on BKZ with return of liver analytes to near baseline indicating possible adaptation.

[1] Open DARRTS session first to allow following link to work:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8060a1f2

Table: Summary of three subjects with potential DILI

ID	Causality Score	Alternate diagnosis	Age (yr)	Sex	Race	Latency from start drug (da)	Latency from stop drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak
(b) (6)	5	Alcohol	49	M	Asian	224	-872	222	194	130	1.52	4.93
	5	Myopathy	29	M	White	7	7	238	682	130	1.4	5.29
	4	Adaptation	53	M	Other	11	-447	92	199	130	0.88	2.04

Causality score: 4 = possible DILI; 5 = unlikely DILI
R-value = (ALT/ULN) ÷ (ALP/ULN)
M = male; F = female

IV. CONCLUSIONS

The three additional subjects with liver injury do not change our prior assessment or recommendation. Please see our prior consult note for details.[2]

V. RECOMMENDED REGULATORY ACTION(S)

No change in recommendations.

Paul H. Hayashi -S

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Date: 2023.04.18 18:00:48 -04'00'

Paul H. Hayashi, MD, MPH
DILI Team Lead, Division of Hepatology and Nutrition
CDER/OND

[2] Open DARRTS session first to allow link to work:
https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af8060a1f2

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/s/

PAUL H HAYASHI
04/18/2023 06:14:19 PM

Memorandum

From: Selena DeConti, PharmD, MPH
Safety Analyst, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Through: Mary Ross Southworth, PharmD
Deputy Director for Safety, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Norman Stockbridge, MD
Director, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Date: April 11, 2023

Subject: **Cardiovascular safety** of bimekizumab (BLA 761151)

This memo responds to the consult requesting a review of cardiovascular (CV) events that were included in a resubmission of BLA 761151, bimekizumab, dated November 21, 2022 for the treatment of moderate to severe psoriasis (PSO) in adults. DCN previously provided a review (dated March 3, 2021) of the CV events reported in the initial BLA submission, which received a complete response (CR) in May 2022 due to deficiencies at a manufacturing facility. The BLA resubmission includes additional safety data from an ongoing open-label extension (OLE) trial (PS0014), as well as an additional ongoing Phase 3b, multicenter, randomized, double-blind, active comparator-controlled, parallel-group trial (PS0015) followed by an OLE period. We received and reviewed the safety updates in the BLA resubmission package: \\CDSESUB1\evsprod\BLA761151.

DCN Summary and Assessment

The previous CV safety analysis from DCN included data from the safety pool, S1, for adults with moderate to severe plaque PSO 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; it was the same pooling as Efficacy Pool 1. The review did not reveal a clinical concern from the cardiovascular perspective and no labeling language was recommended.

This updated CV safety analysis includes data reported for PS0015, an ongoing Phase 3b, multicenter, randomized, double-blind, active comparator-controlled, parallel-group trial to study adults with moderate to severe plaque PSO. 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). Individual patient dossiers for those reporting serious CV events, hypertension, or CV death were reviewed. Other safety data received in the resubmission included the OLE period for studies PS0015 and PS0014, for which there was no comparator arm.

The results of the primary safety analysis for trial PS0015 include:

- The patient characteristics and baseline cardiac risk factors were relatively evenly distributed between the treatment groups. There was a slightly higher proportion of subjects reporting previous or ongoing cardiac disorders and hypertension, as well as baseline elevated blood pressure (BP) in the bimekizumab group compared with the secukinumab group (11%, 29%, 78% versus 9%, 26%, 73%, respectively).
- The total duration of exposure and the total times at risk were similar in both treatment groups.
- The most reported CV adverse event (AE) was hypertension, which had a higher incidence in those treated with bimekizumab (6%) than secukinumab (3%). This may be due to the imbalance of previous or ongoing cardiac disorders and hypertension reported at baseline for the treatment arms. There were no SAEs or discontinuations reported with hypertension.
- The serious CV events were reported in a higher proportion in the secukinumab arm than for bimekizumab, (1.4% versus 0.5%). No trend was observed with respect to the time to onset of any CV event.
- There were no CV deaths or Adjudicated major adverse cardiac event (MACE) with fatal outcome reported in the bimekizumab arm. A description of the Adjudicated MACE with fatal outcome for bimekizumab in the OLE period is provided in the Appendix.
- There was no adjudicated MACE reported for bimekizumab versus three (0.8%) for secukinumab.
- There was no adjudicated extended MACE reported for bimekizumab and four (1.1%) in the secukinumab group.
- The incidence of adjudicated CV events was higher in the secukinumab group (2%) compared with bimekizumab (1%).

Overall, the analysis of the updated safety data did not raise clinical CV concerns and no labeling language is necessary.

Background

UCB Biopharma, Inc submitted BLA 761151 for bimekizumab, a humanized IgG1 monoclonal antibody that targets the human interleukin (IL) 17A, 17F, and 17-AF cytokines, and inhibits their interaction with the IL-17RA/IL-17RC receptor complex. IL-17A and IL-17F are involved in the inflammatory process and independently cooperate with other inflammatory mediators to drive chronic inflammation and damage across multiple tissues. The proposed indication for bimekizumab is for treatment of moderate to severe plaque PSO in adults. The proposed dosage is 320 mg 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. The half-life of bimekizumab is approximately 19-26 days. Bimekizumab was

approved in August 2021 in the European Union (EU) and authorized in 35 countries as of August 2022. No postmarketing CV safety findings have been identified in the EU.

Psoriasis is associated with increased prevalence of CV risk factors including smoking, limited physical activity, obesity, diabetes, hypertension, and hyperlipidemia (Parisi et al, 2015). In addition, PSO patients have an increased risk of vascular inflammation and MACE beyond that attributable to known CV risk factors (Egeberg et al, 2017; Gelfand et al, 2006). Among patients with moderate to severe PSO, the incidence rate of MACE was 6.5/1000 person-years in The Health Improvement Network database (1994-2010) in the United Kingdom (Ogdie et al, 2015). Of note, there are also studies suggesting that low serum levels of IL-17 are associated with a higher risk of MACE (Lockshin et al, 2018; Simon et al, 2012).

Three monoclonal antibody products have been approved for the treatment of moderate-to-severe plaque psoriasis, two targeting IL-17A (secukinumab, ixekizumab) and one against the IL-17 receptor (brodalumab). No CV adverse events are included in the labeling for these products.

For bimekizumab, there were no preclinical findings to suggest CV safety concerns. In the Applicant's repeat-dose toxicity studies in Cynomolgus monkeys there were no abnormalities in the ECG waveform or morphology that could be directly attributed to administration of bimekizumab, no changes in CV variables or heart rate, and no significant effects on ECG Lead II parameters noted at any bimekizumab dose.

MACE, defined as CV death, non-fatal myocardial infarction (MI), or stroke, was a pre-specified safety topic of interest due to epidemiological associations between PSO and CV events and the potential association between other anti-cytokine (immunomodulating biologic) therapies and CV events. MACE was reported as adverse events. Extended MACE was defined as all MACE plus adjudicated event types of hospitalization for unstable angina with urgent revascularization, hospitalization for heart failure, transient ischemic attack, coronary revascularization procedures (percutaneous coronary intervention, coronary artery bypass grafting, or urgent cerebrovascular revascularization procedures (i.e., due to symptoms of brain ischemia or pending infarction.) Events were classified and adjudicated by the CV-CAC. All ECGs were reviewed by the central ECG laboratory. The Applicant conducted analyses on adjudicated MACE, extended MACE, and other serious non-MACE CV events as detailed in the integrated statistical analysis plan. The proposed labeling does not include adverse drug reactions for CV events.

Safety Analysis Pools

The primary safety pool, Safety Set, includes adults exposed to bimekizumab 320 mg (n=373) or secukinumab 300 mg (n=370) in the initial and maintenance treatment periods (total 48 weeks, last dose at week 44) of the Phase 3 trial PS0015. Table 3 in the Appendix provides an overview of the relevant trials constituting the safety pools for the bimekizumab psoriasis program.

Treatment Duration

The total duration of exposure and the total times at risk were similar in both treatment groups. Mean duration of bimekizumab treatment was approximately 321 days (Table 1).

Table 1: Study Drug Treatment Duration for the Combined Initial and Maintenance Treatment Periods, PS0015, Safety Population

	BKZ 320mg (N=373)	SEC 300 mg (N=370)
Duration (days)		
Mean (SD)	321.1 (53.4)	315.6 (63.9)
Median	336	336
Min, Max	27,350	14,364
Total time at risk (participant-years)	340.4	333.6

Abbreviations: BKZ=bimekizumab, SEC=secukinumab, SD= standard deviation; Source: PS00015 CSR-interim Table 11-2

Subject Demographics and Baseline Characteristics

Baseline CV risk factors and history of CV events were relatively evenly distributed between the randomized treatment groups. There was a slightly higher proportion of subjects reporting previous or ongoing cardiac disorders in the bimekizumab group (11%) compared with the secukinumab group (9%). In addition, the incidence of hypertension was higher in the bimekizumab group (29%) versus the secukinumab group (26%).

Cardiovascular Events

Overall, there were no meaningful differences in specific CV events that raised clinical concern. The serious CV events were reported in a higher proportion in the secukinumab arm than for bimekizumab, (1.4% versus 0.5%; Table 4, Appendix). No trend was observed with respect to the time to onset of any CV event.

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 (bimekizumab -29%, 78% versus secukinumab - 26%, 73%, respectively). There were no SAEs or discontinuations reported with hypertension (Table 5, Appendix). For patients reporting the AE hypertension, clinic monitored blood pressures (BP) fluctuated above and below baseline across the visits and there were no patients with a consistent trend in systolic (SBP) or diastolic (DBP) increase from baseline over the treatment period. Overall, mean and median changes from baseline of clinic monitored SBP and DBP were similar and not clinically meaningful for any treatment group (Figures 1-2, Appendix). Further, hypertension reported in the other Phase 3 trials for the bimekizumab PSO program, as well as, the supportive trials in psoriatic arthritis (PA0010, PA0011) was similar among treatment groups.

Table 2 summarizes incidences of adjudicated MACE, extended MACE, and CV events reported for the Initial and Maintenance treatment periods. No adjudicated MACE or extended MACE was reported for the bimekizumab group. Adjudicated CV events were low and had a higher incidence in the secukinumab group (2%) compared with bimekizumab (1%). There were no CV deaths or Adjudicated MACE with fatal outcome reported for bimekizumab. There was one Adjudicated MACE with fatal outcome for bimekizumab in the OLE period (description provided in Table 6 in the Appendix) but the case did not raise CV safety concerns.

Table 2: Adjudicated MACE, Extended MACE, and CV Adverse Events, Combined Initial and Maintenance Periods, PS0015, Safety Population

Variable [n (%)]	BMK 320 mg (N=373)	SEC 300 mg (N=370)	Risk Difference
Adjudicated MACE	**0**	**3 (0.8)**	**-0.8 (-1.9, 0.1)**
Adjudicated Extended MACE	**0**	**4 (1.1)**	**-1.1 (-2.3, -0.03)**
Adjudicated CV Event	**3 (0.8)**	**6 (1.6)**	**-0.8 (-2.7, 0.8)**
Arrhythmia (not associated with ischemia)	1 (0.3)	2 (0.5)	-0.2 (-1.3, 0.7)
Coronary Revascularization Procedure	0	1 (0.3)	-0.3 (-0.8, 0.3)
Transient Ischemic Attack	0	1 (0.3)	-0.3 (-0.8, 0.3)
Other CV event[a]	1 (0.3)	0	0.3 (-0.3, 0.8)
Non-CV event	1 (0.3)	2 (0.5)	-0.2 (-1.3, 0.7)

[b] PT syncope
Abbreviations: BKZ=bimekizumab, CV=cardiovascular, MACE=major adverse cardiac event, SEC=secukinumab
Source: PS0015 CSR-interim Tables 8.2.4.2, 8.2.4.4, 8.2.4.5, 8.2.4.7; verified by reviewer

In conclusion, there is no clinical concern from the cardiovascular perspective and no labeling language is necessary.

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Appendix

Table 3. Phase 2 and 3 Trials Constituting Relevant Safety Pools for BLA 761151 bimekizumab

Study/Design	Treatment Duration	Treatment Groups	Safety Population (S/C)	Safety Pool
Phase 3 Controlled				
PS0008 16-week MC, R, DB, PG, AC ITP, followed by 40-week DoseB, MTP	ITP – 16 weeks	ADA 40mg	159/149	S2
		BKZ 320mg Q4W	158/152	
		BKZ 320mg Q4W/Q8W	161/149	
	MTP – 40 weeks	ADA/BKZ 320mg Q4W	149/133	
		BKZ 320mg Q4W/Q4W	152/143	
		BKZ 320mg Q4W/Q8W	149/143	
PS0009 16-week MC, R, DB, PC and AC ITP, followed by 36-week PG extension period	ITP – 16 weeks	PBO	83/74	S1
		UST 45/90mg	163/157	S2
		BKZ 320mg Q4W	321/306	S1
	EP – 36 weeks	UST 45/90mg	157/141	S2
		BKZ 320mg Q4W	380/352	
PS0013 16-week MC, DB, PC ITP, followed by 40-week PC RWP	ITP – 16 weeks	PBO	86/82	S1
		BKZ 320 mg Q4W	349/340	
	RWP – 40 weeks	PBO/PBO	1/1	S2
		BKZ 320 mg Q4W/PBO	105/33	
		BKZ 320 mg Q4W/Q8W	100/93	
		BKZ 320mg Q4W/Q4W	106/94	
PS0015 16-week MC, DB, AC ITP, followed by 32-week DB AC MTP	ITP – 16 weeks	BKZ 320 mg Q4W	373/285	Safety Set
		SEC 300mg QWX 5, then Q4W	370/276	
	MTP – 32 weeks	BKZ 320 mg Q4W/Q4W	147/124	
		BKZ 320 mg Q4W/Q8W	215/161	
		SEC 300 mg Q4W	354/276	
Phase 3 Uncontrolled				
PS0014[a] OLE	144 weeks	BKZ 320mg Q4W	1285/ongoing	S2
		BKZ 320mg Q8W		
PS0015 OLE	96 weeks	BKZ 320mg Q4W	654/ongoing	OLS
		BKZ 320mg Q8W		
Phase 2 Controlled				
PS0010 MC, R, DB, PC, PG	12 weeks	BKZ 64mg Q4W	39/36	S2
		BKZ 160mg Q4W	43/38	
		BKZ 160mg Q4W w/LD	40/34	
		BKZ 320mg Q4W	43/40	
		BKZ 480mg Q4W	43/39	
		PBO	42/37	
PS0011[b] DB, PC, PG	48 weeks	BKZ 64mg Q4W	15/15	S2
		BKZ 160mg Q4W	111/92	
		BKZ 320mg Q4W	91/75	
PS0016	4 weeks	BKZ 320mg + PBO	32/28	S2

Table 3. Phase 2 and 3 Trials Constituting Relevant Safety Pools for BLA 761151 bimekizumab				
Study/Design	**Treatment Duration**	**Treatment Groups**	**Safety Population (S/C)**	**Safety Pool**
MC, R, DB	16 weeks	BKZ 320mg	17/15	
Phase 2 Uncontrolled				
PS0018[c] OLE	48 weeks	BKZ 320mg + PBO	28/24	S2
		BKZ 320mg	15/13	

Abbreviations: AC=active control, ADA=adalimumab, BKZ=bimekizumab, DB=double-blind, DoseB=dose blind, EP=extension period, ITP=initial treatment period, MC=multi-center, MTP=maintenance treatment period, OLE=open label extension, OLS=open label safety set, PBO=placebo, PC=placebo controlled, PG=parallel group, PSO= psoriasis, R=randomized, RWP=randomized withdrawal period, S/C=number of subjects started/completed, S1=Safety Pool 1 includes only the ITP and placebo-controlled Phase 3; it is the same as Efficacy Pool 1, S2=Safety Pool 2 and combines all treatment periods, SEC=secukinumab, UST = ustekinumab; [a] ongoing; feeder studies PS008, PS009, or PS0013; includes sub-studies DV0002 and DV0006 and an additional OL Cohort B in Japan; clinical cut-off 11/1/19; [b] feeder study PS0010; [c] feeder study PS0016; Source: Integrated Summary of Safety, SAP, Tables for individual trials

Table 4. CV Adverse Events, Combined Initial and Maintenance Treatment Periods, PS0015, Safety Population

CV Event[1]	**BKZ 320mg (N=373)**	**SEC 300 mg (N=370)**	**Risk Difference (95% CI)**
Any AE	32 (8.0)	20 (5.4)	3.4 (-0.8, 7.6)
SAE	2 (0.5)	5 (1.4)	-0.9 (-2.5, 0.6)
SAE with fatal outcome	0	1 (0.3)	-0.3 (-0.8, 0.3)
AE from CV FMQs[2]	34 (9.1)	21 (5.7)	3.4 (-0.8, 7.6)
Acute myocardial infarction[3]	0	1 (0.3)	-0.3 (-0.8, 0.3)
Arrhythmia	1 (0.3)	0	0.3 (-0.3, 0.8)
Atrial fibrillation	3 (0.8)	4 (1.1)	-0.3 (-1.7, 1.1)
Bradycardia[4]	1 (0.3)	1 (0.3)	0 (-0.7, 0.7)
Bundle branch block right	1 (0.3)	0	0.3 (-0.3, 0.8)
Electrocardiogram QT Prolonged	0	1 (0.3)	-0.3 (-0.8, 0.3)
Hypertension[5]	22 (5.9)	12 (3.2)	2.7 (-0.3, 5.7)
Loss of Consciousness	1 (0.3)	0	0.3 (-0.3, 0.8)
Orthostatic hypotension	1 (0.3)	0	0.3 (-0.3, 0.8)
Palpitations	1 (0.3)	0	0.3 (-0.3, 0.8)
Presyncope	0	2 (0.5)	-0.5 (-1.3, 0.2)
Supraventricular Tachycardia	1 (0.3)	0	0.3 (-0.3, 0.8)
Syncope	3 (0.8)	1 (0.3)	0.5 (-0.5, 1.6)
Tachycardia	1 (0.3)	0	0.3 (-0.3, 0.8)

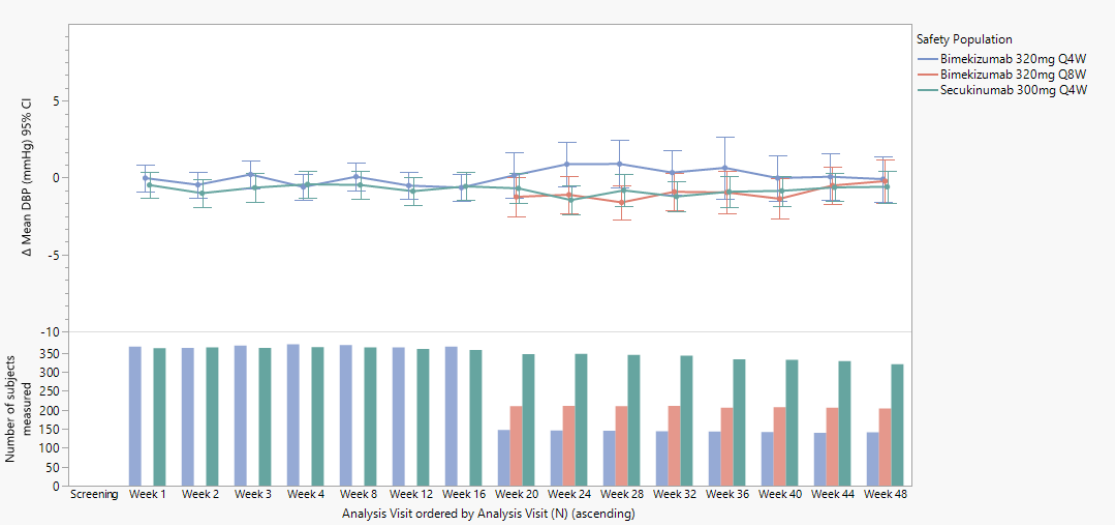
[1] Includes treatment emergent AE defined as any event that had a start date on or following the first dose of drug up to 28 days following the final dose reported in the Cardiac Disorders or Vascular Disorders MedDRA System Organ Class (SOC)
[2] MedDRA preferred term from narrow FMQs Acute Coronary Syndrome, Arrhythmia, Heart Failure, Hypotension, Myocardial Infarction, Myocardial Ischemia, Palpitations, Syncope, Systemic Hypertension
[3] Includes PT myocardial infarction
[4] Includes PT sinus bradycardia
[5] Includes PT blood pressure increased
Abbreviations: AE=adverse event, BKZ=bimekizumab, CV=cardiovascular, FMQ=FDA MedDRA Query, SAE=serious adverse event, SEC=secukinumab Source: Reviewer's Table; MAED, OCS Analysis Studio PS0015, adae.xpt, adsl.xpt,

Table 5. CV Adverse Event Hypertension, Combined Initial and Maintenance Treatment Periods, PS0015, Safety Population

CV Event[1]	BKZ 320mg (N=373)	SEC 300 mg (N=370)	Risk Difference (95% CI)
Hypertension[2]	22 (5.9)	12 (3.2)	2.7 (-0.3, 5.7)
SAE	0	0	0
Resulted in Study Discontinuation	0	0	0
AE Severity[3]			
Mild	14 (3.8)	9 (2.4)	1.4 (-1.4, 4.2)
Moderate	8 (2.1)	3 (0.8)	1.3 (-0.5, 3.4)
Severe	1 (0.3)	0	0.3 (-0.3, 0.8)
Action Taken with Study Drug			
Dose not changed	20 (5.4)	11 (3.0)	2.4 (-0.7, 5.8)
Unreported	2 (0.5)	1 (0.3)	0.2 (-0.7, 1.3)
Vital Signs			
Baseline BP > normal (120/80 mmHg)	290 (77.7)	270 (73.0)	4.7 (-9.5, 18.0)
SBP > 120 mmHg and increased from BL[4]	313 (83.9)	314 (84.9)	-1.0 (-16.7, 12.4)
DBP > 80 mmHg and increase from BL[4]	301 (80.7)	297 (80.3)	0.4 (-14.8, 13.6)
SBP > 140 or DBP > 90 and increased from BL ≥ 20 mmHg[4]	59 (15.8)	53 (14.3)	1.5 (-4.7,7.6)
SBP > 140 or DBP > 90 and increased from BL ≥ 40 mmHg[4]	9 (2.4)	6 (1.6)	0.8 (-1.4, 3.0)
SBP > 180 or DBP > 120 and increased from BL[3]	4 (1.1)	3 (0.8)	0.3 (-1.3, 1.8)
Shift from BP normal BL to Stage 2[4,5]	15 (4.0)	25 (6.8)	-2.8 (-6.8, 0.6)
Shift from BP elevated BL to Stage 2[4,5]	19 (5.1)	14 (3.8)	1.3 (-2.0, 4.7)

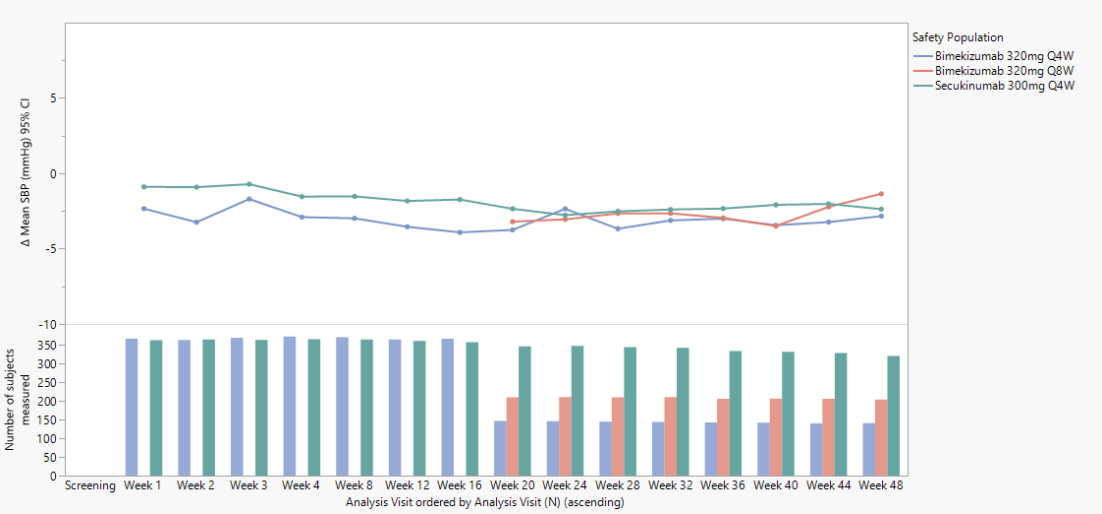
[1] Includes treatment emergent AE defined as any event that had a start date on or following the first dose of drug up to 28 days following the final dose reported in the Cardiac Disorders or Vascular Disorders MedDRA System Organ Class (SOC)
[2] Includes PT blood pressure increased
[3] Graded by investigator
[4] Includes measurement at any visit
[5] Stage 2 = SBP 140-180mmHg or DBP 90-120mmHg
Source: Reviewer's Table; Analysis Studio, adsl.xpt, adae.xpt; JMP, advs.xpt
Abbreviations: AE=adverse event, BL= baseline, BP=blood pressure, BKZ=bimekizumab, DBP=diastolic blood pressure, SBP=systolic blood pressure, SEC=secukinumab

Figure 1. Mean Change from Baseline Diastolic Blood Pressure Measurement by Visit, Initial and Maintenance Treatment Periods, PS0015, Safety Population



Source: Reviewer's Analysis, JMP Clinical, advs.xpt
Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: DBP, diastolic blood pressure; CI, confidence interval

Figure 2. Mean Change from Baseline Systolic Blood Pressure Measurement by Visit, Initial and Maintenance Treatment Periods, PS0015, Safety Population



Source: Reviewer's Analysis, JMP Clinical, advs.xpt
Unscheduled visits removed; baseline as last recorded pre-dose measurement
Abbreviations: SBP, systolic blood pressure; CI, confidence interval

Table 6. Adjudicated MACE with Fatal Outcome for Bimekizumab, PS0015, Open Label Extention Period, Safety Population

Subject ID/ Gender/ Age (yrs)	Study when MACE occurred/ Safety Pool	Study Period	Treatment at time of death	Time to Event (days)	Country	Preferred Term	Comment/CV Risk Factors
(b) (6) M/64	PS0015/ OLS	OLE	BKZ 320 mg Q8W	867	US	Cardiac Arrest	Found dead at home. CV risk factors included current tobacco use, hypertension, obesity, hyperlipidemia, hyperthyroidism, type 2 diabetes mellitus, sleep apnea syndrome, and a family history of heart attacks and hypertension.

BKZ=bimekizumab, MACE=major adverse cardiac event, OLE = open label extension period, OLS=open label safety set, US=Unites States
Source: CRF PS0015

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/s/

SELENA D DECONTI
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MARY R SOUTHWORTH
04/12/2023 05:23:16 AM

NORMAN L STOCKBRIDGE
04/12/2023 05:48:05 AM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	2/22/2023		
To:	Erica Keafer		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From:	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Division): *optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: BLA761151 ICC2201018 Center Tracking (fda.gov) ICCR884335 https://force-dsc.lightning.force.com/lightning/r/Case/5003d0000062USWAA2/view		
Recommendation:	Approval recommended for the pre-filled safety syringe and autoinjector device constituent parts of the combination product. • Refer to section 2 below for pre-approval inspection assessment • Refer to Appendix 1 below for engineering and facilities review and associated recommendation		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (optional)**
Porsche P. Bennett -S Digitally signed by Porsche P. Bennett -S Date: 2023.03.20 09:21:29 -04'00'	Courtney Evans -S Digitally signed by Courtney Evans -S Date: 2023.03.27 17:17:49 -04'00'	

1. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR#884335
Consult Request Link	https://force-dsc.lightning.force.com/lightning/r/Case/5003d0000062USWAA2/view
ICC tracking #	ICC2201018
Submission Number	BLA761151
Sponsor	UCB INC
Drug/Biologic	Bimekizumab
Indications for Use	Psoriasis
Device Constituent	• Pre-filled syringe with needle safety feature • Autoinjector
Related Files	• FEI 3003909356 EIR and 483 • ICC2000619, ICCR 00023177 (Premarket) & ICCR00023181 (Facilities/QS)

2. CDRH REVIEW

ICC Review Request from Choose an item., Choose an item.:	Need a technical engineering consult request for BLA 761151, Class 2 resubmission received on 11/21/2022. BLA was CR'd on 5/12/2022 for deficiencies at the DP manufacturing facility, UCB Braine facility (FEI # 3003909356). Previous CDRH reviewers assigned to the original submission was Matthew Ondeck & Rumi Young.
Device Presentation(s) being evaluated:	• Prefilled syringe with needle safety feature • Autoinjector SDN 68 Salesforce due date 04/03/2023 FDA Action May 21, 2023
Objective of this Memo:	Provide an approval recommendation post the CR hold and response for facilities deficiencies
Review **Comments**:	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.
Review **Recommendation**:	Approval recommended for the pre-filled safety syringe and autoinjector device constituent parts of the combination product.

---END OF REVIEW---

APPENDIX 1: Previous CDRH Consult Review Memo, ICC2000619, ICCR 00023177 (Premarket) & ICCR00023181 (Facilities/QS)

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	3/17/2021		
To:	Anh-Thy Ly (CDER/OPQ/OPRO/DRBPMI/RBPMB1)		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	CDER/OII/DDD
From	Matthew Ondeck OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, MS, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, MS, Acting Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA 761151, bimekizumab ICC2000619 Case #00023177 (Premarket) & #00023181 (Facilities/QS)		
Recommendation	**Filing Recommendation Date: 8/6/2020** Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter.		
	Mid-Cycle Recommendation Date: 10/20/2020 CDRH has no deficiencies to be communicated to the Sponsor at this time. CDRH recommends that a Pre-Approval Inspection (PAI) be completed at UCB Pharma SA, FEI# 3003909356. This recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection is not mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. This was communicated at the November 30, 2020, Mid-cycle meeting. See Section 5.2 for full discussion.		
	Final Recommendation Date: 3/17/2021 CDRH recommends 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. See Section for the Executive Summary.		

Digital Signature Concurrence Table		
Reviewer	**Team Lead (TL)**	**Division (*Optional)**

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761151
Sponsor	UCB, Inc.
Drug/Biologic	bimekizumab
Indications for Use	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Device Constituent	Prefilled Syringe and Auto-Injector
Related Files	IND 128707 – Meeting Request Reviews

Review Team		
Lead Device Reviewer	Matthew Ondeck	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A*	N/A*	N/A*

* No additional CDRH consults necessary for this review

Important Dates	Due Date
Receipt Date	7/15/2020
Filing Date	9/11/2020
CMC Alignment Meeting	11/2/2020
Midcycle Date	12/11/2020
Final Lead Device Review Memo Due	5/10/2021
Action Date	7/15/2021

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends 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.

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. Of note the drug facilities team also requested a Pre-Approval Inspection.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

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3. PURPOSE/BACKGROUND

3.1.Scope

UCB, Inc. has submitted BLA 761151 for review of bimekizumab injection. The device constituents of the combination product is a prefilled syringe (PFS) and autoinjector (AI).

CDER/OPQ has requested the following consults for review of the device constituent of the combination product:

- Case #00023177 (Premarket – Review of PFS and AI devices)
- Case #00023181 (Facilities/QS – Review of Facilities and Quality Systems Information)

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product; however, The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2.Prior Interactions

The Sponsor had submitted previous meeting requests under IND 128707, where CDRH issued comments regarding device information that should be included to support a BLA submission.

3.3.Indications for Use

Combination Product	Indications for Use
bimekizumab injection	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Pre-Filled Syringe and Autoinjector	Delivery of the Drug Product

3.4.Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
device-reviewers-guide	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\12-cover-letters
cover-initial-bla	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\12-cover-letters
drug-product-container-closure-system-maa	\\CDSESUB1\evsprod\BLA761151\0001\m2\23-qos
356h	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\11-forms
description-and-composition-dp-maa-ss-1ml	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p1-desc-comp
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description-and-composition-pfs-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p1-desc-comp
pharmaceutical-development-container-closure-ss-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p2-pharm-dev
pharmaceutical-development-container-closure-ai-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p2-pharm-dev
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Dv0006-body-text-1ml	\\CDSESUB1\evsprod\BLA761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5352-stud-rep-uncontr\dv0006
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4. DEVICE DESCRIPTION

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

- Safety Syringe (SS - PFS); i.e. accessorized PFS
- Autoinjector (AI)

The original "container closure" for the device is a prefilled and prestaked prefilled syringe, intended to deliver 1 mL of bimekizuab 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 (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) needle cover and a (b) (4) rigid shield. Figure 1–1 provides a simplified overview of the primary packaging components.

Figure 1–1: Overview of glass syringe barrel with staked needle and plunger stopper

Table 1–1: Materials of construction of the primary packaging

Component	Description	Supplier
1mL long syringe	Glass barrel: (b) (4) glass with staked stainless steel, 27G ½" special thin wall needle	(b) (4)
Plunger stopper	(b) (4) rubber	
Rigid needle shield (RNS)	Needle shield: (b) (4) (b) (4) Rigid shield: (b) (4)	

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.*

Reviewer Note:
The sponsor clarifies that primary container/PFS components are the only which have fluid contact or are fluid path contacting; therefore, this means that CDER CMC reviewers will address the potential for leachables/extractables of these materials into the drug product, which adequately addresses biocompatibility from CDRH assuming that this data is found to be adequate. Given this information, CDRH will only address biocompatibility of the SS and AI surface/skin contacting components.

The "container closure/PFS" described above is assembled with additional components into a safety syringe (SS-PFS) or autoinjector (AI), which are the final device presentations. See the device description for each device constituent below.

4.1. SS-PFS Description

The following regarding the device "container closure" is taken from docs:

- drug-product-container-closure-system-maa
- description-and-composition-dp-maa-ss-1ml
- pharmaceutical-development-container-closure-ss-1ml-maa

The bimekizumab-SS-1mL consists of the drug product in the PFS and the following device components which are shown in Figure 1–2.

- *Plunger rod*
- *Syringe unit*
- *Small round flange (SRF)* (b) (4).
- *Extended finger flange*
- *Overcap* (b) (4)

Reviewer Note:
It is noted that while the Sponsor speaks to a Prefilled syringe (PFS) and a Safety Syringe (SS), document: pharmaceutical-development-container-closure-pfs-1ml-maa, refers to the PFS as a standard PFS; i.e. a barrel, with plunger, and 27 G, 0.5 inch thin walled needle. The PFS is loaded into the safety syringe and is marketed and supplied to the user in this way.

The bimekizumab-SS-1mL is a customized version of the (b) (4) *1mL safety syringe. The function of the safety syringe components is to protect the user from the needle following injection of the contents of the syringe. The safety syringe components do not have any fluid path and do not have any contact with the drug product contained within the pre-filled syringe. The bimekizumab-SS-1mL has a limited contact duration with intact skin.*

(b) (4)

Figure 1–1: Bimekizumab-SS-1mL before use

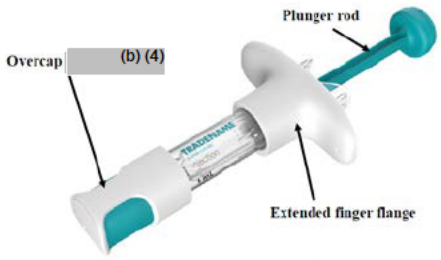
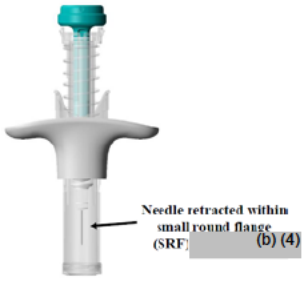


Figure 1–2: Bimekizumab-SS-1mL after use



The (b) (4) *are customized components designed to improve the handling of the safety syringe by the users. Table 1–2 provides an overview of the materials of construction for the bimekizumab-SS-1mL.*

Table 1–2: Materials of construction of the bimekizumab-SS-1mL

Device component	Materials of construction (b) (6)
Plunger rod	
SRF (b) (6)	
Extended finger flange	
Overcap (b) (6)	

The design and development activities for the bimekizumab-SS-1mL are a collaboration between [redacted] *and UCB.* [redacted] *is responsible for the manufacture and supply of the device components for the bimekizumab-SS-1mL. The pre-filled syringe is supplied by* [redacted] *the drug product manufacturing site. The design verification testing was performed at* [redacted] *UCB is responsible for the assembly, release, and supply of the bimekizumab-SS-1mL. The qualification and validation of the assembly process was performed at UCB. Both* [redacted] *and UCB have quality systems in place in accordance with ISO 13485.*

The principles of operation and user steps are below:

The principles of operation of the bimekizumab-SS-1mL safety feature are as follows:

- *At the end of the injection, when the plunger rod is pushed to the end of the syringe, the passive safety feature is activated.*
- *When the plunger rod is released the needle is automatically retracted and locked within the small round flange* [redacted] *to prevent needle stick injury.*

The user follows the instructions for use to perform the injection, and the main steps are summarized below.

1. Setting up for your injection
   a) Ensure the bimekizumab-SS-1mL is at room temperature
   b) Inspect the bimekizumab-SS-1mL
2. Choose and prepare the injection site
3. Inject bimekizumab
   a) Remove the overcap [redacted]
   b) Gently pinch and hold a fold of skin with one hand, with the other hand insert the needle into your skin at about a 45° angle. Push the needle all the way in then gently let go of your skin.
   c) Firmly push the plunger rod all the way down until all the medicine is injected and you cannot push the plunger rod any more.
   d) Lift your thumb off the plunger rod, the needle will automatically move back and lock in place.
4. Dispose of the used bimekizumab-SS-1mL
5. To perform the second injection required for a 320mg dose repeat steps 1 to 4

Reviewer Note:
Based on the principle of operation, this functions identically to a typical PFS with a needle safety device (NSD).

Of note based on current best review practices performance of the PFS devices, only the NSD will require review for device performance (needle safety activation, lockout, preactivation/drop testing, etc.), within FDA Guidance: Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download) and ISO 23908.

4.2. AI Description

The following regarding the device "container closure" is taken from doc: drug-product-container-closure-system-maa AND description-and-composition-dp-maa-ai-1ml.

The bimekizumab-AI-1mL consists of the drug product in the PFS and the following bimekizumab-AI-1mL components which are shown in Figure 1–3.

- *Cap remover sleeve*
- *Housing cover*
- (b) (4)
-

The bimekizumab-AI-1mL is a customized version of the (b) (4) *1mL auto-injector. The function of the auto-injector components is to automate the injection and to protect the user from the needle following injection of the contents of the syringe. The auto-injector components do not have any fluid path and do not have any contact with the drug product contained within the pre-filled syringe. The bimekizumab-AI-1mL has a limited contact duration with intact skin.*

Figure 1–3: Overview of the bimekizumab-AI-1mL

(b) (4)

Figure 1–1: Bimekizumab-AI-1mL before use

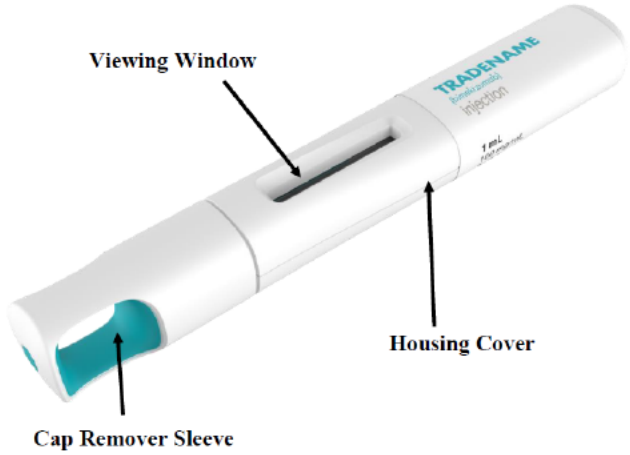
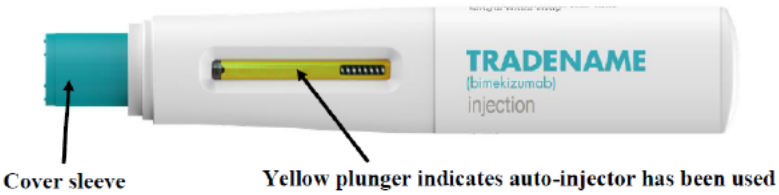


Figure 1–2: Bimekizumab-AI-1mL after use



There is a window to allow the user to inspect the drug appearance prior to injection and confirm the injection has been completed by checking the window is filled with the plunger rod. There is clear audible feedback at the start and end of the injection. The auto-injector conforms to ISO 23908 for the needle protection safety feature. The feature activates and locks to cover the needle

after the injection, once the bimekizumab-AI-1mL is released from the injection site.

The (b) (4) *are customized components designed to improve* (b) (4) *the auto-injector by the users.* (b) (4) *. Table 1–3 provides an overview of the materials of construction for the bimekizumab-AI-1mL.*

Table 1–3: Materials of construction of the bimekizumab-AI-1mL

Device component	Materials of construction
(b) (4)	

The principles of operation and user steps are below:

The principles of operation of the bimekizumab-AI-1mL are as follows:

- *Remove the cap remover sleeve which also removes the rigid needle shield from the prefilled syringe*
- *The pressure applied by the user when pressing the bimekizumab-AI-1mL against the skin retracts the cover sleeve into the device and moves the needle through the skin.*
- *The movement of the cover sleeve stops when the needle reaches the injection depth and the injection starts.*
- *The injection spring is released, a first audible click confirms the start of the injection, and the drug is expelled into the subcutaneous tissue.*
- *The travel of the plunger rod is visible through the viewing window.*
- *At the end of the injection, a second audible click confirms the plunger rod is fully depressed.*
- *When the bimekizumab-AI-1mL is removed from the skin the needle cover deploys automatically and locks into position to prevent needle stick injury.*

The user follows the instructions for use to perform the injection, and the main steps are summarized below.

1. Setting up for your injection
   a) Ensure the bimekizumab-AI-1mL is at room temperature
   b) Inspect the bimekizumab-AI-1mL
2. Choose and prepare the injection site
3. Inject bimekizumab
   a) Remove the cap remover sleeve
   b) Hold the bimekizumab-AI-1mL at a 90° angle to the injection site
   c) Place the bimekizumab-AI-1mL against the skin and firmly press down. You will hear a click sound.
   d) Keep holding the bimekizumab-AI-1mL pressed firmly against the skin. You will hear a second click within approximately 15 seconds after you hear the first click. The second click tells you the injection has finished. You should see the yellow color indicator filling the viewing window.
   e) Remove the bimekizumab-AI-1mL by carefully pulling the auto-injector straight up from your skin. The needle guard will automatically cover the needle.
4. Dispose of the used bimekizumab-AI-1mL
5. To perform the second injection required for a 320mg dose repeat steps 1 to 4

DEVICE DESCRIPTION REVIEW CONCLUSION

The device description is **ADEQUATE**

5. FILING REVIEW

CDRH performed a filing review and the content and results of the filing review can be found below.

5.1.Filing Review Checklist

Filing Review Checklist

Description	Present			
	Yes	No	N/A	Location/Notes
Description of Device Constituent	X			• Seq0001.3.2.P.2 • Seq0001.3.2.P.7 • Seq0001.2.3
Device Constituent Labeling	X			Seq0001.14
Essential Performance Requirements (EPRs) defined by the application Sponsor	X			Seq0001.3.2.P.2 (EPRs referred to as Critical Quality Attributes)
Design Requirements Specifications included in the NDA / BLA by the application Sponsor	X			Seq0001.3.2.P.2 – container closure
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X			Seq0001.3.2.P.2 – container closure
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X*		Seq0001.3.2.P.2 – container closure Risk management files are referenced but not provided. Will be necessary for the autoinjector device.

					*See Section 13.1 – IR to Sponsor – Resolved.
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X			Seq0001.3.2.P.2 – container closure
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X			• Seq0001.3.2.P.2 – container closure • Seq0001.3.2.P.5 Summary testing is provided.
	Engineering Performance	X			Seq0001.3.2.P.2 – container closure
	Biocompatibility/Chemistry	X			Seq0001.3.2.P.2 – container closure Biocompatibility is only referenced in this document. Full test reports need to be provided to determine if methods used are appropriate. See Section 13.1 – IR to Sponsor – Resolved.
	Sterility			X	Device components are not required to be sterile – Only container closure which the review of sterility is deferred to CDER.
	Shelf Life	X			Seq0001.3.2.P.2 – container closure
	Use Life			X	N/A – Single Use
	Transportation	X			Seq0001.3.2.P.3 – process validation ss & AI
	Clinical Validation	X			• Seq0001.3.2.P.2 – microbiology • Seq0001.3.2.R – HF clin summary
	Human Factors Validation	X			• Seq0001.3.2.P.2 – container closure • Seq0001.5.35.4 – pso Note - The review of this information is deferred to CDER/OSE/DMEPA
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X			• Seq0001.3.2.P.2 – container closure • Seq0001.3.2.P.3 – critical steps

	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X			Seq0001.3.2R – quality systems
	CAPA Procedure	X			Seq0001.3.2R – quality systems
	Control Strategy provided for EPRs	X			Seq0001.3.2.P.2 – Manuf Process

Reviewer Comment
As of 8/6/2020, there is some information missing from the submission that will be necessary to conduct a full review; however, it is information that should be able to be provided from the Sponsor during the course of the review clock.

See Section 13.1 – IR to Sponsor. Note that these information requests were
Resolved during the course of the review.

5.2.Facilities Information

This review includes only the final finished device manufacturers. This excludes component manufacturers, device testing facilities, etc.

Upon review of the 356h form, the final finished device manufacturers (PFS and AI) is: **UCB Pharma SA**

Firm Name:	UCB Pharma SA
Address:	Chemin du Foriest Braine-l'Alleud, Belgium 1420
FEI:	3003909356
Responsibilities:	Storage of master and working cell banks; manufacture and storage of drug product; final assembly of finished product; secondary packaging and labeling; quality control testing of drug substance (back-up), drug product, and finished product; stability testing of drug substance (back-up testing of samples only), drug product, and finished product; batch release of drug substance, drug product, and finished product.

Inspectional History
There has been no past device inspections of this manufacturer. Past drug inspections appear to be VAI or NAI inspections

Inspection Recommendation:
A Pre-Approval Inspection is recommended for the following reasons:

- The firm is responsible for major activities related to the manufacturing of the final combination product device constituent, specifically final product assembly, finished product secondary packaging and labeling, and finished product quality control, batch release, and stability testing.
- There has been no previous device inspection of the firm.

Reviewer Note:
On 8/14/2020, Lindsey Fleischman, having received the PAI request, asked the following to the CDRH regarding a PAI recommendation:

Do you know if this is mission critical? In order to travel for a device PAI it must be deemed mission critical given the current situation.

Based on information discussed with CDRH compliance officer reviewer Marc Neubauer and previous ORA investigator LCDR Michael Simpson, it was determined that based on the fact that the devices are intended to deliver low criticality products, where it is not an emergency and there is not a public safety concern, that a PAI inspection is not mission critical. I stated in response to Ms. Fleischman:

The product is not a necessarily a high risk medication, in that it is not an emergency use treatment where there is a public safety concern; therefore, I would say that it is NOT mission critical. However, the device manufacturer had not previously been inspected, so that is why we recommended PAI.

Given this information a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. This was communicated at the November 30, 2020, Mid-cycle meeting. Of note the drug facilities team also requested a Pre-Approval Inspection.

In addition, the CDER facilities team (Wayne Seifert – primary and Zhong Li – secondary) alerted the CDRH lead reviewer at the November 30, 2020, Mid-cycle meeting that there are potential data integrity accusations with the drug substance and drug quality systems, which will lead to a For Cause Inspection recommendation as the subject of an inspection, in addition to recommendations for device and drug quality systems inspections.

Wayne Seifert emailed Lindsey Fleischman (ORA) on November 30, 2020 requesting a status update on the inspections. Ms. Fleischman stated:

This facility was pushed for PAI. The goal date is 7/15/21. We will evaluate this facility to see if it will qualify for 704a4 review when we evaluate the PAI's pushed with July goal dates.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

5.3.Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☑ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☑ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☑ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	

☐ High Risk of cGMP issues:
If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Reviewer Comment
Both devices have low to moderate risk of cGMP issues given that the devices are relatively simple manufacturing/assembly processes. A summary QS review will be conducted in Section 12.

FILING REVIEW CONCLUSION

It is recommended that that BLA 761151 be **FILED**

A **Pre-Approval Inspection is recommended** for the following firm:

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

Reviewer Note:
A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. See Section 5.2 for full discussion.

6. LABELING

6.1.General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?			
	Yes	No	N/A	Comments
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X			N/A
Drug name is visible on device constituent and packaging	X			Packaging provided in Seq001.1.14
Device/Combination Product Name and labeling is consistent with the type of device constituent	X			N/A
Prescriptive Statement/Symbol on device constituent	X			N/A
Warnings	X			N/A

Contraindications	X			N/A
Instructions for Use	X			See Section 6.2 for IFU review
Final Instructions for Use Validated through Human Factors	X – See note			Human Factors validation testing is provided. Note – The review of this information is deferred to CDER/OSE/DMEPA

6.2.Instructions for Use Review

The Sponsor provided the AI and PFS cartons for each product. Below is an image of the AI carton labeling:

	Carton Labeling
AI	(b) (4)
	This appears to contain all required content from a device perspective.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

		(b) (4)

Reviewer Comments
The instructions for use contain necessary components. CDER/OSE/DMEPA will review human factors validation to support that the instructions for use and device design is adequately validated.

LABELING REVIEW CONCLUSION

The Labeling and Instructions for Use is Adequate.

7. DESIGN CONTROL SUMMARY

7.1.Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	Comments
Risk analysis conducted on the combination product	X		In response to a a CDRH IR the sponsor provided aSeq0012.1.11 IR Response #1. Resolved.
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		N/A
Mitigations are adequate to reduce risk to health	X		N/A
Version history demonstrates risk management throughout design / development activities	X		N/A
Design Inputs/Outputs	**Yes**	**No**	**Comments**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**Comments**
Validation of essential requirements covered by clinical and human factors testing	X		Seq001- pharmaceutical-development-container-closure-ai-1ml-maa Seq001- pharmaceutical-development-container-closure-ss-1ml-maa
To-be-marketed device was used in the pivotal clinical trial		X*	In response to CDRH IR the sponsor provided Seq0012.1.11 IR Response #2.

			It is stated that there were minor changes that have occurred to the device design: - PFS-SS – Changes to the finger flanges - AI – Changes to AI housing cover (b) (4) These changes would not appear to change how the device would have been clinically validation; however, this will be reviewed within Section 10 – Clinical Validation.
Bioequivalence Study utilized to-be-marketed device		N/A	See Section 10 – Clinical Study; no BE study completed.
Verification methods relevant to specific use conditions as described in design documents and labeling	X		Yes
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		Sponsor relies on ISO 11608 and other recognized standards for testing. There are no additional testing reliability requirements or recommendation from the Agency based on risk.
Traceability demonstrated for specifications to performance data	X		Seq001- pharmaceutical-development-container-closure-ai-1ml-maa Seq001- pharmaceutical-development-container-closure-ss-1ml-maa

Reviewer Comments
It should be noted that it is DHT3C's internal policy is to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and breakloose and glide force will not be addressed within this review. This approach was discussed with Rumi Young (Injection TL) on 8/6/2020 by email and Skype.

7.2.Design Inputs and Outputs

The Sponsor provides a summary of the inputs and outputs of the devices within documents:

- Seq001- pharmaceutical-development-container-closure-ai-1ml-maa

- Seq001- pharmaceutical-development-container-closure-ss-1ml-maa

Essential Performance Requirements
The following are what the Sponsor deems to be the essential performance requirements (EPRs) for the SS and AI

PFS – SS	
Design Inputs (Essential Performance Requirement)	**Design Outputs (Specification)**
Dose Accuracy (extractable volume)	≥ (b) (4) mL
Cap Removal Force	(b) (4) N
Safety feature activation force	(b) (4) N

Safety feature overriding force	≥ (b) (4) N

AI	
Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Dose Accuracy (extractable volume)	≥ (b) (4) mL
Injection Time	≤ (b) (4) seconds
Actuation Force	(b) (4) N ≤ F ≤ (b) (4) N
Needle Extension	(b) (4) mm
Cap Removal Force	≤ (b) (4) N
Audible Click	Click heard at end of injection
Visual indicators	Yellow color fills viewing window at end of injection

Reviewer Comments
These EPRs or Critical Quality Attributes (CQA) as identified by the Sponsor appear appropriate. As noted in previous sections only the NSD functions of the PFS-SS will be reviewed for safety and efficacy.

As stated previously in the review memo, it is current DHT3C's internal policy to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and break-loose and glide force will not be addressed within this review. This approach was address with Rumi Young (Injection TL) on 8/6/2020 by email and Skype.

DESIGN CONTROL REVIEW CONCLUSION

The Design Control information is adequate.

8. RISK ANALYSIS

8.1.Risk Management Plan

In the original submission (Seq0001), the Sponsor provided a summary of the risk management plan of the SS-PFS and AI. They state:

Risk management activities are conducted in accordance with medical devices risk management standard ISO 14971 and ICH Q9. Potential risks that may arise from the design, use or misuse of the bimekizumab-AI-1mL, and from the assembly process were identified, assessed and mitigated. Risk management covers the lifecycle of the product from design and development planning through lifecycle management and until discontinuation from market.

Risk management activities were conducted throughout the product design and development to identify hazards, estimate and evaluate risks, control these risks and monitor the effectiveness of the controls to ensure patient safety and product functionality. A risk-benefit analysis was conducted and showed the benefits that the bimekizumab-AI-1mL provides to the user outweigh the residual risks. Acceptability of individual residual risks and the overall residual risks associated with the device are documented in the risk-benefit analysis

The sponsor uses an ISO 14971 approach and examines all design, use, and process related risks. The Sponsor uses a semi-quantitative approach to demonstrated adequacy of risk via severity and probability. These documents were provided in response to an IR in Seq0012, #1. The general methodology grading of risk is aligned with ISO 14971:

Table 1: Severity levels of harm and definitions

Severity level	Rating	Definition
Catastrophic	5	Results in patient death
Critical	4	Results in permanent impairment or life-threatening injury
Serious	3	Results in injury or impairment requiring professional medical intervention
Minor	2	Results in temporary injury or impairment not requiring professional medical intervention
Negligible	1	Inconvenience or temporary discomfort
No Harm	0	No Harm

Table 2: Definition and rating of the probability of harm

Probability level	Rating	Probability Range
Frequent	5	$\geq 10^{-3}$
Probable	4	$< 10^{-3}$ and $\geq 10^{-4}$
Occasional	3	$< 10^{-4}$ and $\geq 10^{-5}$
Remote	2	$< 10^{-5}$ and $\geq 10^{-6}$
Improbable	1	$< 10^{-6}$

Table 3: Risk Acceptability Matrix for bimekizumab-AI-1mL

			Qualitative Severity levels					
			No Harm	Negligible	Minor	Serious	Critical	Catastrophic
			0	1	2	3	4	5
Semi-quantitative probability levels	Frequent	5	A	I	U	U	U	U
	Probable	4	A	I	U	U	U	U
	Occasional	3	A	A	I	I	I	U
	Remote	2	A	A	I	I	I	I
	Improbable	1	A	A	A	I	I	I

Table 4: Risk Acceptability Coding Definitions

Coding	Definition
U	Unacceptable risk
I	Investigate further risk reduction (IFRR)
A	Acceptable risk

The approach that the Sponsor provides is acceptable. Note that the SS-PFS risk analysis is not being analyzed for adequacy, only the AI design related risk analysis will be analyzed for adequacy.

8.2.Hazard Analysis and Risk Summary Report

The Sponsor in addition to the design manufacturer conducted a dFMEA for the AI device in Seq0012, doc: pharmaceutical-development-container-closure-ai-1ml-maa. The support of low risk uses probability of harm based on design mitigations and design verification testing. The sponsor utilizes this data to show post mitigation reduction of risk. The risk analysis addresses design related failures and supports adequate mitigation of risk associated with failure with no unacceptable related risks.

RISK ANALYSIS REVIEW CONCLUSION

The risk analysis is adequate.

9. DESIGN VERIFICATION REVIEW

9.1.Performance/Engineering Verification

9.1.1. *Essential Performance Requirement Evaluation*

The verification testing of the AI and SS-PFS devices' EPRs will be reviewed below.

As stated previously in the review memo, it is current DHT3C's internal policy to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and break-loose and glide force will not be addressed within this review. This approach was addressed with Rumi Young (Injection TL) on 8/6/2020 by email and Skype.

9.1.1.1.Safety Syringe – Prefilled Syringe Verification:

Summary testing is provided in doc: pharmaceutical-development-container-closure-ss-1ml-maa. Shipping testing was provided in doc: process-validation-ss-1ml-maa

Essential Performance Requirement (Design Input)	Specification (Design Output)	Method Acceptable (Y/N)	Verification (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Validation (Y/N)
Safety feature activation force	(b) (4) N	Yes – Uses force testing (force cell) to measure force.	All Passed – Safety feature activation force is measured at all preconditions in ISO 11608-1. Between 20-60 samples were tested depending on the conditioning.	All Passed – 60 samples were tested. Safety feature activation force all met specification	All Passed – 48 samples were tested. Safety feature activation force all met specification	Yes – See Section 11. Validated with human factors. The Sponsor also did a "*sharps handling testing*" validation testing, aligned with ISO 23908 (FDA recognized). Results showed "*that no lock-out failures or critical use errors were observed in 560 simulated injections*."

Safety feature overriding force	(b) (4) 0N	Yes – Uses force testing (force cell) to measure force.	All Passed – Safety feature overriding force is measured at all preconditions in ISO 11608-1. Between 20-60 samples were tested depending on the conditioning.	All Passed – 60 samples were tested. Safety feature activation force all met specification	All Passed – 48 samples were tested. Safety feature activation force all met specification	Yes – See Section 11. Validated with human factors. The Sponsor also did a "*sharps handling testing*" validation testing, aligned with ISO 23908 (FDA recognized). Results showed "*that no lock-out failures or critical use errors were observed in 560 simulated injections*."

Reviewer Comments

- While, dose accuracy and break-loose and glide force of the SS-PFS was not part of the CDRH review, the Sponsor provided this information and it appeared that all passed its specification.
- An accelerated aging study at 55 deg C (154 days) was completed to support the EPR meeting its specification up to the expiry.
- Shipping study was conducted per FDA recognized standard ASTM D4169.

9.1.1.2.Autoinjector EPR Verification:

Summary testing is provided in doc: pharmaceutical-development-container-closure-ai-1ml-maa. Shipping testing was provided in doc: process-validation-ai-1ml-maa

Essential Performance Requirement (Design Input)	Specification (Design Output)	Method Acceptable (Y/N)	Verification (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Validation (Y/N)

Dose Accuracy (extractable volume)	(b) (4) mL	Yes – Uses FDA recognized standard ISO 11608-1:2014, with all necessary conditions based on a single dose and fixed dose autoinjector device – cool, standard warm atmosphere, free fall, dry heat/cold storage, vibration, etc.	All Passed – Accuracy after preconditioning as designated in the standard for verification testing. Between 30-60 samples were tested depending on the conditioning. Requirement met.	All Passed – 60 samples were tested. Dose accuracy testing was completed, and all met specification	All Passed –50 samples were tested. Dose accuracy testing was completed, and all met specification.	Yes – See Section 10. Clinically validated.
Injection Time	(b) (4) seconds Note: The sponsor should support the adequacy of a (b) (4) second injection with design validation testing; e.g. human factors testing. Of note the labeling states to wait 15 seconds to remove injector from site.	Yes – measures time for full dose to be delivered. Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	All Passed – Injection time is measured at all preconditions in ISO 11608-1. Between 30-60 samples were tested depending on the conditioning. Note that the max injection time (~11.8 s) is seen after cool atmosphere exposure and cool storage. Requirement met	All Passed – 60 samples were tested. Injection time was completed, and all met specification	All Passed –50 samples were tested. Injection time testing was completed, and all met specification.	Yes – See Section 10 & 11. Clinically validated and with human factors.
Actuation Force	(b) (4)	Yes – Uses force testing (force cell) to measure force.	All Passed – Activation Force is measured at all preconditions in ISO	All Passed – 60 samples were tested. Actuation force was	All Passed –50 samples were tested. Actuation force testing was	Yes – See Section 11. Validated with human factors.

		Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	11608-1. Between 20-60 samples were tested depending on the conditioning. Note that the max actuation force (~8 N) is seen after cool storage. Requirement met	completed, and all met specification	completed, and all met specification.	
Needle Extension	(b) (4) mm	Yes – Cap sleeve is removed and needle length is measured for verification testing.	All Passed – Needle Extension is measured at all preconditions in ISO 11608-1. Between 20-60 samples were tested depending on the conditioning. Note that the min and max needle extension (5.60 and 5.98 mm) is seen at cool atmosphere and cool storage respectively. Requirement met	All Passed – 60 samples were tested. Needle extension was completed, and all met specification	All Passed –50 samples were tested. Needle extension testing was completed, and all met specification.	Yes – See Section 10. Clinically validated.
Cap Removal Force	(b) (4) N Note: The sponsor should support the adequacy of a	Yes – Uses force testing (force cell) to measure force. Uses preconditions as designated in ISO	All Passed – Safety Cap Removal Force is measured at all preconditions in ISO 11608-1. Between 20-60 samples were	All Passed – 60 samples were tested. Cap Removal Force was completed, and all met specification.	All Passed –50 samples were tested. Cap removal force testing was completed, and all met specification.	Yes – See Section 11. Validated with human factors.

	(b) (4) second injection with design validation testing; e.g. human factors testing. Of note the labeling states to wait 15	11608-1: 2014 for verification testing.	tested depending on the conditioning. Note that the max safe cap removal force (~17.19 N) is seen after cool atmosphere exposure. Requirement met			
Audible Click /Visual indicators	Click heard at end of injection Yellow color fills viewing window	Yes- Audible click/visual indicator were observed on dose accuracy testing samples. Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	All Passed – Audible click/visual indicator were observed on dose accuracy samples Requirement met	All Passed – Audible click/visual indicator were observed on dose accuracy samples	All Passed –50 samples were tested. Audible click/visual indicator were observed on dose accuracy samples after dose delivered.	Yes – See Section 11. Validated with human factors.

Reviewer Comments

- Dose accuracy testing was completed per FDA recognized standard ISO 11608-1 for a single dose, fixed dose device. This is acceptable.
- An accelerated aging study at 55 deg C (154 days) was completed to support the EPR meeting its specification up to the expiry.
- Shipping study was conducted per FDA recognized standard ASTM D4169. This is acceptable.

9.1.2. *Verification of Design Inputs Evaluation*

The Sponsor provides summary verification of the design outputs to demonstrate how they support the design inputs in documents: pharmaceutical-development-container-closure-ai-1ml-maa AND pharmaceutical-development-container-closure-ss-1ml-maa, for the AI and SS-PFS respectively.

DESIGN VERIFICATION REVIEW CONCLUSION
The Design Verification Documentation is adequate

9.2.Discipline Specific Sub-Consulted Review Summary

Based on the device designs the following discipline specific reviews are completed to support the adequacy of the device design verification documentation:

Discipline	Review Location	Comments
Biocompatibility	See below	N/A
Sterility	N/A	The device components are not sterile. The container closure of the prefilled syringe is, and this is deferred to CDER
Human Factors	Section 11	A cursory review will be conducted to address validation of the usability related specifications. The adequacy of the human factors study is deferred to CDER/OSE/DMEPA.

Biocompatibility:

The sponsor identifies all components of the SS-PFS and AI devices as skin contacting components with < 24 hours of total intact skin contact. I agree with this assessment of the contact duration and type from the Sponsor. Based on the contact type and duration type, the Sponsor provides cytotoxicity (C), sensitization (S), and irritation (I) testing to support the biocompatibility of the device. Full test reports were requested from the Sponsor in an IR. In Seq0012 will provide a summary of the CSI testing and results for the SS-PFS and AI device below:

Cytotoxicity:

Testing is provided in Seq0012, doc: md-q-101676. Cytotoxicity testing was conducted in accordance FDA recognized standard 10993-5 using L929 mouse fibroblast to support whether the device surface contacting components are cytotoxic. The testing was conducted separately for the SS-PFS and AI. The extraction conditions for each surface contacting component is below:

Sample	Amount	Vehicle	Volume	Ratio	Time/Temperature
Test Article	244.08 cm^2	complete MEM	81.4 mL	3 cm^2/mL	24 ± 2 hours at 37 ± 1 °C
Positive Control	30 cm^2	complete MEM	10.0 mL	3 cm^2/mL	24 ± 2 hours at 37 ± 1 °C
Negative Control	30 cm^2	complete MEM	10.0 mL	3 cm^2/mL	24 ± 2 hours at 37 ± 1 °C
Untreated Control	N/A	complete MEM	10.0 mL	N/A	24 ± 2 hours at 37 ± 1 °C

N/A: Not Applicable

The extracts for each sample above were incubated in fibroblast cell cultures to see the effects. The results were provided – the positive control showed viability issues and the negative and device test samples showed no significant viability issues. This is acceptable.

Sensitization:

Testing is provided in Seq0012, doc: md-q-101678. Sensitization testing was conducted in accordance FDA recognized standard 10993-10 using the Klingman Maximization test. The following extraction conditions were used: *The test article (244.08 cm2 as per Sponsor) was combined with 81.4 mL of vehicle following an 10993—12 ratio of 3 cm2 per 1 mL. The test article was separately extracted in NaCl and 080 at 70 :l: 2 for 24 2 hours*

under dynamic conditions. Intradermal injections were made into Guinea pigs to investigate for Sensitization issues through 7 days. Results were provided that supports that the test samples showed no significant sensitization issues, while the positive control showed significant sensitization issues. This is acceptable.

Irritation:
Testing is provided in Seq0012, doc: md-q-101677. Irritation testing was conducted in accordance FDA recognized standard 10993-10 using the intracutaneous injection testing with new Zealand white rabbits. The following extraction conditions were used: *The test article (244.08 cm2 as per Sponsor) was combined with 81.4 mL of vehicle following an ISO 10993—12 ratio of 3 cm2 per 1 mL. The test article was separately extracted in NaCl and C80 at 70 2 °C for 24 2 hours under dynamic conditions*. Test samples were injected intracutaneously into three rabbits at 5 sites for the test extract, positive, and negative controls. Results in the form of skin reaction scores and animal weights and clinical observations were provided. The results of the test sample extracts support that samples do not result in irritation. This is acceptable.

BIOCOMPATIBILTY REVIEW CONCLUSION
The Biocompatibility Documentation is adequate

10.CLINICAL VALIDATION REVIEW

There is no device specific clinical study information to review; however, this section will serve to discuss how the final device design has been clinically validated. An IR was sent to the Sponsor requesting that they confirm that the final finished device was used in the pivotal clinical study(s) to support validation of the device design. They stated in response in Seq0012

Two minor changes have been made to the device presentations used in clinical studies DV0002 and UP0033 to improve manufacturability. One change was made to the extended finger flange component part of the safety syringe, and the other change was made to the housing cover component part of the auto-injector. The changes do not impact the appearance, materials of construction, functionality, usability or safety of the device presentations. Details of the changes are as follows:

The CDER clinical reviewer stated that the autoinjector presentation was also clinically used in the study DV0006.

Safety Syringe:
Four guidance ribs have been added to the internal detail of the extended finger flange to aid assembly orientation.

Figure 1: Exploded view of the bimekizumab-SS-1ml

(b) (4)

Figure 2: Detailed view of the change to the extended finger flange

(b) (4)

Reviewer Note:
The only changes are to add (b) (4) finger flange component. This appears to be a minor manufacturing change and would be unlikely to affect the EPRs of the device that was seen during clinical testing. In addition, performance testing was conducted with the final finished SS-PFS device and it met its specifications. The design of the SS-PFS device is adequately validated from a clinical perspective.

Auto-injector:
A modification has been made to the (b) (4) *housing cover* (b) (4)

Figure 3: Exploded view of the bimekizumab-AI-1mL

Figure 4: Detailed view of the change to the housing cover

Change made to (b) (4)

Reviewer Note:
The only changes are being made to aid in (b) (4) in the injector body component. This appears to be a minor manufacturing change and would be unlikely to affect the EPRs of the device that was seen during clinical testing. In addition, performance testing was conducted with the final finished SS-PFS device and it met its specifications. The design of the SS-PFS device is adequately validated from a clinical perspective.

This appears to be a minor manufacturing change and would be unlikely to affect the EPRs of the device that was seen during clinical testing. In addition, performance testing was conducted with the final finished SS-PFS device and it met its specifications. The design of the SS-PFS device is adequately validated from a clinical perspective.

Reviewer Note:

The clinical reviewer, Kevin Clark, emailed me on 2/8/2021 regarding potential failures of the autoinjector presentation within the DV0002 clinical study. In his email he stated:

"*In the pivotal Phase 3 trials (PS008, PS0009, and PS0013), only the PFS presentation was used and injections were administered by study staff. The only time the autoinjector presentation was used was in the clinical-use studies DV0002 and DV0006, which were substudies of open-label extension Trial PS0014. We recommended that a minimum of 100 devices per presentation be collected and examined for any evidence of failure*."

In the clinical study document, Dv0002-body-text-1ml, Section 8.3.3, it is stated that of the 254 bimekizumab SS 1 mL device presentations, there no devices that showed structural integrity issues or functionality issues, which is acceptable. However of the 258 bimekizumab AI 1mL devices used in this study they state the following:

- 1 investigational AI device showed signs of "*post-use structural integrity issues*". "*Even with this issue, the site reported (and re-confirmed upon follow up) that the study participant had self-injected the complete dose safely and effectively. An evaluation of the PK trough concentrations associated with self-injection for this study participant (study participant* (b) (6) *) was consistent with incomplete administration of bimekizumab at the Baseline visit.*"
- 2 investigational AI devices showed signs of "*post-use functional compromise*": with 2 study participants:
  - *One of these 2 investigational device presentations (Kit Number 175050) was summarized in Section 8.3.3.1. The source data reports that both investigational device presentations in Kit Number 175050 used at the Baseline self-injections were functionally compromised.*
  - *The second investigational device presentation (1 of 2 in Kit Number 175334) reported with functional compromise, was used by a study participant to self-administer the first injection at Baseline (Listing 6.1b). Even with this reported issue, the site reported that the study participant had self-injected the complete dose safely and effectively using another kit.*

The Sponsor does not provide any additional context to these failures, such as what the failures were, the root causes of these failures, and how they were corrected for the future to be marketed product.

Update 3/10/2021
The Sponsor provided a response regarding the device failures, root causes, and any CAPA related activities in Section 13.3 and 13.4 of the memo. The Sponsor details two different types of failure modes:

- Kit #175343 – The expected root cause is: "*the cap had been removed and then replaced by the treating health care professional, which had activated the auto-injector causing the injection to start*." The Sponsor states that warning is within the labeling to warn the user against recapping the injector. On 3/10/2021, I requested the sponsor detail their full risk mitigation strategy around this failure mode, as labeling only may not be adequate.

  Update 3/17/2021:
  In response to the information request the Sponsor clarifies that it is not the removal or the act of recapping the device that triggers the premature activation, but it is the accidental pressure or contact that a user may apply the needle cover which could trigger activation. The design of the injector, however, should prevent this potential use error. The sponsor also discusses potential mitigation measures to this, which include activation force testing (b) (4). The response is adequate.

- Kit #175050 (PR#185312) – The expected root cause is: "*the absence of a syringe inside the auto-injector*", which caused the yellow plunger to fall out of the device. The Sponsor opened a CAPA related to implemented multiple 100% inspection on assembly related to the prefilled syringe (separate inspections of component presence, proper positioning of the syringe within the AI and prefilled syringe presence) and

retraining of the device manufacturers. These actions are appropriate, and the sponsor describes that this failure mode has not been identified since that time.

CLINICAL VALIDATION REVIEW CONCLUSION

The device has been clinically validated.

11. HUMAN FACTORS VALIDATION REVIEW

The human factors review is deferred to CDER/OSE/DMEPA. This section serves to support how the device EPR specifications have been adequately validated.

PFS-SS Human Factors Validation:

The sponsor provides summary information regarding the performance requirements and how they were validated in document: pharmaceutical-development-container-closure-ss-1ml-maa. The following is a summary of the human factors information (formative and summative):

Table 1–15: Human factors overview for the bimekizumab-SS-1mL

Study	Date	Objective	Conclusion
Formative evaluation 1	Feb 2017	Evaluation of cap removal force and instructions for use	All participants (16) were able to remove the cap at 20N and 30N. Two participants failed to remove the cap at 40N. This was further evaluated in formative evaluation 2 but it should be noted painted prototypes were used and the caps did not have the rubberized finish. **Design changes made as a result:** (b) (4) Improvements made to the instructions for use
Formative evaluation 2	April 2017	Evaluation of cap removal force, instructions for use, packaging concepts	All participants (17) were able to remove the cap at 35N and 40N **Design changes made as a result:** Improvements made to the instructions for use
Formative evaluation 3	September 2017	Evaluate design changes	All participants (40) delivered the full dose of bimekizumab. No unacceptable risks were found and the resulting residual use-related risk was acceptable **Design changes made as a result:** Improvements made to the instructions for use
Validation testing	October 2018	Confirm the user needs and intended user requirements are met	75 participants performed injections and were evaluated against the critical tasks identified. The intended users of the bimekizumab-SS-1mL can use the safety syringe safely and effectively. The residual use-related risk that remains after human factors validation is very low and cannot be further mitigated.

The HF validation report is provided in doc: md-q-101725. This document, specifically the critical tasks and results were briefly reviewed; there did not appear to be any specific concern where a large number of users failed to properly administer the product. I defer full review of the human factors review to CDER/OSE/DMEPA.

AI Human Factors Validation:

The sponsor provides summary information regarding the performance requirements and how they were validated in document: pharmaceutical-development-container-closure-ai-1ml-maa. The following is a summary of the human factors information (formative and summative):

Table 1–22: Human factors overview

Study	Date	Objective	Conclusion
Formative evaluation 1	Feb 2017	Evaluation of cap removal force, actuation force, and instruction for use	All participants (16) were able to remove the cap at 20N, 30N, and 40N and all could activate the bimekizumab-AI-1mL with activation force set out at 10N.
Formative evaluation 2	April 2017	Evaluation of use, instructions for use, packaging concepts	15 of 17 participants could perform a simulated injection and delivered a full dose on their first attempt. Two participants lifted the bimekizumab-AI-1mL away from the injection pad early resulting in a full dose not being delivered. These participants could self-correct when directed to refer to the instructions for use **Design changes made as a result:** Plunger color changed to yellow to improve visibility of injection progress Improvements made to the instructions for use
Formative evaluation 3	September 2017	Evaluate design changes	45 simulated injections were performed. All users delivered the full dose of bimekizumab. No unacceptable risks were found, and the resulting residual use-related risk was acceptable
Validation testing	October 2018	Confirm the user needs and intended user requirements are met	75 participants performed injections and were evaluated against the critical tasks identified. The intended users of the bimekizumab-AI-1mL can use the auto-injector safely and effectively. The residual use-related risk that remains after human factors validation is very low and cannot be further mitigated.

The HF validation report is provided in doc: md-q-101724. This document was briefly reviewed to analyze how the usability related essential performance requirements (needle cap removal force, injection time, activation force) were validated. See summary results below:

EPR	Validation Notes:
Safety Cap removal force	It is noticed that there is on user who couldn't' remove the cap and two other'\s that experienced difficulties. After review of the failure and difficulties they were not associated with the removal force. One user recapped the device prior to administering and others did not attempt to remove the cap. They also reference testing in formative evaluation where users were able to remove the safe cap. Given the low risk associated with failure to meet this specification and that the design verification consistently met this requirement, this specification is adequately validated through human factors testing.
Activation Force	There does not appear to be any failure or difficulties directly do the activation force of the device. Given this information, this specification is adequately validated through human factors testing.
Injection Time/Audible Click	It states within the human factors report that *6/75 participants removed the bimekizumab-AI-1mL early. Of the second attempts given, 1participant pulled away too early*. It is noted that the injection time specification is (b) (4) seconds and the instructions for use states to hold the activated device to inject for 15 seconds. This is a known issue with usability associated with autoinjectors, in that users can have difficulty holding it in place for the full injection. It is noted that it is a general thought that an injection over about 10 seconds can create difficulties for the user. Given that the specification for injection for this device is (b) (4) seconds and that all users, except for one held the device in place to inject (inclusive of first and second try), the specification is adequately validated and demonstrates that users are capable of injecting the full dose.

I defer full review of the human factors review to CDER/OSE/DMEPA.

HUMAN FACTORS VALIDATION REVIEW CONCLUSION

The human factors validation review is deferred to CDER/OSE/DMEPA.

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

See Section 5.2 of the subject review memo. A preapproval device QS inspection was recommended for UCB Pharma SA; however, the PAI inspection is not mission critical. Of note the drug facilities team also requested a Pre-Approval Inspection.

The CDER facilities team (Wayne Seifert – primary and Zhong Li – secondary) alerted the CDRH lead reviewer at the November 30, 2020, Mid-cycle meeting that there are potential data integrity accusations with the drug substance and drug quality systems, which will lead to a For Cause Inspection recommendation as the subject of an inspection, in addition to recommendations for device and drug quality systems inspections.

Wayne Seifert emailed Lindsey Fleischman (ORA) on November 30, 2020 requesting a status update on the inspections. Ms. Fleischman stated:

This facility was pushed for PAI. The goal date is 7/15/21. We will evaluate this facility to see if it will qualify for 704a4 review when we evaluate the PAI's pushed with July goal dates.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

Facility Regulatory History Review	
Firm Name:	UCB Pharma SA
Address & FEI:	Chemin du Foriest Braine-l'Alleud, Belgium 142 FEI#: 3003909356
Responsibilities:	Storage of master and working cell banks; manufacture and storage of drug product; final assembly of finished product; secondary packaging and labeling; quality control testing of drug substance (back-up), drug product, and finished product; stability testing of drug substance (back-up testing of samples only), drug product, and finished product; batch release of drug substance, drug product, and finished product. **Reviewer Note:** From a device perspective, the firm is the final device manufacturer and is responsible for final assembly of the combination product. The device quality systems will be reviewed to see if it is acceptable for approval.
Site Inspection Recommendation:	N/A – See Inspection Report Review below

Inspectional Report Review:
The inspection could not be conducted during this review cycle.

12.2. Quality Systems Documentation Review

As described in Section 5.3 of the review memo the device has low cGMP risk based on the intended use and device design. Based on the device design and overall complication of the manufacturing, the QS information will be reviewed for AI device and the assembly of the SS-PFS.

In support of the device manufacturer's ability to appropriately manufacture the device constituents, the Sponsor includes process validation of the device constituent's ability to meet the essential performance requirements specifications for three lots of product in documents: process-validation-ai-1ml-maa AND process-validation-ss-1ml-maa for the AI and SS-PFS respectively. All product met specification.

12.2.1. *Description of the Device Manufacturing Process - AI*

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the AI combination product, including the drug product/biologic and device constituent parts for the AI device in document: manuf-process-and-controls-ai-1ml-maal. The following is a summary.

Figure 1–1: Assembly process of the bimekizumab-AI-1mL

The Sponsor describes the receipt of the device components and assembly of the drug and device component in (doc: manuf-process-and-controls-ai-1ml-maa).

At the final assembly site (UCB, Braine), (b) (4) *inspection to verify the conformity to specifications and is internally released before being assembled into the bimekizumab-AI-1mL (see Section 3.2.P.7 – Auto-injector).* (b) (4) (b) (4)

- (b) (4)
-
-
-
-

Figure 1–2: Bimekizumab-AI-1mL components

(b) (4)

Assembly:

(b) (4)

The device manufacturing information is adequate.

12.2.2. *Description of the Device Manufacturing Process – SS-PFS*

(b) (4)

Figure 1–1: Assembly process of the bimekizumab-SS-1mL

(b) (4)

The Sponsor describes the receipt of the device components and assembly of the drug and device component in (doc: manuf-process-and-controls-ai-1ml-maa).

At the final assembly site (UCB, Braine), the device components (b) (4)

Figure 1–2: Bimekizumab-SS-1mL components

Assembly:

Device Manufacturing Process Conclusion
The Sponsor provided adequate information for the summary of the manufacturing process / production flow

12.2.3. *cGMP Review*

As described in Section 5.3 of the review memo the device has low cGMP risk based on the intended use and device design. Based on the device design and overall complication of the manufacturing, the QS information will be reviewed for AI device only, not the SS-PFS. The Sponsor chose a drug based, device cGMP streamlined approach. The information is taken from document: regional-us-quality-system-app-maa

21 CFR 820.20 Summary of Management Responsibility	Firm(s): UCB Pharma SA	**Reviewer Discussion** – The following information is provided within the submission: *The corporate quality system policy describes the main elements and interactions between the quality function and the other global and local functions needed to develop, implement, maintain, and improve the corporate quality system. It outlines management responsibilities so that a suitable, effective and adequately resourced quality system is in place to achieve quality objectives. Management is responsible for ensuring the provision of adequate and appropriate resources (human, financial, material, facilities, equipment, training) to implement and*

		maintain the quality management system and continually improve its effectiveness. *The corporate quality system policy also outlines the corporate quality responsibilities, including maintenance of the global infrastructure for the management of quality for UCB. This implies ensuring effective quality systems are in place to achieve the quality objectives, ensuring the system is maintained in accordance with current regulations and best industry practices and that effective communication and escalation occurs to raise quality issues to the appropriate levels of management. The quality agreement between UCB sites details the quality roles and responsibilities for intergroup commercial supply and distribution of products, including testing, release and supply chain oversight.* This information adequately fulfills this requirement.
21 CFR 820.30 Summary of Design Controls	Firm(s): UCB Pharma SA	**Reviewer Discussion** – Reviewed in detail in Section 7 . The following information is provided within the submission (b) (4)  *Lifecycle management activities* This information adequately fulfills this requirement.
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): UCB Pharma SA	**Reviewer Discussion** – The following information is provided within the submission: (b) (4)  This information adequately fulfills this requirement.

21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): UCB Pharma SA	**Reviewer Discussion** – The following information is provided within the submission (b) (4) This information adequately fulfills this requirement.

GMP Compliance Summary Conclusion
The Sponsor provided adequate summary information about the GMP compliance activities

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents for the AI (doc: control-critical-steps-ai-1ml-maa) and SS-PFS (doc: control-critical-steps-ss-1ml-maa). The Sponsor also described process validation of the device functionalities – AI (doc: process-validation-ai-1ml-maa) and SS-PFS (process-validation-ss-1ml-maa). This is reviewed within the table below.

Essential Performance Requirements Control Strategy Table

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N)
Autoinjector Control Strategy		

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The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

The facilities and quality systems information is adequate.

As stated in Section 5's recommendation, a Pre-Approval Inspection was recommended for:

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place.

At a late cycle with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be able to be conducted in this review cycle. Therefore, assuming that there are no approval deficiencies from the review team the CDER team will continue the review past the goal date, so that a review decision on this application can be made.

<<END OF REVIEW>>

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	March 28, 2023
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761151
Product Name, Dosage Form, and Strength:	Bimzelx (bimekizumab-bkzx) injection, 160 mg/mL single-dose prefilled syringe and 160 mg/mL single-dose autoinjector
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	UCB, Inc.,
FDA Received Date:	January 31, 2022, November 21, 2022, and January 27, 2023
TTT ID #:	2022-2953
DMEPA 1 Safety Evaluator:	Corwin D. Howard, PharmD, RPh
Acting DMEPA 1 Team Leader:	Madhuri R. Patel, PharmD

1 REASON FOR REVIEW

As part of the approval process for Bimzelx (bimekizumab-bkzx) injection, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Bimzelx Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed Prescribing Information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling, may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for UCB, Inc.,.

4 RECOMMEDATIONS FOR DIVISION OF DERMATOLOGY AND DENTISTRY (DDD)

Table 2. Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information – General Issues			
Highlights of Prescribing Information			
1.	The Dosage and Administration section contains an error-prone symbol (i.e., ≥).	Use of error-prone symbols to describe dosage information may lead to misinterpretation and medication error (e.g., mistaken as opposite of intended).[a]	Consider replacing the symbol "≥" with the intended meaning (e.g., greater than or equal to).
Full Prescribing Information – Section 2 Dosage and Administration			
1.	As currently presented, Section 2.2 Dosage contains the symbol "≥".	Use of error prone symbols to describe dosage information may lead to misinterpretation and medication error (e.g., mistaken as opposite of intended).[a]	Consider replacing the symbol "≥" with the intended meaning (e.g., greater than or equal to).
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	We note there is a space between the slash, "/" and unit of measurement, "mL" in the strength.	Inconsistent with the other the sections of the PI.	Consider revising the strength to remove the space so that the statement states "160 mg/mL".

[a] ISMP's List of Error-Prone Abbreviations, Symbols, and Dose Designations [Internet]. Horsham (PA): Institute for Safe Medication Practices. 2021 [cited 2022 JUN 6]. Available from: http://www.ismp.org/tools/errorproneabbreviations.pdf.

5 RECOMMENDATIONS FOR UCB, INC.,

Table 3. Identified Issues and Recommendations for UCB, Inc., (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton & Sample Carton Labeling			
1.	The volume lacks adequate spacing between the numerical value and unit of measure (i.e. 1mL).	Lack of adequate spacing may impact readability and might result in wrong strength errors. For example, the "m" in mL can sometimes be mistaken as a zero or two zeros.	We recommend placing adequate space between the numerical value and unit of measure (e.g., [1 mL instead of 1mL]) to improve readability.
2.	As currently presented, the inclusion of a machine-readable (2D data matrix barcode) product identifier is not indicated.	The Drug Supply Chain Security Act (DSCSA) guidance on product identifiers recommends a machine-readable (2D data matrix barcode) product identifier and a human-readable product identifier. The guidance also recommends the format of the human-readable portion be located near the 2D data matrix barcode as the following: NDC: [insert NDC] SERIAL: [insert serial number] LOT: [insert lot number] EXP: [insert expiration date]	We recommend that you review the guidance*. If you determine that the product identifier requirements apply to your product's labeling, we request you add a placeholder for the machine readable (2D data matric barcode) product identifier to the carton labeling. *The guidance is available from: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Bimzelx that UCB, Inc., submitted on November 21, 2022.

Table 4. Relevant Proposed Product Information for Bimzelx	
Initial Approval Date	N/A
Active Ingredient	bimekizumab
Indication	Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.
Route of Administration	Subcutaneous
Dosage Form	Injections
Strength	160 mg/mL
Dose and Frequency	320 mg (two 160 mg injections) 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.
How Supplied	A sterile, preservative-free, clear to slightly opalescent and pale brownish-yellow solution. Each prefilled autoinjector or prefilled syringe contains 1 mL of a 160mg/mL solution. Supplied as: Autoinjector: • NDC 50474-781-85: Carton of two 160 mg/mL single-dose autoinjectors. Each prefilled autoinjector is fixed with a 27 gauge ½ inch needle. Prefilled Syringe: • NDC 50474-780-79: Carton of two 160 mg/mL single-dose prefilled syringes. Each prefilled syringe is fixed with a 27 gauge ½ inch needle with needle guard.
Storage	Store cartons refrigerated between 2°C to 8°C (36°F to 46 F). Keep the product in the original carton to protect it from light until the time of use. Do not freeze. Do not shake. Do not use beyond expiration date. Does not contain a preservative; discard any unused portion. Not made with natural rubber latex. When necessary, prefilled syringes or autoinjectors may be stored at room temperature up to 25° C (77°F) in the original carton for a single period of up to 30 days. Once prefilled

	syringes or autoinjectors have been stored at room temperature, do not place back in refrigerator. Write the date removed from the refrigerator in the space provided on the carton and discard if not used within a 30-day period.

APPENDIX B. PREVIOUS DMEPA REVIEWS

On March 13, 2023, we searched for previous DMEPA reviews relevant to this current review using the terms, "761151". Our search identified '3' previous reviews[b,c,d], and we considered our previous recommendations to see if they are applicable for this current review.

[b] Owens, L. Memorandum Review of Revised Label and Labeling for Bimzelx (bimekizumab-bkzx) (BLA 761151). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2021 AUG 19. OSE RCM No.: 2020-1496-2 and 2020-1506-2.

[c] Owens, L. Memorandum Review of Revised Label and Labeling Review for Bimzelx (bimekizumab-bkzx) (BLA 761151). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 27. OSE RCM No.: 2020-1496-1 and 2020-1506-1.

[d] Owens, L. Human Factors Study Report and Label and Labeling Review for Bimzelx (bimekizumab-bkzx) (BLA 761151). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 04. OSE RCM No.: 2020-1496 and 2020-1506.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[e] along with postmarket medication error data, we reviewed the following Bimzelx labels and labeling submitted by UCB, Inc.,.

- Container label(s) received on January 27, 2023
- Carton labeling received on January 31, 2022
- Professional Sample Carton Labeling received on January 31, 2022
- Instructions for Use (Images not shown) received on November 21, 2022, available from \\CDSESUB1\EVSPROD\bla761151\0068\m1\us\114-labeling\draft\labeling\ifu-pfs-202008i-sub-highlighted.pdf \\CDSESUB1\EVSPROD\bla761151\0068\m1\us\114-labeling\draft\labeling\ifu-ai-202008i-sub-highlighted.pdf
- Medication Guide (Image not shown) received on November 21, 2022, available from \\CDSESUB1\EVSPROD\bla761151\0068\m1\us\114-labeling\draft\labeling\medguide-202008i-sub-highlighted.pdf
- Prescribing Information (Image not shown) received on November 21, 2022, available from \\CDSESUB1\EVSPROD\bla761151\0068\m1\us\114-labeling\draft\labeling\cir-202008i-sub-highlighted.pdf

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[e] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: September 29, 2021

To: Kevin Clark, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Gordana Diglisic, MD, Clinical Team Leader, DDD
Strother Dixon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments BIMZELX®(bimekizumab-bkzx) injection, for subcutaneous use

BLA: 761151

In response to DDD's consult request dated September 15, 2021, OPDP has reviewed the proposed product labeling (PI) and Medication Guide for the original BLA submission for BIMZELX® (bimekizumab-bkzx) injection, for subcutaneous use (Bimzelx).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on September 21, 2021, and our comments are provided below.

Medication Guide: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide will be sent under separate cover.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	September 29, 2021
To:	Strother Dixon, PharmD Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Sharon R. Mills, BSN, RN, CCRP Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Susan Redwood, MPH, BSN, RN Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG)
Drug Name (established name):	BIMZELX (bimekizumab-bkzx)
Dosage Form and Route:	injection, for subcutaneous use
Application Type/Number:	BLA 761151
Applicant:	UCB, Inc.

1 INTRODUCTION

On July 15, 2020, UCB, Inc., submitted for the Agency's review an original Biologics License Application (BLA) 761151 for BIMZELX (bimekizumab-bkzx) injection, seeking Agency approval to market BIMZELX (bimekizumab-bkzx), injection, for the proposed use for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of DDD on September 21,2021, respectively, for DMPP and OPDP to provide an additional review of the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for BIMZELX (bimekizumab-bkzx), injection due to additional changes to the proposed Prescribing Information (PI). Based on clarification with DDD, it was determined that the IFU does not need additional review at this time. DMPP and OPDP previously completed a collaborative review of the MG and IFU for BIMZELX (bimekizumab-bkzx) injection on August 31, 2021.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs will be forthcoming.

2 MATERIAL REVIEWED

- Draft BIMZELX (bimekizumab-bkzx) MG received on July 16, 2020, and received by DMPP and OPDP on September 21, 2021.
- Draft BIMZELX (bimekizumab-bkzx) Prescribing Information (PI) received on July 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on September 21, 2021.
- Approved COSENTYX (secukinumab) comparator labeling dated May 28, 2021.
- Approved TALTZ (ixekizumab) comparator labeling dated March 10, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG using the Arial font, size 10.

In our collaborative review of the MG we:

- simplified wording and clarified concepts where possible

- ensured that the MG is consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG is consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

5 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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/s/

SUSAN W REDWOOD
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09/29/2021 04:19:25 PM

LASHAWN M GRIFFITHS
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Date	9/27/2021		
To:	Anh-Thy Ly (CDER/OPQ/OPRO/DRBPMI/RBPMB1)		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	CDER/OII/DDD
From	Matthew Ondeck OPEQ/OHT3/DHT3C		
Through (Team)	Suzanne Hudak, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CAPT. Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	BLA 761151, bimekizumab ICC2100783 Case #00735613		
Final Recommendation	CDRH recommends that the device constituent parts of the combination product (Autoinjector and Safety Syringe) be approved pending an adequate pre-approval inspection of UCB Pharma SA, which is aligned with the filing (8/6/2020), mid-cycle (10/20/2020), and final recommendations (3/17/2021) under CDRH's previous review of BLA 761151 under ICC200619 and under Salesforce Cases: #00023177 and #0002318. See Section 2 for the Executive Summary, which further clarifies this recommendation.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Matthew Ondeck -S Digitally signed by Matthew Ondeck -S Date: 2021.09.27 16:32:48 -04'00'	Suzanne J. Hudak -S Digitally signed by Suzanne J. Hudak -S Date: 2021.09.29 08:56:52 -04'00'	

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761151
Sponsor	UCB, Inc.
Drug/Biologic	bimekizumab
Indications for Use	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Device Constituent	Prefilled Syringe and Auto-Injector
Related Files	IND 128707 – Meeting Request Reviews BLA761151/ ICC2100783 – CDRH current review memo

Review Team		
Lead Device Reviewer	Matthew Ondeck	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A*	N/A*	N/A*

* No additional CDRH consults necessary for this review

Important Dates	Due Date
Due Date	9/27/2021

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends that the device constituent parts of the combination product (Autoinjector and Safety Syringe) be approved pending an adequate pre-approval inspection of UCB Pharma SA, per the original CDRH review memo (ICC2100783), dated 3/17/2021,

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. Of note the drug facilities team also requested a Pre-Approval Inspection.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

At a post late cycle meeting that took place on 9/16/2021, CDER/OPQ stated that ORA is unable to send a device quality systems specific inspector on a foreign, non-mission critical, inspection at this time. In addition, they stated that while the drug inspection will be taking place on-site at the firm in the future, there was no ability for ORA to send a device investigator to the future on-site inspection. While CDRH clarified, per the finalized 3/17/2021 memo, that CDRH was open to a 704(a)(4) inspection (paper-based inspection), CDER/OPQ insisted that CDRH provide a "current recommendation" via a signed memo, even though it was made clear to the team that the CDRH recommendation regarding the recommended inspection had not changed in the time since the original BLA 761151 review memo.

Therefore, to further clarify CDRH's unchanged inspection recommendation, that was documented in the BLA 761151/ under CDRH's previous review of BLA 761151 under ICC200619 and Salesforce Cases: #00023177 and #0002318, was stated over email with CDER/OPQ, and was discussed in the 9/16/2021 with CDER/OPQ, please see the following statement:

If ORA is unable to send an investigator with device quality systems focus, for a non-mission critical inspection (with respect to the device), to tag along with the future on-site drug inspection that is expected to occur in the future, then a 704(a)(4) inspection (paper-based inspection) would be acceptable from CDRH's standpoint. However, if there is a way to send out a device specific investigator to the future on-site inspection for the drug product, then that would be CDRH's preference, so that efforts are not duplicated with multiple inspections occurring (paper and on-site).

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/s/

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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Pharmacovigilance and Epidemiology

Integrated Safety Review

Date: September 8, 2021

Reviewers: Jessica Weintraub, PharmD, BCPS, Safety Evaluator
LCDR Melissa Reyes, MD, MPH, DTMH, Medical Officer
Division of Pharmacovigilance I

Benjamin J. Booth, PhD, MS, Epidemiologist
Division of Epidemiology I

Team Leaders: CDR Vicky Chan, PharmD, BCPS, Safety Evaluator Team Leader
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Catherine C. Lerro, PhD, MPH, Epidemiology Acting Team Leader
Division of Epidemiology I

(Deputy) Division Directors: Cindy Kortepeter, PharmD, Division Director
Division of Pharmacovigilance I

CAPT Sukhminder K. Sandhu, PhD, MPH, MS, Deputy Division Director
Division of Epidemiology I

Established Name	Trade Name	BLA Number	Applicant
Bimekizumab	Bimzelx	761151	UCB
Secukinumab	Cosentyx	125504	Novartis Pharmaceuticals
Ixekizumab	Taltz	125521	Eli Lilly
Brodalumab	Siliq	761032	Bausch Health

Subject: Hepatitis B reactivation

OSE RCM #s: 2021-1238, 2021-1272

Thank you to the DPV Oncology and Hematology Malignancies Team and the Anti-infectives, Anti-virals, and Ophthalmology Team for their reviews on hepatitis B reactivation which were helpful in this review.

TABLE OF CONTENTS

EXECUTIVE SUMMARY

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for cases or observational studies of hepatitis B virus (HBV) reactivation (HBV-R) reported with secukinumab, ixekizumab, or brodalumab, the currently approved monoclonal antibodies (mAbs) with activity against interleukin (IL)-17 cytokines or receptors. The three currently approved biologics with activity against IL-17 cytokines or receptors will be referred to collectively as anti-IL-17 mAbs in this review. The Division of Dermatology and Dentistry (DDD) requested the Division of Epidemiology-I (DEPI) and the Division of Pharmacovigilance (DPV) to conduct this review to inform the labeling for bimekizumab, another IL-17 antagonist, related to the potential for HBV-R. Bimekizumab has a prescription drug user fee act (PDUFA) date of October 15, 2021.

We identified cases reporting HBV-R with secukinumab use. The information in the cases reporting ixekizumab and brodalumab use was not sufficient to assess their potential role in HBV-R at this time. The cases with secukinumab did not report serious clinical outcomes; however, HBV-R is preventable and potentially life-threatening. These findings are relevant to bimekizumab, based on the potential signal for liver injury with bimekizumab.

We identified three relevant epidemiologic studies evaluating HBV-R and secukinumab through a search of the published observational literature, though only one study directly evaluated the relationship between secukinumab and HBV-R using adjusted comparative analysis. However, this study found that patients treated with secukinumab were less likely to experience HBV-R compared to patients treated with a TNF-α inhibitor. We did not identify studies that examined anti-IL-17 mAbs other than secukinumab in relation to HBV-R. There is not enough high-quality epidemiologic evidence examining the relationship between anti-IL-17 mAbs and HBV-R at this time to meaningfully inform labeling for bimekizumab or other anti-IL-17 mAbs.

We support the proposed inclusion of HBV-R as a secondary outcome in the long-term safety PMR drafted by DDD. Although the limited published epidemiologic literature at this time is insufficient to provide labeling recommendations for bimekizumab, based on our review of the postmarketing case series, and consistent with the AASLD and AAD/NPF guidelines, we recommend that DDD consider the following:

- (b) (4)
-
-

DPV will continue to monitor for cases reporting HBV-R with the anti-IL-17 mAbs.

1 INTRODUCTION

This review evaluates FDA Adverse Event Reporting System (FAERS) reports and the medical literature for cases or observational studies of hepatitis B virus (HBV) reactivation (HBV-R) reported with secukinumab, ixekizumab, or brodalumab, the currently approved monoclonal antibodies (mAbs) with activity against interleukin (IL)-17 cytokines or receptors. The three currently approved biologics with activity against IL-17 cytokines or receptors will be referred to collectively as anti-IL-17 mAbs in this review. The Division of Dermatology and Dentistry (DDD) requested the Division of Epidemiology-I (DEPI) and the Division of Pharmacovigilance (DPV) to conduct this review to inform the labeling for bimekizumab, another IL-17 antagonist, related to the potential for HBV-R. Bimekizumab has a prescription drug user fee act (PDUFA) date of October 15, 2021.

1.1 BACKGROUND

Consult

On July 15, 2020, UCB submitted a biologics license application (BLA 761151) for bimekizumab, a humanized mAb that binds to IL-17A, IL-17F, and IL-17AF cytokines, for the proposed indication of the treatment of moderate to severe plaque psoriasis.[1] DDD consulted the Drug-Induced Liver Injury (DILI) team to evaluate cases of elevated transaminases and jaundice with bimekizumab. The DILI team noted that no cases of HBV-R were seen in the bimekizumab clinical trials. However, based on published reports of HBV-R with secukinumab, another IL-17 antagonist, they recommended that DDD should consider labeling for bimekizumab to screen for HBV infection prior to starting treatment, and if appropriate, monitor for reactivation and consider prophylactic antiviral treatment.[2,3] They also recommended that DDD consult the Office of Surveillance and Epidemiology (OSE) to evaluate FAERS and the literature for HBV-R with the anti-IL-17 mAbs.

DDD issued a consult on June 22, 2021, requesting DEPI to review an article titled "Safety Profile of Secukinumab in the Treatment of Patients with Psoriasis and Concurrent Hepatitis B or C: A Multicentric Prospective Cohort Study" and to perform a literature review to determine if HBV-R has been reported in postmarketing studies for currently approved anti-IL-17A mAbs.[4] The consult request states:

> Please review and provide information regarding whether HBV reactivation has been reported post-marketing for other currently approved anti-IL-17 products, which are listed below:
>
> - Cosentyx (secukinumab), BLA 125504, anti-IL-17A mAb
> - Taltz (ixekizumab), BLA 125521, anti-IL-17A mAb
> - Siliq (brodalumab), BLA 761032, mAb that blocks IL-17A receptor
>
> Based on your findings please provide recommendations for labeling(s).

One of the articles included in the consult is a case series, and upon cursory literature search, DEPI identified additional case series and reports. Thus, DEPI suggested to DDD to also consult DPV to review the literature case series and other relevant pharmacovigilance data on HBV-R with the anti-IL-17 mAbs.

On July 25, 2021, in a follow-up e-mail to DPV, the DILI team suggested consideration of labeling for secukinumab for HBV-R in WARNINGS AND PRECAUTIONS or ADVERSE REACTIONS, and for ixekizumab and brodalumab either continued monitoring or labeling for HBV-R referencing the cases reported with secukinumab.[5]

DDD has proposed a postmarketing requirement (PMR) for a prospective, observational study to address the long-term safety of bimekizumab. The proposed study will include "serious infection (including reactivation of Hepatitis B)" as a secondary outcome. See Appendix A for proposed PMR language as of July 21, 2021.

Anti-IL-17 mAbs

Secukinumab is a human immunoglobulin (Ig) G1 mAb that selectively binds to the IL-17A cytokine and inhibits its interaction with the IL-17 receptor, inhibiting the release of proinflammatory cytokines and chemokines.[6] Ixekizumab is a humanized IgG4 mAb that selectively binds with the IL-17A cytokine and inhibits its interaction with the IL-17 receptor, inhibiting the release of proinflammatory cytokines and chemokines.[7] Brodalumab is a human IgG2 mAb that selectively binds to human IL-17 receptor A and inhibits its interactions with cytokines IL-17A, IL-17F, IL-17C, IL-17A/F heterodimer, and IL-25, inhibiting IL-17 cytokine-induced responses including the release of proinflammatory cytokines and chemokines.[8]

Hepatitis B

Hepatitis B is a vaccine-preventable liver infection caused by HBV and spread through blood, semen, or other body fluids from an infected person.[9] HBV infection can be an asymptomatic short-term illness or can become a long-term chronic infection leading to cirrhosis or liver cancer. The Centers for Disease Control and Prevention (CDC) estimates that 862,000 people were living with HBV infection in the United States in 2016, and that in 2018, there were 21,600 new cases of HBV. The prevalence of chronic HBV infection (CHB) ranges from <2% in low prevalence areas, including the United States and Canada, to 2-7% in intermediate prevalence areas such as China and Japan, to >8% in high prevalence areas such as Western Africa.[10] Data on the prevalence of HBV in patients with psoriasis compared to the general population are conflicting, with studies in some countries showing a higher prevalence of HBV in patients with psoriasis, while in other countries psoriasis was not associated with a higher prevalence of HBV.[11] A cross-sectional study using the Northwestern Medicine Enterprise Data Warehouse, an electronic medical record data repository of patients primarily in the Chicago area, screened patients for HBV between September 2010 and September 2016. They found non-significantly lower prevalence of HBV in patients with psoriasis compared to those without (OR = 0.56, 95% CI = 0.34-1.03); due to the cross-sectional design of the study, a temporal relationship could not be established. Prevalence of HBV was 0.5% in patients with psoriasis and 0.8% in patients without psoriasis.[12]

Screening for HBV infection includes measurement of HBV-specific antigens and antibodies. See Table 1 for the serologic markers and their interpretation.[13]

Table 1. Interpretation of Hepatitis B Serologic Test Results				
	HBsAg	**anti-HBc**	**anti-HBs**	**IgM anti-HBc**
Susceptible	Negative	Negative	Negative	
Resolved infection	Negative	Positive	Positive	
Immune due to vaccination	Negative	Negative	Positive	
Acutely infected	Positive	Positive	Negative	Positive
Chronically infected (CHB)	Positive	Positive	Negative	Negative
Interpretation unclear*	Negative	Positive	Negative	

Abbreviations: HBsAg=Hepatitis B surface antigen, anti-HBc=Total hepatitis B core antibody, anti-HBs=Hepatitis B surface antibody, IgM anti-HBc=IgM antibody to hepatitis B core antigen, CHB=Chronic hepatitis B

* Possibilities include 1) resolved infection (most common), 2) false-positive anti-HBc and thus susceptible, 3) "low-level" chronic infection, and 4) resolving acute infection

Clinical recovery from HBV infection is not an indicator of complete cure, defined as complete eradication of HBV DNA from each hepatocyte. Replication-competent HBV DNA may persist in hepatocytes in the absence of detectable HBsAg. CHB is defined as sustained, detectable HBsAg for at least six months in serum. Patients with CHB can transition through phases with variable levels of alanine aminotransferase (ALT), HBV DNA, and HBV antigens.[14] They can be subdivided into different categories based on HBV DNA levels, presence or absence of Hepatitis B e Antigen (HBeAg), and the extent of liver involvement. Although some patients with CHB have HBV DNA levels that vary widely, generally patients with inactive CHB have HBV DNA levels <2,000 IU/mL, and those with immune-active CHB have HBV DNA levels >20,000 IU/mL.[14] Patients with HBV DNA >20,000 IU/mL are typically positive for HBeAg, while lower HBV DNA levels are typically seen in CHB patients negative for HBeAg.

Different definitions of HBV-R have been proposed based on virologic criteria, serologic criteria, or both. According to The American Association for the Study of Liver Diseases (AASLD), HBV-R is reasonably defined as one of the following:[14]

- In patients who are HBsAg positive and anti-HBc positive:
  - A $\geq$2 log (100-fold) increase in HBV DNA compared to baseline OR
  - HBV DNA $\geq$3 log (1,000) IU/mL in patients with previously undetectable HBV DNA OR
  - HBV DNA $\geq$4 log (10,000) IU/mL if baseline level is not available
- In patients who are HBsAg negative and anti-HBc positive:
  - HBV DNA is detectable OR
  - Reverse seroconversion occurs (reappearance of HBsAg)

Although HBV-R can occur spontaneously, it is more commonly triggered by immunosuppression-mediated weakening of host immune control.[15] The intensity of immunosuppression varies based on factors including the type of therapy, dose, and duration of therapy. Additional risk factors for HBV-R include the extent of HBV control of replication prior to immunosuppressive treatment (patients with CHB are at higher risk than patients with

resolved infection), non-A HBV genotype, male sex, older age, underlying diseases, such as lymphoma, and use of direct-acting antivirals for hepatitis C virus (HCV) coinfection.[10]

Clinical manifestations of HBV-R can range from silent viral load elevation without hepatitis to elevated viral load with fulminant liver failure, hepatic synthetic dysfunction, encephalopathy, and coagulopathy.[15] HBV-R can be prevented through screening of at-risk individuals and initiation of antiviral prophylaxis if indicated.

The AASLD 2018 Hepatitis B Guidance advises that "all persons who are positive for anti-HBc (with or without anti-HBs) should be considered potentially at risk for HBV reactivation" in the setting of treatment with chemotherapeutic or immunosuppressive drugs.[14] The guidelines note that because "HBsAg-positive patients are at high risk of HBV reactivation, especially if their HBV-DNA levels are elevated,…they should receive anti-HBV prophylaxis before the initiation of immunosuppressive or cytotoxic therapy…HBsAg-negative, anti-HBc–positive patients are at lower risk of HBV reactivation than HBsAg-positive patients, and depending on their clinical situation and feasibility of close monitoring, they could be initiated on anti-HBV prophylaxis or monitored with the intent of on-demand anti-HBV therapy initiation at the first sign of HBV reactivation."

Previous OSE Reviews

The Food and Drug Administration Amendments Act Section 915 Postmarket Safety Summary Analysis for secukinumab, completed on March 23, 2017, identified no cases of HBV-R.[16] A subsequent DPV review of infection-related deaths did not identify deaths related to HBV-R.[17] The Postmarket Drug Safety Surveillance Summary (surveillance summary) for ixekizumab, completed on November 6, 2017, reported no cases of reactivation of viral hepatitis.[18] The surveillance summary for brodalumab, completed on May 13, 2016, included a poorly documented foreign case of a patient with a history of HBV infection with a detectable level of HBV DNA after starting brodalumab. The case did not provide concomitant medications, report treatment for HBV, and reported that brodalumab was restarted with the events reported as resolved.[19]

1.2 REGULATORY HISTORY

Table 2 includes the initial FDA approval dates and approved indications for the anti-IL-17 mAbs.

Table 2. Initial FDA Approval Dates and Approved Indications for the Anti-IL-17 Monoclonal Antibodies

Name	BLA Number	Initial FDA Approval Date	Approved Indications*
Secukinumab	125504	January 21, 2015	• For the treatment of moderate to severe plaque psoriasis in patients 6 years and older who are candidates for systemic therapy or phototherapy • For the treatment of adult patients with active psoriatic arthritis

Table 2. Initial FDA Approval Dates and Approved Indications for the Anti-IL-17 Monoclonal Antibodies			
Name	**BLA Number**	**Initial FDA Approval Date**	**Approved Indications***
			• For the treatment of adult patients with active ankylosing spondylitis • For the treatment of adult patients with active non-radiographic axial spondylitis with objective signs of inflammation
Ixekizumab	125521	March 22, 2016	• For the treatment of patients 6 years of age and older with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy • For the treatment of adult patients with active psoriatic arthritis • For the treatment of adult patients with active ankylosing spondylitis • For the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation
Brodalumab	761032	February 15, 2017	• For the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies
*As of June 29, 2021			

1.3 RELEVANT PRODUCT LABELING

Secukinumab, ixekizumab, and brodalumab are not labeled for HBV-R and do not include recommendations for serologic testing for HBV. Labeling relevant to infections from the WARNINGS AND PRECAUTIONS sections are excerpted below. The secukinumab labeling lists increased transaminases occurring in <1% of subjects in the *Clinical Trials Experience* subsection of ADVERSE REACTIONS. The ixekizumab and brodalumab labeling does not include liver-related adverse reactions.

1.3.1 Secukinumab

5 WARNINGS AND PRECAUTIONS

5.1 Infections
COSENTYX may increase the risk of infections. In clinical trials, a higher rate of infections was observed in COSENTYX treated subjects compared to placebo-treated subjects. In placebo-controlled clinical trials in subjects with moderate to severe plaque psoriasis, higher rates of common infections, such as nasopharyngitis (11.4% versus 8.6%), upper respiratory tract infection (2.5% versus 0.7%) and mucocutaneous infections with candida (1.2% versus 0.3%)

were observed with COSENTYX compared with placebo. A similar increase in risk of infection was seen in placebo-controlled trials in subjects with psoriatic arthritis, ankylosing spondylitis and non-radiographic axial spondyloarthritis. The incidence of some types of infections appeared to be dose-dependent in clinical studies *[see Adverse Reactions (6.1)]*. In the postmarketing setting, serious and some fatal infections have been reported in patients receiving COSENTYX.

Exercise caution when considering the use of COSENTYX in patients with a chronic infection or a history of recurrent infection.

Instruct patients to seek medical advice if signs or symptoms suggestive of an infection occur. If a patient develops a serious infection, monitor the patient closely and discontinue COSENTYX until the infection resolves.

5.2 Pre-Treatment Evaluation for Tuberculosis
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with COSENTYX. Avoid administration of COSENTYX to patients with active TB infection. Initiate treatment of latent TB prior to administering COSENTYX. Consider anti-TB therapy prior to initiation of COSENTYX in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Monitor patients closely for signs and symptoms of active TB during and after treatment.

5.6 Immunizations
Prior to initiating therapy with COSENTYX, consider completion of all age appropriate immunizations according to current immunization guidelines. COSENTYX may alter a patient`s immune response to live vaccines. Avoid use of live vaccines in patients treated with COSENTYX.

1.3.2 Ixekizumab

5 WARNINGS AND PRECAUTIONS

5.1 Infections
TALTZ may increase the risk of infection. In clinical trials in adult patients with plaque psoriasis, the TALTZ group had a higher rate of infections than the placebo group (27% vs. 23%). Upper respiratory tract infections, oral candidiasis, conjunctivitis and tinea infections occurred more frequently in the TALTZ group than in the placebo group. A similar increase in risk of infection was seen in placebo-controlled trials in patients with pediatric psoriasis, psoriatic arthritis, ankylosing spondylitis, and non-radiographic axial spondyloarthritis *[see Adverse Reactions (6.1)]*.

Instruct patients treated with TALTZ to seek medical advice if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy, monitor the patient closely and discontinue TALTZ until the infection resolves.

5.2 Pre-Treatment Evaluation for Tuberculosis

Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with TALTZ. Do not administer to patients with active TB infection. Initiate treatment of latent TB prior to administering TALTZ. Consider anti-TB therapy prior to initiating TALTZ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Patients receiving TALTZ should be monitored closely for signs and symptoms of active TB during and after treatment.

5.5 Immunizations
Prior to initiating therapy with TALTZ, consider completion of all age appropriate immunizations according to current immunization guidelines. Avoid use of live vaccines in patients treated with TALTZ. No data are available on the response to live vaccines.

1.3.3 Brodalumab

5 WARNINGS AND PRECAUTIONS

5.3 Infections
SILIQ may increase the risk of infections. In clinical trials, subjects treated with SILIQ had a higher rate of serious infections than subjects treated with placebo (0.5% versus 0.2%) and higher rates of fungal infections (2.4% versus 0.9%). One case of cryptococcal meningitis occurred in a subject treated with SILIQ during the 12-week randomized treatment period and led to discontinuation of therapy [see Adverse Reactions (6.1)].

During the course of clinical trials for plaque psoriasis, the exposure-adjusted rates for infections and serious infections were similar in the subjects treated with SILIQ and those treated with ustekinumab.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing SILIQ. Instruct patients to seek medical help if signs or symptoms of clinically important chronic or acute infection occur. If a patient develops a serious infection or is not responding to standard therapy for the infection, monitor the patient closely and discontinue SILIQ therapy until the infection resolves.

5.4 Risk for Latent Tuberculosis Reactivation
Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with SILIQ. Do not administer SILIQ to patients with active TB infection. Initiate treatment for latent TB prior to administering SILIQ.

Consider anti-TB therapy prior to initiation of SILIQ in patients with a past history of latent or active TB in whom an adequate course of treatment cannot be confirmed. Closely monitor patients receiving SILIQ for signs and symptoms of active TB during and after treatment.

5.6 Immunizations
Avoid use of live vaccines in patients treated with SILIQ. No data are available on the ability of live or inactive vaccines to elicit an immune response in patients being treated with SILIQ.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We included cases meeting one of the criteria below:

Category I: Cases with diagnostic evidence
A case reporting a prior history of HBV exposure AND diagnostic evidence of HBV-R with secukinumab, ixekizumab, or brodalumab treatment as defined by one or more of the following:

- An increase in or appearance of HBV DNA
- Detection of HBsAg in a patient who was previously HBsAg negative and anti-HBc positive

Category II: Cases without diagnostic evidence
A case reporting HBV-R with secukinumab, ixekizumab, or brodalumab treatment without supportive clinical or diagnostic evidence of HBV-R (for example, serologies) to meet above criteria for Category I.

2.2 CAUSALITY CRITERIA

We used the criteria in Table 3 to assess the possible causal relationship between the anti-IL-17 mAb and HBV-R.

Table 3. Causality Assessment Categories and Criteria	
Temporal relationship without other possible contributory risk factors reported	• Case reporting the temporal relationship of HBV-R from starting an anti-IL-17 mAb AND • Case reporting that there was no use of concomitant immunosuppressants or other factors suspected to contribute to HBV-R
Temporal relationship with other possible contributory risk factors reported	• Case reporting the temporal relationship of HBV-R from starting an anti-IL-17 mAb AND • Case reporting one or more factors, such as immunosuppressant use, that could contribute to HBV-R
Insufficient information to assess temporal relationship or other possible contributory risk factors	• Case not reporting the temporal relationship of HBV-R from starting an anti-IL-17 mAb OR • Case providing no information to assess for concomitant immunosuppressant use or other factors that could contribute to HBV-R

2.3 FAERS SEARCH STRATEGY

DPV searched the FAERS database with the strategy described in Table 4.

Table 4. FAERS Search Strategy*	
Date of search	July 8, 2021
Time period of search	January 21, 2015† - July 7, 2021

Table 4. FAERS Search Strategy*	
Search type	FDA Business Intelligence Solution (FBIS) Quick Query
Product terms	Product active ingredients: Secukinumab, Ixekizumab, Brodalumab
MedDRA search terms (Version 24.0)	Preferred Terms: *Acute hepatitis B, Chronic hepatitis B, Congenital hepatitis B infection, Hepatitis B, Hepatitis B antibody, Hepatitis B antibody abnormal, Hepatitis B antibody negative, Hepatitis B antibody normal, Hepatitis B antibody positive, Hepatitis B antigen, Hepatitis B antigen positive, Hepatitis B core antibody, Hepatitis B core antibody negative, Hepatitis B core antibody positive, Hepatitis B core antigen, Hepatitis B core antigen positive, Hepatitis B DNA assay, Hepatitis B DNA assay negative, Hepatitis B DNA assay positive Hepatitis B DNA decreased, Hepatitis B DNA increased, Hepatitis B e antibody, Hepatitis B e antibody negative, Hepatitis B e antibody positive, Hepatitis B e antigen, Hepatitis B e antigen negative, Hepatitis B e antigen positive, Hepatitis B immunization, Hepatitis B reactivation, Hepatitis B surface antibody, Hepatitis B surface antibody negative, Hepatitis B surface antibody positive, Hepatitis B surface antigen, Hepatitis B surface antigen negative, Hepatitis B surface antigen positive, Hepatitis B test negative, Hepatitis B virus test, Hepatitis B virus test positive*
* See Appendix B for a description of the FAERS database. † U.S. approval date for secukinumab Abbreviations: MedDRA=Medical Dictionary for Regulatory Activities	

2.4 LITERATURE SEARCH STRATEGY

DPV searched the medical literature with the strategy described in Table 5 to identify cases reporting HBV-R with anti-IL-17 mAb use.

Table 5. Literature Search Strategy	
Date of search	July 2, 2021
Database	Embase, PubMed
Search terms	(secukinumab OR ixekizumab OR brodalumab) AND hepatitis
Years included in search	All
Filters	English language

DEPI focused on observational studies of currently approved anti-IL-17 mAbs and HBV-R published in medical literature, including:

- One article submitted to DEPI from DDD[2]

We also conducted a literature review to identify additional observational studies that evaluated the association between currently approved anti-IL-17 mAbs (secukinumab, ixekizumab, and

brodalumab) and HBV-R. We searched PubMed on June 28, 2021 using the following search terms:

1. *(secukinumab AND ("hepatitis b" OR "HB" OR "HBV") AND reactiv*)*
2. *(ixekizumab AND ("hepatitis b" OR "HB" OR "HBV") AND reactiv*)*
3. *(brodalumab AND ("hepatitis b" OR "HB" OR "HBV") AND reactiv*)*
4. *(bimekizumab AND ("hepatitis b" OR "HB" OR "HBV") AND reactiv*)*

The first search yielded seven possible articles. Of these articles, one was previously identified by DDD,[2] one was not relevant to our search[a], two were case reports, one was a case series, and two were reviews. One additional article was identified through review of the references in these articles[20] and one more was identified through review of articles that cited these articles.[21]

The second, third, and fourth searches yielded zero possible articles.

2.5 PERIODIC SAFETY REPORTS

DPV screened the following periodic safety reports (PSRs) for information on HBV-R with the anti-IL-17 mAbs.

2.5.1 Secukinumab

- Periodic Safety Update Report (PSUR) covering December 26, 2019 to December 25, 2020[22]

2.5.2 Ixekizumab

- PSUR covering March 23, 2020 to March 22, 2021[23]

2.5.3 Brodalumab

- Periodic Adverse Experience Report (PAER) covering February 15, 2020 to February 14, 2021[24]

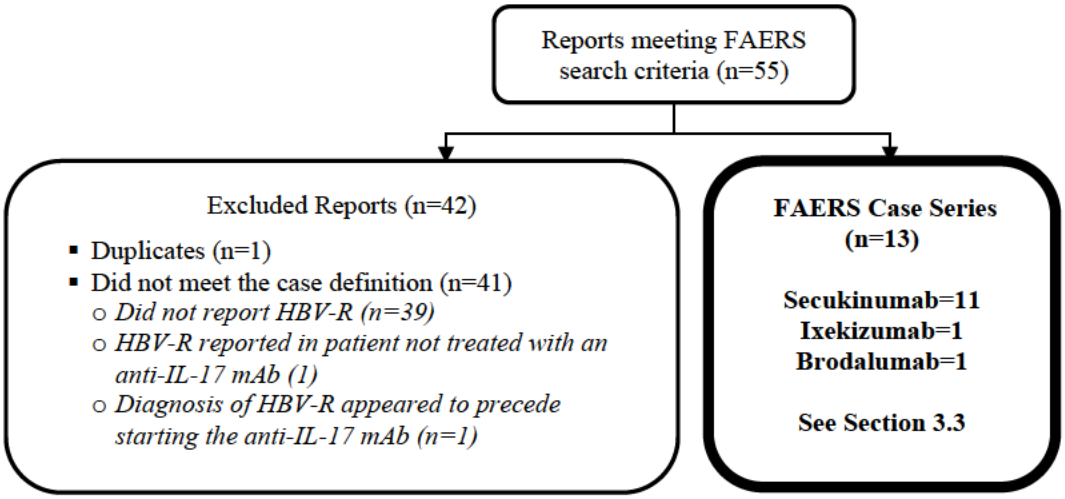
3 RESULTS

3.1 FAERS CASE SELECTION

The FAERS search retrieved 55 reports. After applying the case definition in Section 2.1 and accounting for duplicate reports, 13 FAERS cases were included in the case series of HBV-R reported with anti-IL-17 mAb use (see Figure 1).

[a] This article only mentioned HBV in its exclusion criteria and did not mention reactivation.

Figure 1. FAERS Case Selection



Eight of the 13 FAERS cases were also published in the medical literature.[2,25] Additional case characteristics are provided in Section 3.3.

3.2 Literature Case Reports

We identified one additional published case reporting HBV-R with secukinumab use that met our case definition that was not identified in our FAERS search.[26] The case is summarized below and is included in our case series (see Tables 7 and 8).

Parmar et al. reported HBV-R in a 48-year-old woman an unspecified time after starting secukinumab for severe plaque psoriasis. The patient had a history of HBV infection (diagnostic information not provided). Concomitant medication was not reported, but previous treatments for her psoriasis included MTX, cyclosporine, adalimumab, and ustekinumab (time relative to secukinumab treatment not reported). Her psoriasis improved on secukinumab, but she experienced HBV-R (diagnostic information not provided). She was treated with tenofovir and secukinumab was continued. Four months after starting secukinumab, she developed a widespread eczematous reaction and intense generalized pruritus, and secukinumab was stopped. No additional follow up was provided.[26]

Reviewer's comment: This case met our case definition criteria of Category II (without diagnostic evidence), based on the lack of diagnostic information. We categorized the causality assessment as insufficient information to assess time to onset of HBV-R from starting secukinumab and lack of information on concomitant medication use.

Anti-IL17 mAb use in patients with HBV

Publications reporting cases with HBV treated with anti-IL-17 mAbs that included information on HBV status during or after anti-IL-17 mAb treatment are included in Table 6. The cases reporting HBV-R are included in our case series.

Table 6. Publications Reporting Cases with Hepatitis B Virus (HBV) Infection and Treatment with Anti-IL-17 mAbs				
First Author Publication Year	**Cases with HBV**	**Pretreatment HBV Status (n)**	**Cases Receiving Antivirals with Anti-IL-17 mAb**	**Cases Reporting HBV Reactivation***
Secukinumab				
Siegel SAR[27] 2017	2	HBV (1)	1	0
		HBV, HCV (1)	1	0
Snast I[20] 2017 (see Section 3.4 for summary)	3	HBsAg –, anti-HBc +, anti-HBs + (2)	0	0
		HBsAg –, anti-HBc +, anti-HBs – (1)	0	0
Yanagihara S[28] 2017	1	HBsAg +, anti-HBc +, anti-HBs –, HBV DNA –	1	0
Bevans SL[29] 2018	1	"seropositive HBV"	NS	0
Chiu H-Y[2]2018 (see Section 3.4 for summary)	49	HBsAg + anti-HBs – (25)	3	6 (none received antivirals)
		HBsAg –, anti-HBc +, anti-HBs + (13)	0	0
		HBsAg –, anti-HBc +, anti-HBs – (11)	0	1
Feaster B[30] 2018	1	Congenital HBV, "viral loads stable"	NS	0
Lasagni C[31] 2018	2	HBsAg –, anti-HBc +, anti-HBs + (1)	0	0
		HBsAg –, anti-HBC +, anti-HBs –, HCV + (1)	1 (taken irregularly)	0
Peccerillo F[32] 2018	1	HBsAg –, anti-HBc +, anti-HBs +, HBV-DNA –, anti-HCV +	1	0
Shibata T[33] 2019	1	Anti-HBs +, HBV DNA –	NS	0
Galluzzo M[34] 2020	6	HBsAg –, anti-HBc +, HBV DNA – (3)	0	0
		HBsAg +, anti-HBc +, HBV DNA + (2)	2	0
		CHB and HCV coinfection (1)	NS	0
Moneva-Leniz LM[35] 2020	4	HBsAg + (CHB), HBV DNA – (2)	1	0
		HBsAg –, anti-HBc +, anti-HBs +, HBV DNA – (2)	1	0

Table 6. Publications Reporting Cases with Hepatitis B Virus (HBV) Infection and Treatment with Anti-IL-17 mAbs				
First Author Publication Year	**Cases with HBV**	**Pretreatment HBV Status (n)**	**Cases Receiving Antivirals with Anti-IL-17 mAb**	**Cases Reporting HBV Reactivation***
Özçelik S[36] 2020	4	HBsAg –, anti-HBc +, anti-HBs + (2)	0	0
		HBsAg –, anti-HBc +, anti-HBs – (2)	0	0
Santhanam S[37] 2020	1	Anti-HBc +	1	0
Zhu S-M[38] 2020	1	HBsAg –, anti-HBc +, HBV DNA –, HCV +	0	0
Parmar S[26] 2021 (see Section 3.2 for summary)	1	HBV	0	1
Ixekizumab				
Eguchi K[25] 2018 (see Section 3.3.2 for summary)	1	HBsAg –, anti-HBc +, anti-HBs –	0	1
Koike Y[39] 2019	1	HBsAg +, HBV DNA 2.8 log IU/mL	1	0
Lora V[40] 2019	1	HBsAg –, anti-HBc +, anti-HBs +, HBV DNA –, anti-HCV +	1	0

Abbreviations: HBsAg=Hepatitis B surface antigen, anti-HBc=Hepatitis B core antibody, anti-HBs=Hepatitis B surface antibody, CHB=Chronic hepatitis B, NS=Not specified, HBV=Hepatitis B virus, HCV=Hepatitis C virus
*All cases reporting HBV reactivation are included in our case series.

3.3 CASE CHARACTERISTICS FOR FAERS AND LITERATURE CASES

Table 7 summarizes the 11 FAERS cases and 1 additional literature case of HBV-R reported with secukinumab use. The cases reporting HBV-R with ixekizumab and brodalumab are summarized in Sections 3.3.2 and 3.3.3, respectively. Table 8 in Section 3.3.4 includes additional case characteristics for the overall case series. Appendix C includes a line listing of the 14 cases in this case series.

3.3.1 Secukinumab

Table 7. Descriptive Characteristics of Cases Reporting Hepatitis B Virus Reactivation (HBV-R) with Secukinumab in FAERS and the Literature, Received by FDA or Published Through July 7, 2021		
	(N=12)	
Case Source*	FAERS	11
	Literature	1
Year received by FDA or published	2018	9
	2019	1
	2020	1
	2021	1
Reported outcome† (FAERS cases only, n=11)	Other serious	11
Country	Brazil	1
	Great Britain	1
	Hong Kong	1
	Italy	1
	Taiwan	8
Age (years; n=9)	Mean	55
	Median	49
	Range	36-68
Sex (n=11)	Male	10
	Female	1
Reason for secukinumab use (n=11)	Psoriasis	8
	Psoriatic arthropathy	3
Secukinumab dose‡ (n=9)	150 mg at Weeks 0, 1, 2, 3, then every 4 weeks	1
	150 mg every week	1
	300 mg at Weeks 0, 1, 2, 3, then every 4 weeks	6
	300 mg every 4 weeks	1
Time to onset from starting secukinumab (months; n=9)	Mean	5.8
	Median	3
	Range	1-12
Concomitant immunosuppressants (n=8)	Methotrexate 5 mg weekly	1
	None	7

* FAERS- Includes any case identified in either FAERS alone or in both FAERS and the literature
Literature- Includes cases only identified in the literature

† For the purposes of this review, the following outcomes qualify as serious: death, life-threatening, hospitalization (initial or prolonged), disability, congenital anomaly, required intervention and other serious important medical events.

‡ The recommended dose for patients with psoriasis and for patients with psoriatic arthritis with coexistent moderate to severe plaque psoriasis is 300 mg subcutaneously at Weeks 0, 1, 2, 3, and 4, followed by every 4 weeks. For some patients a dose of 150 mg may be acceptable.

3.3.2 Ixekizumab

One case reported in the foreign medical literature and submitted to FDA with a partial translation reported HBV-R with ixekizumab and MTX:[25]

FAERS Case #14820225 Version 2, Japan (2018), Other serious

A 50-year-old woman was diagnosed with HBV-R 6 months after starting ixekizumab (dosage not specified) and MTX 8 mg (route and interval not specified) for the treatment of rheumatoid arthritis in an unspecified clinical trial. An unspecified time prior to starting ixekizumab and MTX, the patient was HBsAg negative, anti-HBc positive, and anti-HBs negative (reported as 7.09 mIU/mL). Pretreatment HBV DNA was not reported. Other medical history and concomitant medications were not provided. Six months after starting ixekizumab and MTX, HBV DNA was detected at <2.1 LC/mL (approximately 21 IU/mL assuming LC stands for "log copies"). HBsAg remained negative, and liver enzymes were not reported. The patient did not receive antiviral therapy. The action taken for ixekizumab and MTX and additional follow-up were not provided.[25]

Reviewer's comment: This case met our case definition as a Category I (with diagnostic evidence) case. Based on the concomitant use of MTX, we categorized the causality as temporal relationship with other possible contributory risk factors reported. According to the AASLD guidelines, this patient was lower risk for HBV-R based on her pretreatment serology results and fulfills the criteria for HBV-R due to detectable HBV DNA (although pretreatment HBV DNA was not reported). The case did not include additional information regarding the clinical outcome.

3.3.3 Brodalumab

FAERS Case #15823614 Version 2, Japan (2019), Other serious

HBV was detected in a 75-year-old man approximately 5.5 months after starting, and 4 months after stopping brodalumab 210 mg (interval not specified) for psoriasis. HBV was detected prior to starting brodalumab, "but did not exceed the reference value." According to the report, the patient had no medical history and concomitant medication was not reported. At an unspecified time, the patient was HBsAg negative and "HBV core antigen positive." The patient was treated with brodalumab for approximately 1.5 months, after which it was stopped for "introduction of clinical trials for other drug." Approximately 4 months after stopping the brodalumab, HBV was detected (level not reported), and "introduction of clinical trials was canceled." Brodalumab was restarted and a repeat HBV DNA on an unspecified date was negative. Five months later, HBV had not been detected again. The case did not report if the patient received an antiviral.

Reviewer's comment: This case met our case definition as a Category I (with diagnostic evidence) case, with causality assessed as insufficient information to assess for risk factors based on the lack of information on concomitant medication use. The case reported an increase in HBV DNA four months after his last dose of brodalumab, but HBV appears to have been detected prior to starting brodalumab, so the time of HBV-R relative to brodalumab use is unclear. At the time of reporting, the patient continued brodalumab without evidence of HBV-R. Although the brodalumab labeling does not include a half-life, the recommended brodalumab dosing interval for maintenance therapy is 2 weeks.[8]

3.3.4 Case Series

Table 8 includes case characteristics for the case series.

Table 8. Descriptive Characteristics of Cases Reporting Hepatitis B Virus Reactivation (HBV-R) with anti-IL-17 Monoclonal Antibodies in FAERS and the Literature, Received by FDA or Published Through July 7, 2021 (N=14)

		SECU (n=12)	IXE (n=1)	BROD (n=1)
Pretreatment HBV serologies and HBV DNA	HBsAg – , anti-HBc +, anti HBs –	1	1	0
	HBV DNA 20 IU/mL	1		
	HBV unknown		1	
	HBsAg +, anti-HBc +, anti HBs –	6	0	0
	HBV DNA undetectable	1		
	HBV DNA 20-4310 IU/mL	5		
	HBsAg –, "HB core antigen +"	0	0	1
	HBV detected, <reference value			1
	Unknown	5	0	0
HBV DNA at time of HBV-R	<2,000 IU/mL	4		
	2,277 IU/mL	1		
	8,630 IU/mL	1		
	68,800 IU/mL	1		
	"54 log 1.73 IU/mL"	1		
	"20 IU and over"			1
	<2.1 LC/mL		1	
	Unknown	4		
Pretreatment alanine aminotransferase*	12-34 IU/L	3		
	40-71 IU/L	3		
	133 IU/L	1		
	Unknown	5	1	1
Alanine aminotransferase at time of HBV-R*	19 IU/L	1		
	37-72 IU/L	6		
	Unspecified liver test "deranged"	1		
	Unknown	4	1	1
Antiviral therapy prior to HBV-R	Not treated with antiviral	7		
	Unknown	5	1	1
Action taken for anti-1L-17 mAb for HBV-R and antiviral therapy for HBV-R	Stopped	1	0	Stopped prior to HBV-R
	Treated with antiviral	1		
	Unknown			1
	Continued	8	0	0
	Treated with antiviral	4		
	Not treated with antiviral	4		
	Unknown	3	1	0
	Treated with antiviral	1		
	Not treated with antiviral		1	
	Unknown	2		

Table 8. Descriptive Characteristics of Cases Reporting Hepatitis B Virus Reactivation (HBV-R) with anti-IL-17 Monoclonal Antibodies in FAERS and the Literature, Received by FDA or Published Through July 7, 2021 (N=14)				
		SECU (n=12)	**IXE (n=1)**	**BROD (n=1)**
Case definition criteria and causality assessment	Category I (with diagnostic evidence)	7	1	1
	Without other risk factors reported	7		
	With other risk factors reported		1	
	Insufficient information to assess			1
	Category II (without diagnostic evidence)	5	0	0
	With other risk factors reported	1		
	Insufficient information to assess	4		
* The American Association for the Study of Liver Diseases defines normal alanine aminotransferase as ≤35 U/L for men and ≤25 U/L for women. The cases reporting alanine aminotransferase were men. Abbreviations: BROD=Brodalumab, IXE=Ixekizumab, SECU=Secukinumab, HBsAg=Hepatitis B surface antigen, anti-HBc=Hepatitis B core antibody, anti-HBs=Hepatitis B surface antibody				

One case (FAERS Case #14794247) that provided minimal information reported reactivation of both HCV and HBV in a patient of unspecified age and sex an unspecified time after starting secukinumab. The case did not report diagnostic information, the action taken for secukinumab, or additional follow-up.

Of the three cases that were HBsAg negative prior to starting the anti-IL-17 mAb, one case reported that HBsAg continued to be negative, and the remaining two cases did not report subsequent HBsAg status.

3.4 OBSERVATIONAL STUDIES

See Appendix D for a tabular summary of the study results.

Chiu et al., 2018, conducted a prospective cohort study to investigate the rate of reactivation of HBV or HCV in patients with psoriasis treated with secukinumab. Patients treated with secukinumab from June 2015 to January 2018 were identified from four dermatology centers in Taiwan. Of the 284 patients identified, 49 had HBV infection and 14 had HCV infection. HBV-R was defined as a 10-fold increase in HBV-DNA load compared against baseline, a change from undetectable to detectable status, or a hepatitis B e antigen seroconversion from negative to positive. No secukinumab unexposed comparator group was included in this study. Seven of the 49 (14.3%) HBV patients experienced reactivation of HBV after a mean of 3.4 months of follow-up. HBV reactivation occurred in 0/3 patients who received antiviral prophylaxis, compared to 7/46 of those who did not receive antiviral prophylaxis.

Chiu et al., 2021, conducted a retrospective cohort study to determine the predictors of HBV and HCV reactivation in patients with psoriasis receiving tumor necrosis factor (TNF)-α blockers, anti-IL-12/23, or anti-IL-17 (secukinumab). Researchers identified 2,060 patients with 3,562 treatment episodes from 2009 to 2018 in 10 dermatology centers in Taiwan. Among 359 patients (561 treatment episodes) with HBV, 104 treatment episodes were from secukinumab, 235

treatment episodes were with anti-IL-12/23, and 222 treatment episodes were with TNF-α inhibitors. Fifty-one HBV patients received antiviral prophylaxis prior to the initiation of biologic therapy, though the frequency of antiviral prophylaxis by psoriasis treatment group (anti-IL-17, anti-IL-12/23, TNF-α inhibitors) was not reported. HBV-R was defined as an increase in the HBV-DNA load of more than 10-fold compared with baseline, a detectable value of HBV DNA in patients with previously undetectable HBV DNA, hepatitis B e-antigen seroconversion from negative to positive, or an increase in DNA level exceeding 6-log 10 copies/mL after biologic therapy. Eighty-eight of the 561 (15.7%) treatment episodes across all biologics for HBV experienced reactivation; the number of patients treated with secukinumab who experienced HBV-R was not provided. Cox proportional hazards models were used to identify risk factors for HBV-R and compare HBV-R between types of biologics. Models were adjusted for age, sex, fatty liver, alcohol consumption, smoking, diabetes, viral hepatitis profiles, psoriasis disease profiles, and concomitant immunosuppressant medication use. In patients not taking antiviral prophylaxis, reactivation of HBV was more common among those who received TNF-α inhibitors compared to secukinumab (adjusted hazard ratio = 2.67; 95% confidence interval = 1.08-6.58). Time to HBV-R (times were not reported) was shorter among patients treated with TNF-α inhibitors compared to secukinumab (p = 0.003). A comparison between secukinumab and anti-IL-12/23 was only provided in the form of a Kaplan-Meier curve which compared the cumulative rate of HBV-R over time among patients not taking antiviral prophylaxis. The graph showed similar HBV-R rates between secukinumab and anti-IL-12/23. Among all patients with psoriasis with HBV, absence of antiviral prophylaxis was associated with a higher incidence of HBV-R (p=0.046) though differences across psoriasis treatment groups were not described.

Snast et al. performed a retrospective cohort study in Israel to evaluate the risk of reactivation of HBV and HCV in patients with psoriasis treated with biologic therapies. Using the electronic database from a medical center dermatology department, 207 patients with psoriasis were identified from 2005 forward (no end date provided; article was accepted for publication in January 2017). Of these 207 patients, 26 had HBV before treatment initiation defined as an increase in the alanine transaminase level to five times the upper limit of normal. HBV-R was defined as an increase in HBV of at least 1 log 10 copies/mL or conversion of serum HBV DNA results from negative to positive. The mean duration of follow-up was 5.3 years. Three of the 26 patients received secukinumab (all were treated with at least one other biologic therapy). The remaining 23 patients were treated with at least one of the following: adalimumab, alefacept, cyclosporine, etanercept, golimumab, infliximab, methotrexate, ustekinumab. Two patients received antiviral prophylaxis; neither was treated with secukinumab during the study period. Zero of the 26 psoriasis patients with HBV had evidence of viral reactivation.

3.5 PERIODIC SAFETY REPORTS

We identified the following information in the PSRs related to HBV-R.

3.5.1 Secukinumab

The secukinumab PSUR covering December 26, 2019 to December 25, 2020 identifies HBV-R as an important potential risk and includes an evaluation of cases of HBV-R.[22] The Applicant noted that there were no cases of HBV-R across the registration programs in psoriasis, pediatric psoriasis, psoriatic arthritis, and ankylosing spondylitis. The Applicant identified one case this

interval reporting HBV-R with "deranged liver function tests" (results not provided). According to the Applicant, the case had partial information to assess the causal relation to secukinumab. The Applicant reported that "no noteworthy case was identified and the analysis revealed no new safety concerns."

Cumulatively, the Applicant identified nine cases of HBV-R, and based on cumulative exposure of (b) (4) patient treatment years (PTY), they calculated a reporting rate of 0.001 per 100 PTY. The Applicant concluded that the data pertaining to the risk of HBV-R is consistent with the known safety profile of Cosentyx, and the evaluation revealed no new safety concerns regarding this risk. They concluded that no special actions have been taken or are being proposed and that the risk will be evaluated again in the next PSUR.[22]

3.5.2 Ixekizumab

The PSUR covering March 23, 2020 to March 22, 2021, lists the use of ixekizumab in patients with HBV as missing information.[23] The cumulative summary tables of serious adverse events from clinical trials and the interval and cumulative summary tables of suspected adverse reactions from postmarketing sources do not include cases coded with the PT *Hepatitis B reactivation.*

The Applicant estimates that during the 12-month period of this PSUR, (b) (4) patients received ixekizumab from postmarketing sources. Cumulatively, approximately (b) (4) patients have received ixekizumab worldwide.

3.5.3 Brodalumab

The PAER covering February 15, 2020 to February 14, 2021 did not mention HBV-R or report cases of HBV-R during the interval.[24]

The Applicant estimates that cumulatively through February 14, 2021, (b) (4) patients used brodalumab in the United States. They did not provide an estimate of worldwide drug utilization.

4 DISCUSSION

4.1 FAERS AND LITERATURE CASES

We identified 14 cases reporting HBV-R with anti-IL-17 mAb use, primarily with secukinumab. Based on the information provided, none of the cases reported a hepatitis flare, defined as an ALT of ≥3 times baseline and >100 IU/L.[14] No cases reported liver transplant, hospitalization, or death. Half of the cases were from the publication by Chiu, et al., in patients who were not taking concomitant immunosuppressants.[2] None of the cases that reported concomitant medication use reported antiviral use at the time of HBV-R, including the six cases that were HBsAg positive prior to starting therapy, and who were therefore at higher risk of HBV-R. Of the three cases that were HBsAg negative prior to starting the anti-IL-17 mAb, and therefore at lower risk of HBV-R, one case reported an additional risk factor of concomitant MTX use, one case reported no other risk factors, and one case did not provide information to assess for risk factors. Six of the cases reported initiation of an antiviral, including one case that reported stopping secukinumab and MTX, in response to the HBV-R. Although the temporal relationship from starting the anti-

IL-17 mAb to HBV-R varied and time to onset was not reported in all cases, six cases reported a time to onset of within three months of starting the anti-IL-17 mAb.

As noted in Section 3.4, Chiu, et al. defined HBV-R as a 10-fold increase in HBV DNA compared to baseline, a change from undetectable to detectable status, or a HBeAg seroconversion from negative to positive.[2] These criteria are less stringent than the criteria recommended by AASLD (see Section 1.1). Of the six cases in our case series that were HBsAg positive prior to starting the anti-IL-17 mAb, all from the Chiu publication, none meet the criteria for HBV-R using the AASLD criteria (see the diagnostic information in the line listing in Appendix C). Of the three cases that were HBsAg negative prior to starting therapy, two cases had detectable HBV DNA prior to starting the anti-IL-17 mAb, which subsequently increased, and one case did not specify the HBV DNA prior to starting therapy. According to the AASLD guidelines, the two cases with detectable HBV DNA at baseline could be considered as meeting the criteria for HBV-R prior to starting the anti-IL-17 mAb. The cases that were not from the Chiu publication, including the one case each reported with ixekizumab and brodalumab, provided limited information for case assessment. The case reporting ixekizumab use reported the concomitant use of MTX. Although HBV-R has been reported with MTX, most cases reported concomitant corticosteroid use.[41]

Although the Applicants did not report comparable measurements of drug utilization in their PSRs, differences in drug utilization and time of marketing may have contributed to the higher number of cases with secukinumab. All cases in our case series were foreign, primarily from Asian countries. Factors such as a higher prevalence of HBV compared to the United States, differences in HBV vaccination rates, pretreatment screening for HBV, or adverse event reporting practices may have contributed. The Joint American Academy of Dermatology and National Psoriasis Foundation (AAD/NPF) Guidelines for the Care and Management of Psoriasis with Biologics recommend baseline serologic testing for HBV prior to starting the anti-IL-17 mAbs.[42] The guidelines state that patients with currently active HBV may receive IL-17 inhibitors after evaluation by an appropriate healthcare professional and may require antiviral treatment. They recommend that patients with resolved HBV infection require monitoring because of the risk of reactivation. These recommendations are essentially the same as for the TNF-α inhibitors and ustekinumab.[42] However, adherence to these guidelines and similar guidelines for other inflammatory conditions likely vary and may be suboptimal. Patterson et al., using electronic health data and chart review in a large U.S. university health system, assessed screening for latent TB, HBV, and HCV from 12 months before to 60 days after initiation of a biologic or tofacitinib among 2,027 ambulatory patients.[43] From 2013 to 2017, across all indications, screening for HBV was completed in 52% of patients and screening for TB was completed in 62% of patients. The percentage screened for HBV in dermatology patients was 43.2% and 34.6% in rheumatology patients.[43]

IL-17 deficiency in humans can increase susceptibility to chronic mucocutaneous candidiasis, recurrent staphylococcal skin infections, mycobacterial, and other infections.[44] IL-17A is important in the recruitment of neutrophils and the production of granulocyte macrophage colony-stimulating factor. In viral infections, depending on the virus, IL-17 cytokines may increase the efficiency of antigen-presenting cells, the cytotoxicity of CD8 T-cells, or the antiviral activity of B-cells.[45] Although IL-17 appears to be crucial in suppressing certain viral

infections, it is also implicated in inducing harmful responses, including tissue damage and chronic inflammation in target organs.[45] Arababadi et al. reviewed the role of IL-17A in HBV infection, hepatocellular cancer (HCC), and liver cirrhosis.[46] They noted that during acute HBV infection, HBV-specific T-cells were unable to produce IL-17A in response to infected hepatocytes, suggesting that the inflammation within the liver may not be directly related to IL-17A but due to the overexpression of other cytokines. In contrast to acute HBV infection, during chronic HBV infection, IL-17A is upregulated, especially in patients with liver cirrhosis and HCC. This suggests that IL-17A could be considered a risk factor for liver complications.[46]

The anti-IL-17 mAb labeling includes information in the WARNINGS AND PRECAUTIONS section about the increased risk of infection and advises caution in patients with chronic or recurrent infection; however, there is no recommendation for pretreatment assessment for HBV, as there is for TB. More explicit labeling for the anti-IL-17 mAbs regarding pretreatment assessment for HBV may be warranted and is consistent with current guidelines.[42] According to the CDER Labeling Review Tool, tests that should be performed prior to dose initiation should be included in the DOSAGE AND ADMINISTRATION section.[47] Based on our case series, we believe the addition of HBV-R to the *Postmarketing Experience* section of the secukinumab labeling may be warranted. Given the lack of cases meeting the AASLD criteria or with evidence of hepatitis flares or other serious clinical outcomes, the evidence at this time does not support the addition to WARNINGS AND PRECAUTIONS.[48]

For bimekizumab, pretreatment assessment for HBV is relevant because of the potential signal for liver injury. We do not have sufficient evidence to draw conclusions about the potential for HBV-R with bimekizumab or the other anti-IL-17 mAbs at this time.

FAERS data have limitations. We used a broad search for PTs related to HBV to retrieve cases reporting diagnostic information consistent with HBV-R that did not specifically report HBV-R. However, some cases did not report pretreatment HBV status, or pretreatment HBV status may not have been assessed, limiting our ability to evaluate the cases.

Based on a publication by Chiu, et al. on HBV-R with ustekinumab, evaluation of HBV-R with other classes of mAbs indicated for the treatment of psoriasis may also be warranted.[49] They reported that of 11 cases in their case series who were HBsAg positive prior to starting ustekinumab, two cases who were not on antivirals met the criteria for HBV-R of an increase in HBV DNA >6 log 10 copies/mL. Neither case experienced an increase in ALT.[49]

4.2 PUBLISHED OBSERVATIONAL STUDIES

Three observational studies were identified in the medical literature that examined secukinumab exposure in psoriasis patients and HBV-R. One study found no evidence of HBV-R among psoriasis patients with HBV regardless of treatment, including secukinumab.[20] Another study observed reactivation in patients treated with secukinumab, but no reactivation in a subset of patients treated with secukinumab who also received antiviral prophylaxis.[2] All patients in this study were treated with secukinumab, with no control group provided for comparative analysis. The final study observed HBV-R in psoriasis patients with HBV who had not received antiviral

prophylaxis but found reactivation to be *less* likely among secukinumab treated patients compared to TNF-α inhibitor treated patients.[21]

We found no observational studies in the published medical literature that mentioned HBV-R among psoriasis patients treated with brodalumab, ixekizumab, or bimekizumab.

Small sample sizes: One study included three patients with HBV who had been treated with secukinumab: zero had HBV-R.[20] Another study included 49 patients with HBV treated with secukinumab: seven had HBV-R.[2] Only one reviewed study had adequate sample size to conduct adjusted comparative analyses.[21] They examined 104 treatment episodes in HBV patients treated with secukinumab and 457 treatment episodes in patients treated with another biologic. Eighty-eight of the total 561 treatment episodes among HBV patients treated with any of the biologics had HBV-R; the number of patients treated with secukinumab specifically was not provided.

Comparison groups: One study included no comparison group,[2] and another enrolled secukinumab treated and untreated patients but made no direct comparisons.[20] It is unclear whether HBV-R would have occurred in patients not treated with an anti-IL-17 product in these studies and the extent of that occurrence, if any. The third study had two comparison groups for other psoriasis biologics but no comparison group of patients not treated with biologics.[21] Although the use of these control groups is reasonable as they may potentially adjust for severity of disease, the results may not be generalizable to plaque psoriasis patients not treated with a biologic.

Confounding: The absence of comparative analysis in two of the three studies prevented the researchers from adjusting for potential confounders (e.g., age, comorbidities, concomitant medication use, psoriasis treatment history) or accounting for differences in HBV-R based on psoriasis severity (confounding by indication). The single study that adjusted for potential confounding covered a comprehensive list of relevant covariates that appear to be adequate for the research question.[21]

Inconsistent HBV reactivation definitions: HBV definitions were not consistent between the three studies. Differences in outcome definitions may limit the comparability of the findings between the studies.

Antiviral therapy: While the effectiveness of antiviral therapy in this setting was not the focus of our review, each study reported antiviral prophylaxis use. One study reported that 0 of 3 secukinumab exposed patients who received antiviral therapy had HBV-R, compared to 7 of 46 patients who did not receive antiviral therapy.[2] However, it is difficult to assess the significance of this finding given the small number of patients who received antiviral therapy. Another study observed 51 patients had received antiviral prophylaxis; however, the study did not report how many of these patients received secukinumab, so we could not evaluate the extent to which prophylaxis impacts reactivation in secukinumab treated patients.[21] Absence of antiviral prophylaxis was associated with a higher risk of HBV-R in this study. The final study included only two patients who received antiviral therapy.[20] No patients in this study experienced HBV-R, regardless of whether they received antiviral therapy.

Anti-IL-17 mAb labeling: As summarized in Section 1.3, labeling for each of the currently approved anti-IL-17 mAbs (brodalumab, ixekizumab, secukinumab) does not contain information pertaining to HBV-R at this time. No instances of HBV-R have been observed in patients treated with bimekizumab to date, although this is expected as HBV patients were excluded from bimekizumab clinical trials.[50] Based on the epidemiologic studies included in this review, there is currently not enough information, particularly in the form of comparative analyses, to inform bimekizumab labeling.

5 CONCLUSION

We identified cases reporting HBV-R with secukinumab use. The information in the cases reporting ixekizumab and brodalumab use was not sufficient to assess their potential role in HBV-R at this time. The cases with secukinumab did not report serious clinical outcomes; however, HBV-R is preventable and potentially life-threatening. These findings are relevant to bimekizumab, based on the potential signal for liver injury with bimekizumab.

We identified three relevant epidemiologic studies evaluating secukinumab and HBV-R through a search of the published observational literature, though only one study directly evaluated the relationship between secukinumab and HBV-R using adjusted comparative analysis.[21] However, this study found that patients treated with secukinumab were less likely to experience HBV-R compared to patients treated with a TNF-α inhibitor. We did not identify studies that examined anti-IL-17 mAbs other than secukinumab in relation to HBV-R. There is not enough high-quality epidemiologic evidence examining the relationship between anti-IL-17 mAbs and HBV-R at this time to meaningfully inform labeling for bimekizumab or other anti-IL-17 mAbs.

6 RECOMMENDATIONS

We support the proposed inclusion of HBV-R as a secondary outcome in the long-term safety PMR drafted by DDD. Although the limited published epidemiologic literature at this time is insufficient to provide labeling recommendations for bimekizumab, based on our review of the postmarketing case series, and consistent with the AASLD and AAD/NPF guidelines, we recommend that DDD consider the following:

- Addition of HBV-R to the *Postmarketing Experience* section of the secukinumab labeling
- Addition of pretreatment assessment for HBV to the DOSAGE AND ADMINISTRATION section of the secukinumab, ixekizumab, and brodalumab labeling
- Inclusion of pretreatment assessment for HBV in the DOSAGE AND ADMINISTRATION section of the bimekizumab labeling

DPV will continue to monitor for cases reporting HBV-R with the anti-IL-17 mAbs.

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8 APPENDICES

8.1 APPENDIX A. PROPOSED PMR LANGUAGE FOR LONG-TERM SAFETY STUDY[b]

Conduct a prospective, observational study to assess the long-term safety of bimekizumab compared to other therapies used in the treatment of adults with moderate-to-severe plaque psoriasis who are candidates for systemic therapy or phototherapy (b) (4)

[redacted]

8.2 APPENDIX B. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

FDA Adverse Event Reporting System (FAERS)

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support FDA's postmarketing safety surveillance program for drug and therapeutic biological products. The informatic structure of the database adheres to the international safety reporting guidance issued by the International Council on Harmonisation. Adverse events and medication errors are coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. The suspect products are coded to valid tradenames or active ingredients in the FAERS Product Dictionary (FPD).

FAERS data have limitations. First, there is no certainty that the reported event was actually due to the product. FDA does not require that a causal relationship between a product and event be proven, and reports do not always contain enough detail to properly evaluate an event. Further, FDA does not receive reports for every adverse event or medication error that occurs with a product. Many factors can influence whether or not an event will be reported, such as the time a product has been marketed and publicity about an event. Therefore, FAERS data cannot be used to calculate the incidence of an adverse event or medication error in the U.S. population.

[b] Draft PMR language was provided to DEPI from DDD through email July 8, 2021. Finalized PMR language will be issued upon approval.

8.3 APPENDIX C. FAERS LINE LISTING OF HEPATITIS B REACTIVATION WITH ANTI-IL-17 MONOCLONAL ANTIBODY USE CASE SERIES

Duplicate cases are indicated in [brackets].

FAERS Case # (Version #), Mfg Control #	Year FDA Received or Published, Report Type, Country	Age, Sex, Coded outcome *	Indication for Use, Dose, Time to Onset (days)	Medical History, Concomitant Medications	Pretreatment Diagnostic Information	Diagnostic information at time of HBV-R	Action Taken for Anti-IL-17, Antiviral started	Case Definition†, Causality Assessment	Clinical Outcome Notes
Secukinumab (n=12)									
14794247 (1) PHHY2018TW069378	2018 Expedited TWN	NS NS OT	NS NS NS	NS NS	NS	NS	NS NS	Category II Insufficient	NS HBV and HCV reactivation reported
15098401 (3) PHHY2018BR004758	2018 Expedited BRA	68 Male OT	Psoriatic arthropathy 150 mg weekly 46	HBV, iron overload, gastritis NS	NS	NS	NS NS	Category II Insufficient	NS
15153521 (1)[2] PHHY2018TW044422	2018 Expedited TWN	62 Male OT	Psoriasis 300 mg weeks 0,1,2,3 then every 4 weeks 30	CHB‡ No immunosuppressants or antivirals	HBsAg +, anti-HBc +, anti HBs –, HBeAg –, anti-HBe –, HBV DNA Undetectable ALT 34 IU/L	HBV DNA 22 IU/mL, ALT 48 IU/L	Continued None	Category I No other risk factors	Stable
15153524 (1)[2] PHHY2018TW044424	2018 Expedited TWN	38 Male OT	Psoriasis 300 mg weeks 0,1,2,3 then every 4 weeks 270	CHB‡ No immunosuppressants or antivirals	HBsAg +, anti-HBc +, anti HBs –, HBeAg +, anti-HBe – HBV DNA 4,310 IU/mL ALT 133 IU/L	HBV DNA 68,800 IU/mL ALT 61 IU/L	Continued None	Category I No other risk factors	Asymptomatic

FAERS Case # (Version #), Mfg Control #	Year FDA Received or Published, Report Type, Country	Age, Sex, Coded outcome *	Indication for Use, Dose, Time to Onset (days)	Medical History, Concomitant Medications	Pretreatment Diagnostic Information	Diagnostic information at time of HBV-R	Action Taken for Anti-IL-17, Antiviral started	Case Definition†, Causality Assessment	Clinical Outcome Notes
15159740 (1)[2] PHHY2018TW044414	2018 Expedited TWN	59 Male OT	Psoriasis 300 mg weeks 0,1,2,3 then every 4 weeks 30	CHB‡ No immunosuppressants or antivirals	HBsAg +, anti-HBc +, anti HBs –, HBeAg –, anti-HBe –, HBV DNA 31 IU/mL, ALT 12 IU/L	HBV DNA 833 IU/mL, ALT 19 IU/L	Continued Telbivudine	Category I No other risk factors	Viral load decreased; improved
15159751 (1)[2] PHHY2018TW044417	2018 Expedited TWN	36 Male OT	Psoriasis 150 mg weeks 0,1,2,3 then every 4 weeks 90	CHB‡ No immunosuppressants or antivirals	HBsAg +, anti-HBc +, anti HBs –, HBeAg –, anti-HBe –, HBV DNA 515 IU/mL, ALT 40 IU/L	HBV DNA 8,630 IU/mL, ALT 37 IU/L	Continued Entecavir	Category I No other risk factors	Viral load decreased; improved
15159754 (1)[2] PHHY2018TW044408	2018 Expedited TWN	44 Male OT	Psoriasis 300 mg weeks 0,1,2,3 then every 4 weeks 180	CHB‡ No immunosuppressants or antivirals	HBsAg +, anti-HBc +, anti HBs –, HBeAg –, anti-HBe +, HBV DNA 180 IU/mL, ALT 58 IU/L	HBV DNA 2,277 IU/mL, ALT 70 IU/L	Continued Telbivudine	Category I No other risk factors	Viral load decreased; improved
15159755 (1)[2] PHHY2018TW044423	2018 Expedited TWN	55 Male OT	Psoriasis 300 mg weeks 0,1,2,3 then every 4 weeks 30	CHB‡ No immunosuppressants or antivirals	HBsAg +, anti-HBc +, anti HBs –, HBeAg –, anti-HBe +, HBV DNA 20 IU/mL, ALT 28 IU/L	HBV DNA 220 IU/mL, ALT 41 IU/L	Continued None	Category I No other risk factors	Stable
15159757 (1)[2]	2018 Expedited TWN	38 Male OT	Psoriasis 300 mg weeks 0,1,2,3	Occult HBV‡ No immunosuppre	HBsAg – , anti-HBc +, anti HBs –,	220 IU/mL, ALT 72 IU/L	Continued None	Category I No other risk factors	Stable

FAERS Case # (Version #), Mfg Control #	Year FDA Received or Published, Report Type, Country	Age, Sex, Coded outcome *	Indication for Use, Dose, Time to Onset (days)	Medical History, Concomitant Medications	Pretreatment Diagnostic Information	Diagnostic information at time of HBV-R	Action Taken for Anti-IL-17, Antiviral started	Case Definition†, Causality Assessment	Clinical Outcome Notes
PHHY2018TW044402			then every 4 weeks 90	ssants or antivirals	HBeAg –, anti-HBe –, HBV DNA 20 IU/mL, ALT 71 IU/L				
16362986 (2) PHHY2019IT121556 [16439745 (2) IT-PFIZER INC-2019248953]	2019 Expedited ITA	NS Male OT	Psoriatic arthropathy 300 mg monthly 365	Blood transfusions, hyperlipidemia MTX, aspirin, rosuvastatin, omega-3 triglycerides	NS	HBsAg +, anti-HBc +, HBV DNA 54 log 1.73 IU/mL	Stopped Entecavir	Category II Other risk factor	NS Concomitant MTX
18307416 (2) NVSC2020HK258883	2020 Expedited HKG	50 Male OT	Psoriatic arthropathy NS NS	Occult HBV NS	NS	"deranged liver function test"	NS Entecavir	Category II Insufficient	NS
Parmar, et al.[26]	2021 Not applicable GBR	48 Female Not applicable	Psoriasis NS NS	Hepatitis B NS	NS	NS	Continued Tenofovir	Category II Insufficient	NS
Ixekizumab (n=1)									
14820225 (2)[25] JP-ELI_LILLY_AND_COMPANY-JP201804013446	2018 Expedited JPN	50 Female OT	Rheumatoid arthritis NS 180	HBV MTX 8 mg NS	HBsAg –, anti-HBC +, anti-HBs – (7.09 IU/mL)	HBsAg –, HBV DNA <2.1 LC/mL	NS None	Category I Other risk factor reported	NS Concomitant MTX
Brodalumab (n=1)									

FAERS Case # (Version #), Mfg Control #	Year FDA Received or Published, Report Type, Country	Age, Sex, Coded outcome *	Indication for Use, Dose, Time to Onset (days)	Medical History, Concomitant Medications	Pretreatment Diagnostic Information	Diagnostic information at time of HBV-R	Action Taken for Anti-IL-17, Antiviral started	Case Definition†, Causality Assessment	Clinical Outcome Notes
15823614 (2) JP-BAUSCH-BL-2018-021250	2019 Expedited JPN	75 Male OT	Psoriasis 210 mg NS 172 days from starting (4 months after stopping)	HBV NS	HBsAg -, "HB core antigen +", HBV virus detected, did not exceed reference value	HBV DNA 20 IU and over	Already off; later restarted without further HBV detection None	Category I Insufficient information	Recovered Not on brodalumab at time of HBV-R

*As per 21 CFR 314.80, the regulatory definition of serious is any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, a congenital anomaly/birth defect, or other serious important medical events.
† See Section 2.1; Category I cases included diagnostic evidence, Category II cases did not include diagnostic evidence
‡The publication did not provide additional information on medical history
Abbreviations: anti-HBc=Hepatitis B core antibody, anti-HBe=Hepatitis B e antibody, anti-HBs=Hepatitis B surface antibody, CHB=Chronic hepatitis B, HBeAg=Hepatitis B e antigen, HBsAg=Hepatitis B surface antigen, HBV=Hepatitis B virus, HBV-R=HBV reactivation, MTX=Methotrexate, NS=Not specified, OT=other medically significant

8.4 APPENDIX D. SUMMARY OF OBSERVATIONAL STUDY RESULTS

Summary of Observational Studies Evaluating the Association Between Anti-IL-17 Use and Hepatitis B Virus Reactivation

First Author (Year)	Country	Design (Timeframe)	N_{Total}	N_{HBV}	$N_{HBV\ Reactivation}$	Exposure (comparison group)	Outcome	Follow-up	Risk Estimate (95% Confidence Interval)
Snast (2017)	Israel	Retrospective cohort (2005-2016*)	207 treated with biologic therapies	26 treated with any biologic therapies 3 treated with secukinumab	0 treated with any biologic therapies 0 treated with secukinumab	Any secukinumab exposure (no comparison group)	HBV reactivation was defined as an increase in HBV of at least 1 log 10 copies/mL or conversion of serum HBV DNA results from negative to positive.	Median = 5.3 years	0/3 (0%) reactivation of HBV
Chiu (2018)	Taiwan	Prospective cohort (2015-2018)	284 treated with secukinumab	49 treated with secukinumab	7 treated with secukinumab	Secukinumab treatment for ≥ 3 months (no comparison group)	HBV reactivation was defined as a 10-fold increase in HBV-DNA load compared against baseline, a change from undetectable to detectable status, or a hepatitis B e antigen seroconversion from negative to positive after secukinumab therapy.	Mean among HBV reactivation patients = 3.4 months	7/49 (14.3%) reactivation of HBV 0/3 (0%) patients who received antiviral prophylaxis experienced HBV reactivation.
Chiu (2021)	Taiwan	Retrospective cohort (2009-2018)	2,060 treated with biologic therapies (3,562 treatment episodes)	561 treatment episodes with any biologic therapies (359 patients) 104 treatment	88 treatment episodes with any biologic therapies Unknown treated with secukinumab	Any secukinumab exposure (any TNFi exposure or any anti-IL-12/23 exposure)	HBV reactivation was defined as an increase in the HBV-DNA load of more than 10-fold compared with baseline, a detectable value of HBV DNA in patients with previously undetectable HBV	Mean = 1.57 months (8,809 months from 561 patients treated with biologic therapies)	$HR_{TNFi\ vs\ IL\text{-}17i}$ = 2.67 (1.08-6.58)

First Author (Year)	Country	Design (Timeframe)	N_{Total}	N_{HBV}	$N_{HBV\ Reactivation}$	Exposure (comparison group)	Outcome	Follow-up	Risk Estimate (95% Confidence Interval)
				episodes with secukinumab 222 treatment episodes with TNFi 235 treatment episodes with anti-IL-12/23	Unknown treated with TNFi Unknown treated with anti-IL-12/23		DNA, hepatitis B e-antigen seroconversion from negative to positive, or an increase in DNA level exceeding 6-log 10 copies/mL after biologic therapy.		

HBV: hepatitis B virus, IL-17i: interleukin-17 inhibitor, HR: hazard ratio, TNFi: tumor necrosis factor-α inhibitor
*End date not provided. This study also performed a literature review in May 2016, which may be near the time the study ended.

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CINDY M KORTEPETER
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	August 31, 2021
To:	Strother Dixon, PharmD Senior Regulatory Project Manager **Division of Dermatology and Dentistry (DDD)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Shawna Hutchins, MPH, BSN, RN Senior Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** Laurie Buonaccorsi, PharmD Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Medication Guide (MG) and and Instructions for Use (IFUs)
Drug Name (established name):	BIMZELX (bimekizumab-bkzx)
Dosage Form and Route:	Injection, for subcutaneous use
Application Type/Number:	BLA 671151
Applicant:	UCB, Inc.

1 INTRODUCTION

On July 15, 2020, UCB, Inc., submitted for the Agency's review an original Biologics Application (BLA 761151) for BIMZELX (bimekizumab-bkzx), Injection, for subcutaneous use, seeking Agency to market BIMZELX (bimekizumab-bkzx), Injection, for subcutaneous use, for the proposed use for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of DDD on July 16, 2020 for DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFUs) for BIMZELX (bimekizumab-bkzx), Injection, for subcutaneous use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFUs will be forthcoming.

2 MATERIAL REVIEWED

- Draft BIMZELX (bimekizumab-bkzx) MG and IFUs received on July 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 25, 2021.
- Draft BIMZELX (bimekizumab-bkzx) Prescribing Information (PI) received on July 16, 2020, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on August 25, 2021.
- Approved COSENTYX (secukinumab) comparator labeling dated May 28, 2021.
- Approved TALTZ (ixekizumab) comparator labeling dated March 10, 2021.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the MG and IFUs the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the MG and IFU documents using the Arial font, size 10.

In our collaborative review of the MG and IFUs we:

- simplified wording and clarified concepts where possible

- ensured that the MG and IFUs are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the MG and IFUs are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFUs meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the MG and IFUs are consistent with the approved comparator labeling where applicable.

4 CONCLUSIONS

The MG and IFUs are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG and IFUs are appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG and IFUs.

Please let us know if you have any questions.

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FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: August 31, 2021

To: Kevin Clark, MD, Clinical Reviewer,
Division of Dermatology and Dentistry (DDD)
Gordana Diglisic, MD, Clinical Team Leader, DDD
Strother Dixon, Regulatory Project Manager, DDD

From: Laurie Buonaccorsi, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Matthew Falter, Team Leader, OPDP

Subject: OPDP Labeling Comments BIMZELX®(bimekizumab-bkzx) injection, for subcutaneous use

BLA: 761151

In response to DDD's consult request dated July 16, 2020, OPDP has reviewed the proposed product labeling (PI), Medication Guide, Instructions for Use (IFU), and carton and container labeling for the original BLA submission for BIMZELX® (bimekizumab-bkzx) injection, for subcutaneous use (Bimzelx).

Labeling

PI: OPDP's comments on the proposed labeling are based on the draft PI received by electronic mail from DDD on August 25, 2021, and our comments are provided below.

Medication Guide and IFU: A combined OPDP and Division of Medical Policy Programs (DMPP) review will be completed, and comments on the proposed Medication Guide and IFU will be sent under separate cover.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling received by the electronic document room on August 13, 2021, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Laurie Buonaccorsi at (240) 402-6297 or laurie.buonaccorsi@fda.hhs.gov.

Bimzelx Container/Carton comments:

The nonproprietary name is less than half the size of the proprietary name and the light font does not have a prominence commensurate with the prominence of the proprietary name. According to 21CFR 201.10(g)(2), the established name (nonproprietary name) shall be at least half as large as the letters comprising the proprietary name or designation and shall have a prominence commensurate with the prominence with which such proprietary name or designation appears, taking into account all pertinent factors, including typography, layout, contrast, and other printing features. Therefore, we recommend revising the nonproprietary name on all proposed carton and container labeling.

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LAURIE J BUONACCORSI
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MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 19, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761151
Product Name and Strength:	Bimzelx (bimekizumab-bkzx) injection, 160 mg/mL single-dose safety syringe and 160 mg/mL single-dose auto-injector
Applicant/Sponsor Name:	UCB, Inc.
OSE RCM #:	2020-1496-2 and 2020-1506-2
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
Human Factors Team Lead (Acting):	Murewa Oguntimein, PhD, MHS, CHES, CPH
Associate Director for Human Factors (ADHF)	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised carton labeling received on August 13, 2021 for Bimzelx. Division of Dermatology and Dentistry (DDD) requested that we review the revised carton labeling for Bimzelx (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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[a] Owens, L. Label and Labeling Review for Bimzelx (BLA 761151). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 27. RCM No.: 2020-1496-1 and 2020-1506-1.

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Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

BLA	761151
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Bimekizumab
Indication	plaque psoriasis (PSO)
Applicant	UCB, Inc.
Requesting Division	Division of Dermatology and Dentistry (DDD)
Primary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Reviewer **Office of Pharmacoepidemiology**	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	Aug 6, 2021

Context: Bimekizumab (BKZ) is a humanized monoclonal antibody that binds IL-17A and 17F. In this BLA, it is used for the treatment of plaque psoriasis (PSO). DDD noted a case of elevated high transaminases and jaundice. They requested that DHN's DILI Team comment on whether this case meets Hy's Law criteria, and whether this case and others with liver injury impact BKZ approvability and labeling.

Executive Summary: BKZ can lead to hepatocellular or mixed liver injury, but we do not think the risk of severe DILI is high enough to hold up approval if BKZ benefit and need are clear. There were no definite or probable Hy's Law cases. There were two possible cases, but both had reasonable alternative diagnoses that were as or more likely than DILI. There were three probable cases of notable BKZ liver injury but without jaundice. The total number of patients exposed was over 1700. Nevertheless, significant DILI may still arise when BKZ is given to larger numbers of patients post-marketing, and any labeling should discuss this possibility. Use in patients with certain baseline liver problems (e.g., cirrhosis) should be avoided. Screening for hepatitis B reactivation risk and prophylactic therapy should be considered. While patients with signs of chronic hepatitis B infection were excluded from studies in this BLA, reactivation has been reported with another monoclonal antibody that inhibits IL-17A. Full recommendations and suggested wording for the label are in Section 5.0.

Full Consultation Sections:

Section 1.0 – Disease and Rationale
Section 2.0 - ADME data related to DILI
Section 3.0 - Non-clinical data related to DILI
Section 4.0 - Clinical data
Section 5.0 – Summary & Recommendations.

Abbreviations:
ALT: alanine aminotransferase
ANA: anti-nuclear antibody
Anti-HBc: anti-hepatitis B core antibody
AP: alkaline phosphatase
ASMA: anti-smooth muscle antibody
AST: aspartate aminotransferase
BKZ: bimekizumab
CMV: cytomegalovirus
DILI: drug-induced liver injury
DMC: Data Monitoring Committee
EBV: Epstein Barr virus
HAC: Hepatology Assessment Committee
HBsAg: hepatitis B surface antigen
HEV: hepatitis E virus
IL: interleukin
IP: investigational product
PSO: psoriasis
SC: subcutaneous
TNF: tumor necrosis factor

1.0 Disease and Rationale:

1.1 Disease: Psoriasis is a systemic disease, but its predominant clinical presentation and symptoms are dermatologic changes including erythematous plaques of hyperplastic skin cells. It a common disorder effecting all ages and across different races. However, it is less common before adolescence and less common to rare in certain races (e.g. Japanese, Alaska natives, West African blacks).[1] Estimates of prevalence range from 0.5 to 11.4% in adults and up to 1.4% in children.[2] The four major types are chronic plaque, guttate, pustular and erythrodermic.[3] Plaque type is the most common at around 75%. Non-skin manifestations include arthritis (30% of cases) and eye manifestations (e.g., uveitis). Skin manifestations lead to significant morbidity, including social inhibition and depression.

Pathophysiology is based on a complex interplay of T-lymphocytes, dendritic cells and cytokines, including interleukin-23 (IL-23), IL-17 and tumor necrosis factor (TNF). IL-17 is involved with the inflammatory process associated with psoriatic skin lesions. Of the 6 forms of IL-17, subtypes A, C and F are considered most pertinent with over expression associated with worse disease.

[1] Farber EM et al. Dematologica (1974)
[2] Michalek IM, et al. JEur Acad Dermatol Venereol (2017)
[3] UpToDate. www.uptodate.com (accessed May 18, 2021)

1.2 Rationale: Current therapy options are many and range from topicals and phototherapy to oral immunosuppressive agents, to monoclonal antibodies targeting TNF-alpha, IL-12/23 and IL-17A. Three anti-IL-17A agents, secukinumab, ixekizumab and brodalumab are currently approved. All have shown significantly higher response compared to placebo. Secukinumab and ixekizumab were superior to entanercept (anti-TNF) as well. Brodalumab was approved for more refractory disease, outperforming ustekinumab.[3]

The sponsor hypothesizes that having an agent target both IL-17A and F may have added efficacy. Bimekizumab (BKZ) is a humanized, IgG1 monoclonal antibody designed to target and inhibit IL-17A and F.

2.0 ADME

2.1 Absorption: Bioavailability was 69-90% after subcutaneous (SC) injection in monkeys. Mean terminal ½ life was 8.9 to 15.4 days. In healthy volunteers, bioavailability was 70.1% but with an inter-person variability of 45%.

2.2 Distribution: Mean volume of distribution ranged from 93.7 to 109 mL/kg. Full distribution studies were not done.

2.3 Metabolism: No organ specific metabolism studies were done. Breakdown of BKZ is presumed to occur by widespread cellular uptake and lysosomal degradation.

2.4 Excretion: No excretion studies were done. Elimination is presumed to be by target or non-specific cell uptake and protein degradation by lysosomes.

3.0 Non-clinical data related to DILI

3.1 BKZ was given to cynomolgus monkeys for 8-26 weeks in doses ranging from 20 to 200 mg/kg/week. No liver histopathologic findings were seen. No other animal model studies were found by this reviewer.

4.0 Clinical data

4.1 Class Risk of DILI. Secukinumab, ixekizumab and brodalumab are anti-IL-17A monoclonal antibodies approved in 2015, 2016 and 2017 respectively. None showed a significant risk of DILI in clinical trials. There have been no reports of significant liver injury in the post-marketing literature. However, their approvals are relatively recent.

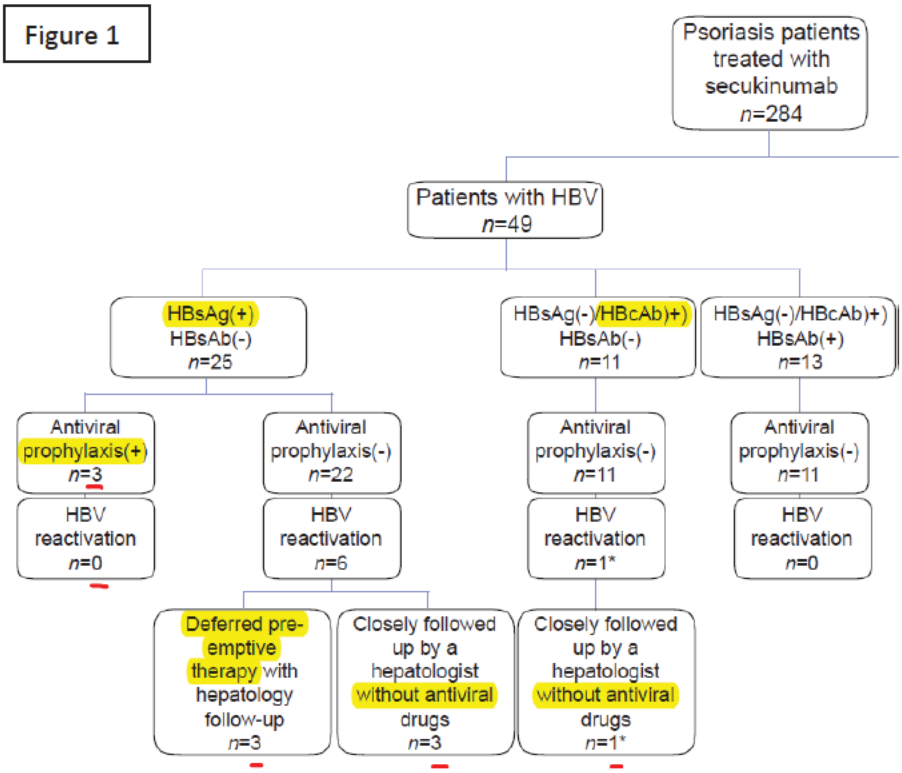
Indirect DILI from hepatitis B reactivation has been reported with secukinumab. The rate of reactivation was as high as 24% amongst HBsAg positive patients in one study.[4] [5] The total number of reactivation cases was seven, six in the HBsAg positive group. All had mild courses of reactivation. However, all 7 were followed by “hepatology” or a “hepatologist”, and 3 were put on “deferred pre-emptive therapy” presumably upon reactivation. The other 4 were followed closely without therapy. Also, three other HBsAg

[4] Chiu H-Y, et al. Acta Derm Venereol (2018).

[5] LiverTox https://www.ncbi.nlm.nih.gov/books/NBK547852/?term=Secukinumab (accessed May 23, 2021)

positive patients were put on prophylactic therapy and did not have reactivation (Figure 1).

Figure 1



Some have recommended extension of hepatitis B prophylaxis recommendations for patients on all anti-IL17A therapies if found to be HBsAg and/or anti-HBc antibody positive on screening.[6] The EuroGuiDerm Guidelines and another review on the systemic treatment of psoriasis vulgaris recommends screening for hepatitis B and consulting hepatology for possible prophylaxis in HBsAg positive patients when using "biologics" or "biological" disease-modifying antirheumatic drugs.[7],[8] The studies in this BLA excluded hepatitis B infected patients.

4.2 Summary of Studies (Table 1):

Table 1

Study	Phase	Design	Participants and Number	Placebo or SOC
RA0124	1	OL, single dose	HV; 30	No
UP0031	1	R, OL, single dose	HV; 12	No
UP0033	1	R, OL	HV; 189	No
UP0042	1	R, DB, PBO	HV; 48	Yes

[6] Manolo IF, et al. J Am Acad Dermatol (2015)
[7] Nast A, et al. JEADV 2021
[8] Bonifati C, et al. WJG 2016

UP0008	2A	R, SB, PBO	PSO; 39	Yes
PA0007	2A	R, SB, PBO	PsA; 53	Yes
UP0034	1	R, OL, single dose	HV; 28 BKZ; 28 no treatment	NA
PS0016	**2A**	**R, SB**	**PSO; 49**	**Yes**
PS0018	**2A**	**OLE from PS0016**	**PSO; 43**	**No**
PS0010	**2B**	**R, DB, PBO**	**PSO; 250**	**Yes**
PS0011	**2B**	**Ext from PS0010**	**PSO; 217**	**Yes**
PS0008	**3**	**R, DB, active con**	**PSO; 487**	**Yes**
PS0009	**3**	**R, DB, PBO**	**PSO; 567**	**Yes**
PS0013	**3**	**R, DB, PBO**	**PSO; 435**	**Yes**
PS0014	**3**	**OLE for Phase 3's**	**PSO; 1343**	**No**

Pool S2

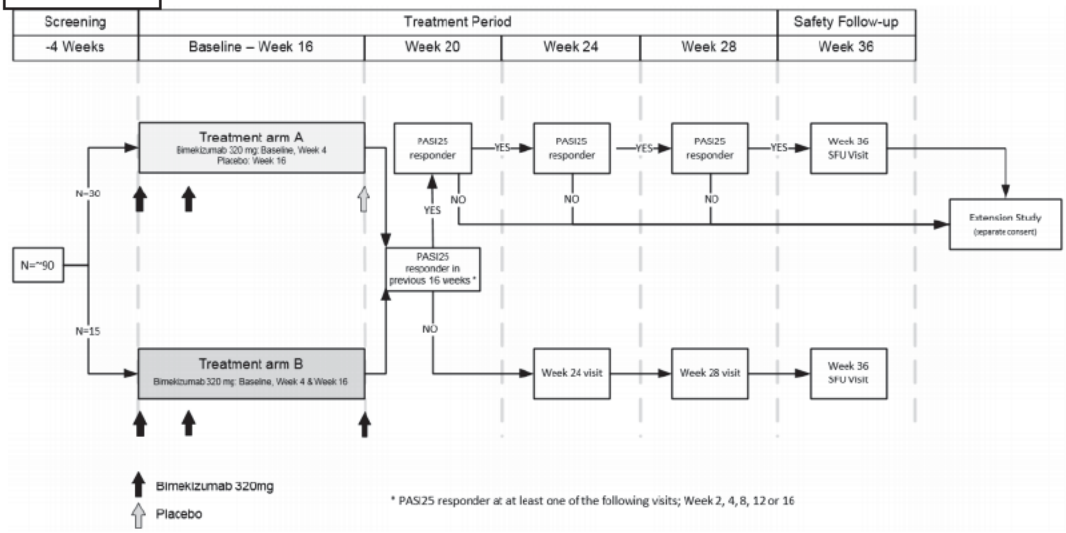
R = randomized, OL = Open label; SB = single blind; DB = double blind; PBO = placebo; HV = healthy volunteer; PSO = psoriasis patient; OLE = Open label extension.

The total number of patients exposed to BKZ in the Pool S2 dataset (bolded studies above) was 1789.

4.3 One Phase 2A and one open label extension (OLE):

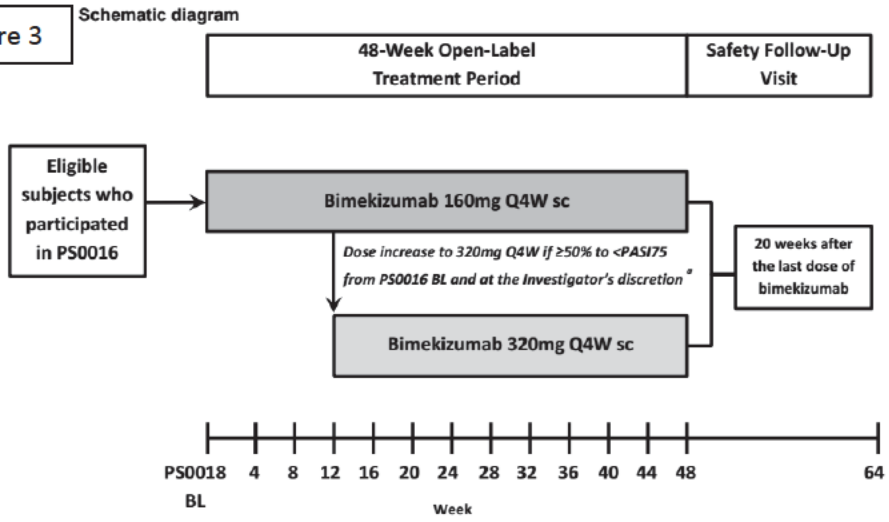
4.3.1 PS0016

Figure 2 **Schematic diagram of PS0016**



4.3.2 PS0018 OLE

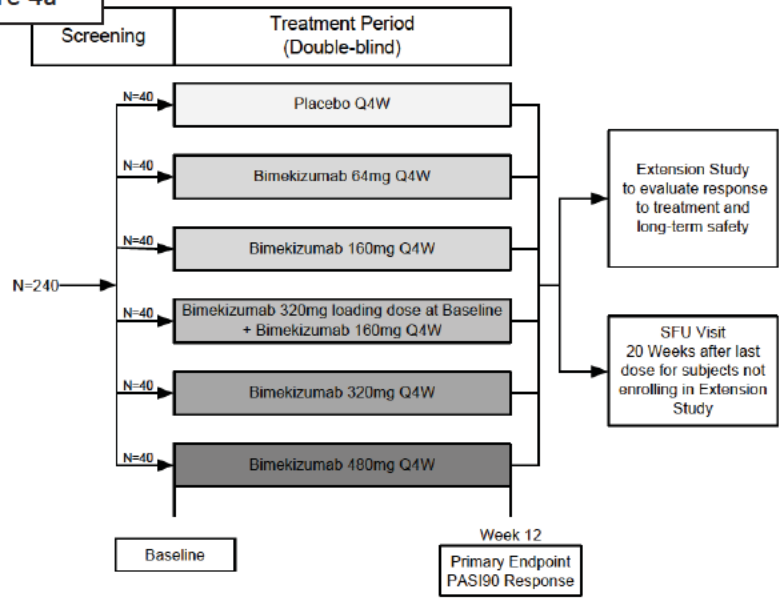
Figure 3 Schematic diagram



4.4 One Phase 2B and Extension:

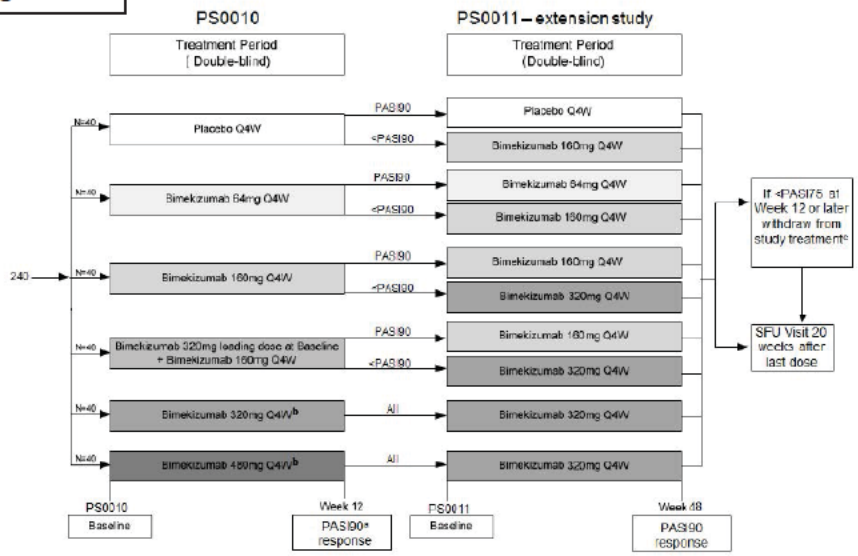
4.4.1 PS0010 (Figures 4a and 4b)

Figure 4a **Schematic diagram of PS0010**



4.4.2 PS0011 (extension of PS0010):

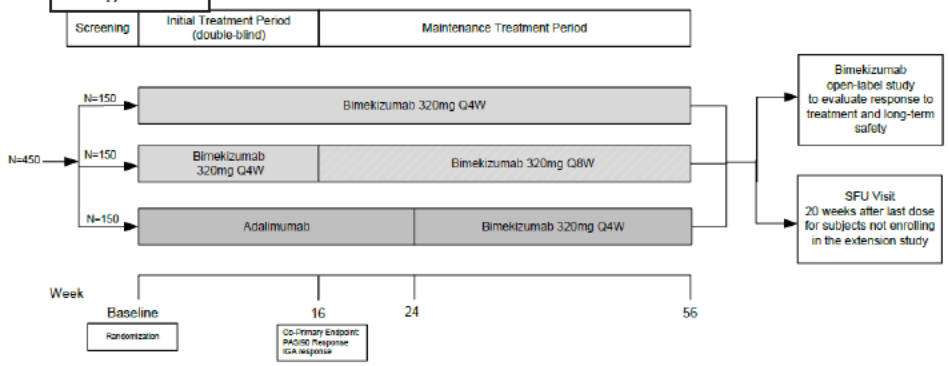
Figure 4b **Schematic diagram of PS0011**



4.5 Three Phase 3 Studies with 1 OLE

4.5.1 PS0008 (Figure 5)

Figure 5 Schematic



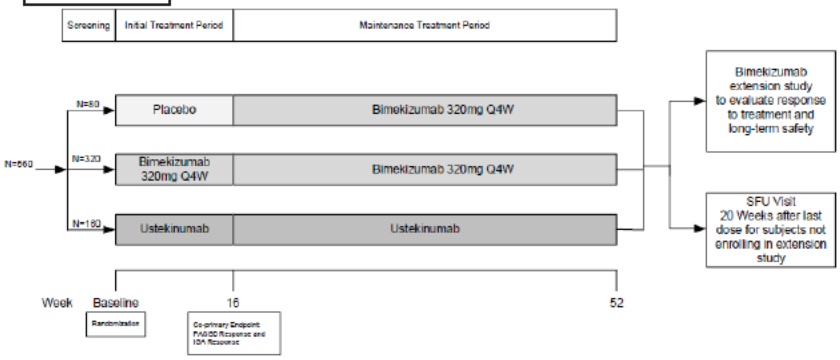
IGA=Investigator's Global Assessment; IMP=investigational medicinal product; N=number; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks; SFU=Safety Follow-Up

Note: Refer to Section 3.2.2 for treatments during the Initial Treatment Period and to Section 3.2.3 for treatments during the Maintenance Treatment Period.

Note: At Week 36 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 were defined as nonresponders and should have discontinued IMP.

4.5.2 PS0009 (Figure 6)

Figure 6 schematic

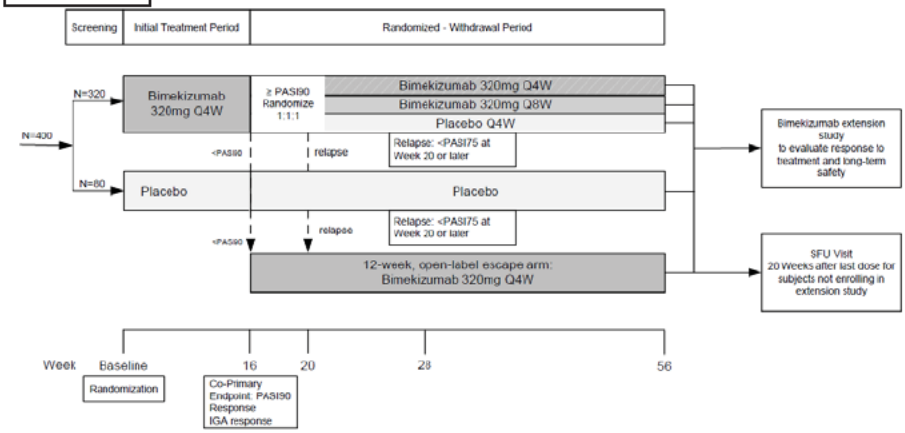


IGA=Investigator's Global Assessment; IMP=investigational medicinal product; N=number; PASI=Psoriasis Area Severity Index; Q4W=every 4 weeks; SFU=Safety Follow-Up

Note: At Week 24 and all following visits, 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 were defined as nonresponders and should have discontinued IMP.

4.5.3 PS0013 (Figure 7)

Figure 7 Schematic



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

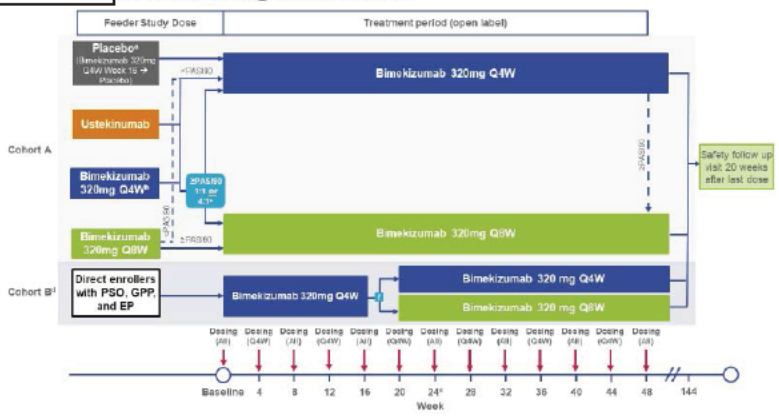
Note: Study participants who did not achieve a PASI90 response at Week 16 were allocated to an escape arm and receive open-label bimekizumab 320mg Q4W for 12 weeks.

Note: Relapse was defined as not achieving a PASI75 response. All study participants who relapsed at Week 20 or later were allocated to an escape arm and received open-label bimekizumab 320mg Q4Wfor 12 weeks.

Note: Study participants in the placebo treatment arm in the Initial Treatment Period continued to receive placebo Q4W at Week 16 and later visits provided a PASI90 response was achieved at Week 16.

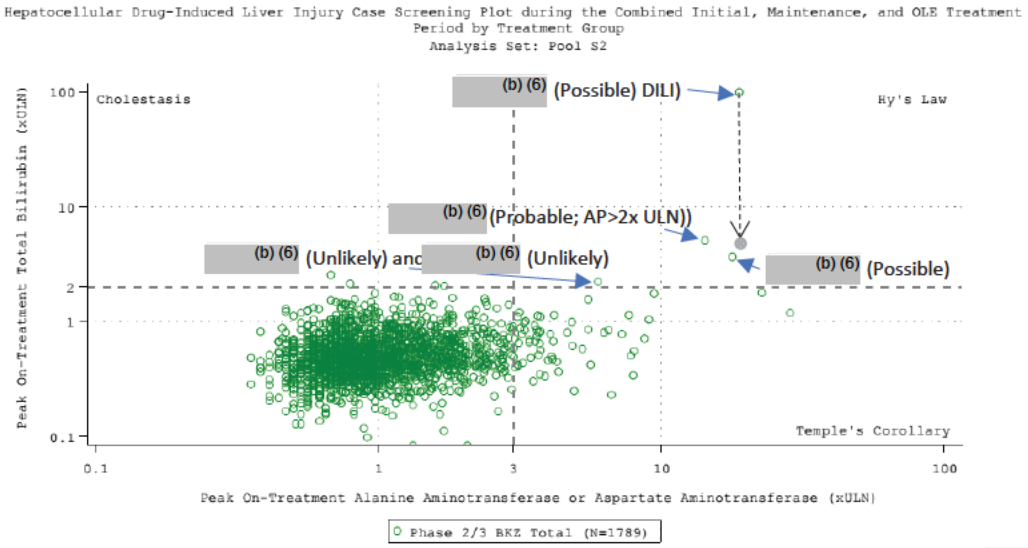
4.5.4 PS0014: Open label extension for Phase 3 studies. Schematic (Figure 8)

Figure 8 **Schematic diagram of PS0014**



4.6 Scatterplots for Pool S2 (Figures 9 and 10)

Figure 9 Bilirubin by transaminase (eDISH)

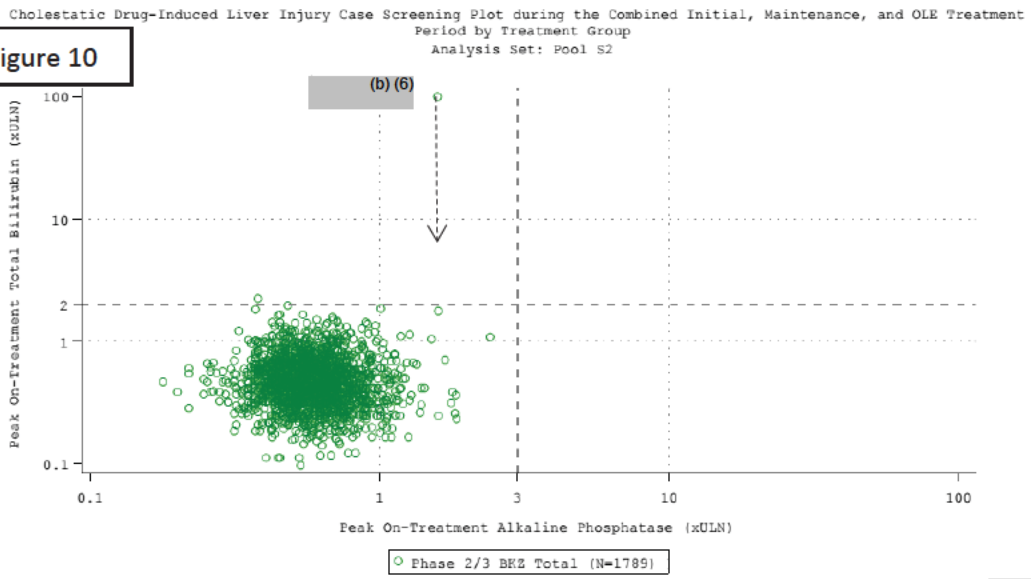


Note 1: One case had an error in peak bilirubin entry (Subject PS0008 (b) (6) (b) (6)). The value was not 100x ULN as shown, but rather 3.8x ULN (see dotted arrow line).

Note 2: Two cases had nearly identical max transaminase and bilirubin x ULN ((b) (6)) so green dots likely overlying each other.

4.6.2 Bilirubin by alkaline phosphatase

Figure 10



Note 1: One case had an error in peak bilirubin entry (Subject PS0008 (b) (6) (b) (6)). The value was not 100x ULN as shown, but rather 3.8x ULN (see dotted arrow line).

Table 2

4.7 Summary data of transaminase elevations for Pool 2 (Table 2)

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%

4.8 Treatment emergent adverse events (TEAE): Patients were exposed to BKZ for longer than comparator arms (i.e. adalimumab—24 weeks; ustekinumab—52 weeks). Therefore, the sponsor gave participant-years of exposure data (Summary of Clinical Safety, 2.7.4, p. 96). Hepatic TEAEs were higher for the BKZ exposed patients compared to comparator arms (Table 3):

Table 3

Treatment	Hepatic TEAE per 100-patient-years of exposure
BKZ (n=1789)	18.3
ustekinumab (n=163)	1.6
adalimumab (n=159)	0.7

4.9 Case level analysis: A total of 30 patients with ALT >5x ULN and/or bilirubin >2x ULN at some point after BKZ start were identified and evaluated by this review team. Twenty cases were deemed unlikely liver injury due to BKZ. The most common alternative diagnosis was fatty liver injury, either alcohol or non-alcohol related (10 cases). The next most common was "unknown" (6) cases. In these six, other factors made BKZ liver injury unlikely (e.g., inconsistent timing, resolution while still on drug). The remaining 4 cases were explained by gallstone disease, acute hepatitis C, hepatitis E and acetaminophen use.

There were 8 cases of possible DILI due to BKZ (Table 2). The alternate diagnoses were alcohol related liver injury (2), unknown (2), autoimmune hepatitis (2), gallstone disease (1), and non-alcoholic fatty liver disease (1). Two cases met liver enzyme and bilirubin criteria for Hy's Law. There were 2 probable cases of DILI due to BKZ, but neither met Hy's Law criteria.

At the Agency's request, a hepatic adjudication committee (HAC) consisting of three hepatologists assessed all cases in Pool 2 with transaminases > 5x ULN and/or >3x ULN with bilirubin > 2x ULN. Their case assessments were similar to our review, except three cases ((b) (6)) where we disagreed between possible and probable in each direction in two cases and possible (DILI Team) versus unlikely (HAC) in one (see Table 4).

Table 4

#	ID	Causality Score*	HAC score*	Alternate diagnosis	Age (y)	Gender	Race	Symptoms	Hy's Law liver test criteria	Latency from start drug (da)	Latency from stop drug (da)	ALT peak (U/L)	AST peak (U/L)	ALP peak (U/L)	Bilirubin peak (mg/dL)	R value peak (ALT)	R value peak (AST)
1	(b) (6)	3	4	gallsone dz	61	F	White	Yes	No	28	0	454	486	361	6.1	3.95	3.89
2		4	NA	NAFLD	45	M	Asian	No	No	311	-25	216	127	130	0.41	4.80	2.82
3		4	4	gallsone dz	21	F	White	Yes	Yes	189	20	824	474	166	4.62	14.34	8.25
4		4	5	AIH	33	F	White	No	No	336	28	257	140	130	1.2	5.71	3.11
5		3	3		35	M	Asian	Yes	No	56	0	366	230	145	1.99	7.29	4.58
6		4	3	unknown	34	M	Asian	No	No	198	30	303	161	130	0.99	6.73	3.58
7		4	4	AIH	38	F	Asian	No	Yes	140	35	460	608	145	4.39	9.16	12.11
8		4	4	alcohol	44	M	Asian	Yes	No	140	0	252	321	347	2.11	2.10	2.67
9		4	4	unknown	58	M	White	No	No	112	-112	248	190	130	1.2	5.51	4.22
10		4	4	alcohol	47	M	White	No	No	338	0	287	203	130	1.2	6.38	4.51
				Mean	41.6				Mean	89.6	26.4	133	143	69	1.6	2.2	2.1
				std dev	11.4				std dev	106.3	40.5	175	162	87	1.8	3.2	2.8
				Median	41				Median	164.5	0.0	295	217	138	1.6	6.0	4.1
				Min	21				Min	28.0	-112.0	216	127	130	0.4	2.1	2.7
				Max	61				Max	338.0	35.0	824	608	361	6.1	14.3	12.1

*Score definitions
1=definite
2=highly likely
3=probable
4=possible
5=unlikely
6=indeterminate

AIH = autoimmune hepatitis
HAC = hepatic adjudication committee

Of the 20 cases assessed as unlikely DILI due to BKZ by the DILI team. Nine were assessed as unlikely by the HAC and nine were not assessed because liver tests did not reach their charter's assessment criteria (i.e., transaminases greater than 5x ULN, or greater than 3x ULN with elevated bilirubin). The HAC assessed two cases as possible, whereas the DILI team assessed them as unlikely.

We highlight five cases below starting with the two that met Hy's Law liver enzyme and bilirubin criteria; both were considered possible DILI due to BKZ. We also detail all three cases assessed as probable DILI due to BKZ by either the DILI team or the HAC.

4.9.1 PS0008 (b) (6) (Possible DILI due to BKZ; 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.

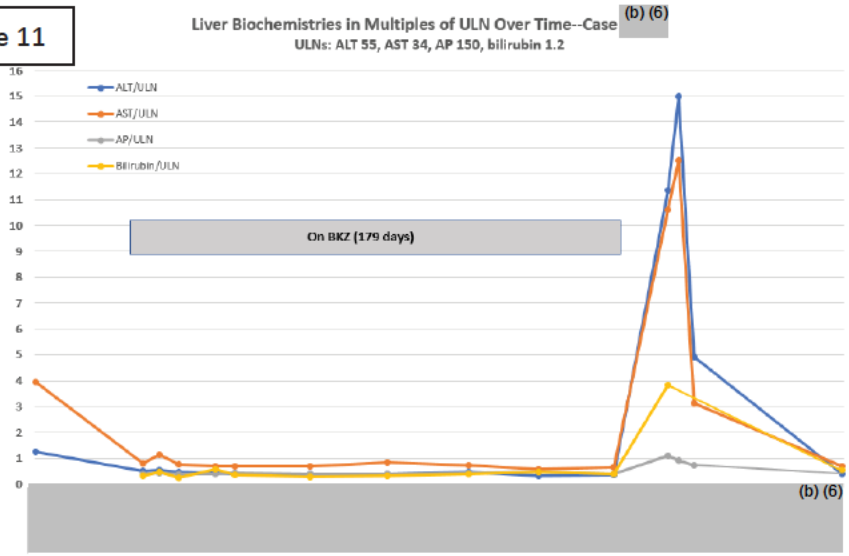
On (b) (6) she received ciprofloxacin for abdominal pain, but liver enzymes were documented as normal on (b) (6) and (b) (6). Ultrasound on (b) (6) was "normal". No gallstones mentioned. Pain resolved.

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 three 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 (Figure 11). DILI from monoclonal biologics typically have a longer washout.

Figure 11



4.9.2 PS0014-(b) (6) (Possible DILI due to BKZ 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 [redacted]. The dosing interval was decreased to q8w after 100 days.

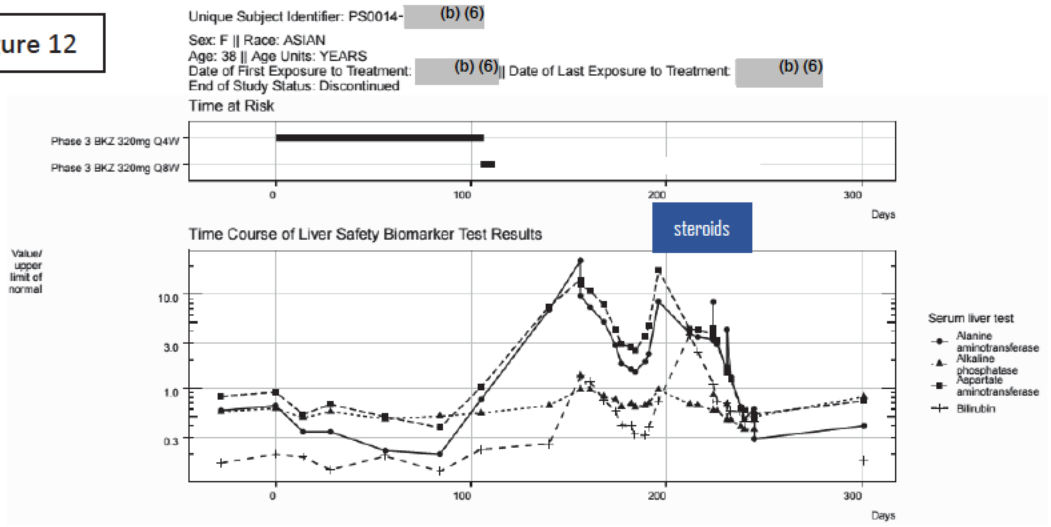
She had oral candidiasis on [redacted], for which she got miconazole nitrate [redacted]019). She was placed on famotidine for dyspepsia on [redacted] She had been on this medication previously without issues.

Elevated liver enzymes were noted on routine follow-up, [redacted]. She was otherwise asymptomatic. BKZ was held with last dose 35 days prior to injury onset. Enzymes rose a bit more through June and then fell to the 80s by mid-[redacted] (Figure 12). However, they rose again on [redacted] 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 [redacted] showed changes consistent with autoimmune hepatitis (AIH) versus DILI. No mention of plasma cells. There was "peripheral" fibrosis. From [redacted], 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, [redacted]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.

Figure 12



4.9.3 PS0009-(b) (6) (Probable DILI due to BKZ)

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).

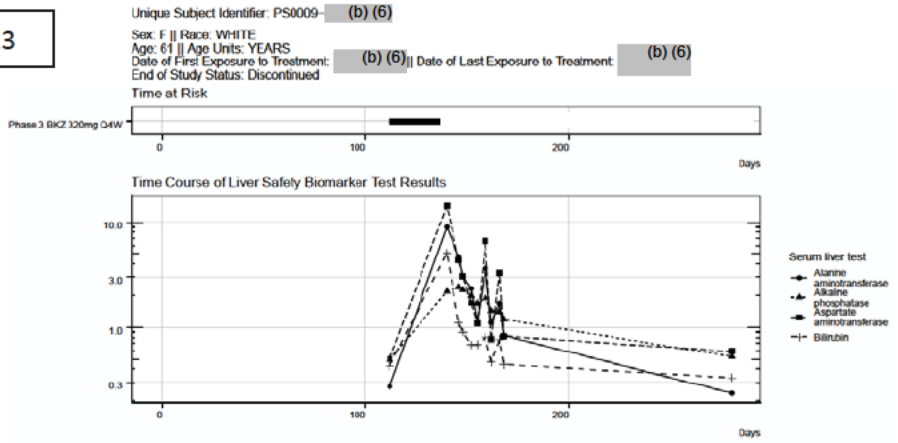
Hepatitis A and B serologies negative. No mention of HCV or HEV testing. ANA titer was 1:40. No mention of anti-smooth muscle antibody. MRI/MRCP (b) (6), was "negative" showing "intrahepatic and extrahepatic biliary tree" as "nondistended with no intraluminal abnormalities". Concomitant medications were 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 (Figure 13).

Assessment: This case is possible, if not probable DILI due to BKZ. Latency fits. De-challenge was rapid but uneven (see figure). 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 [redacted] 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.

Figure 13



4.9.4 PS0009 [redacted] (Probable DILI due to BKZ)

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 [redacted].

On [redacted], 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 [redacted], prednisone was given for "treatment of DILI". The prednisone is listed as "ongoing" with no further mention of course, taper or dosing.

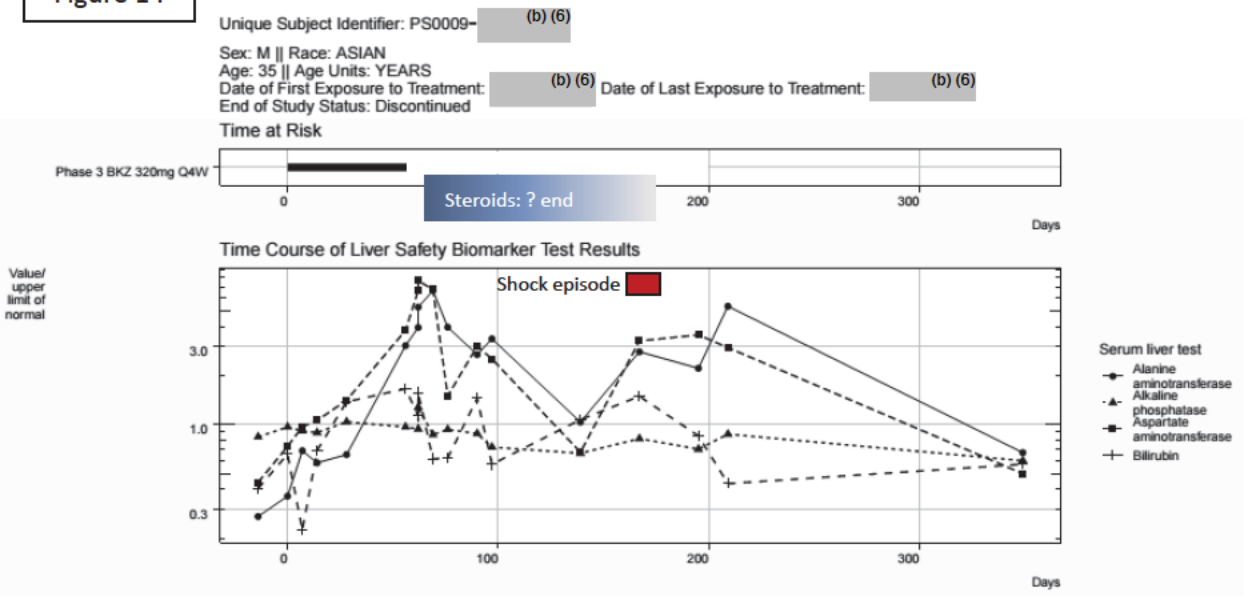
Liver enzymes did fall to normal, but then rose again 4 months later, at the time of severe epistaxis episode with "shock" and drop in Hgb (Figure 14).

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.

Figure 14



4.9.5 PS0014 (b) (6) (Possible DILI due to BKZ)

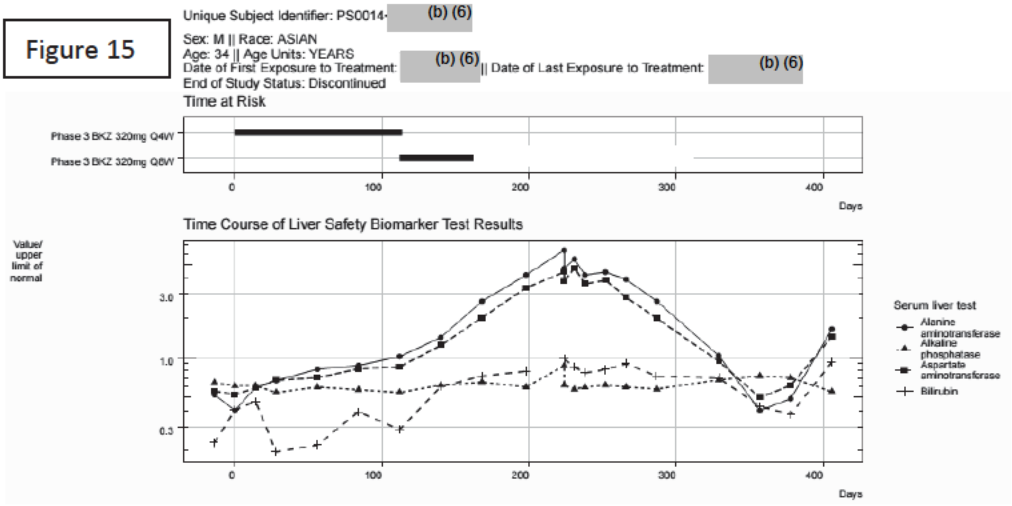
Summary: This is 34-year-old Asian man with history of latent tuberculosis (TB) and "occasional" alcohol use, BMI of 37 kg/m^2 and fatty liver. He had a significant rise in liver tests 28 weeks after first injection and 31 days after last.

Latent tuberculosis was diagnosed in screening, and he failed entry. He was treated with isoniazid (b) (6) to (b) (6), but it was stopped due to elevated liver tests. Liver tests fell and rifampicin started (b) (6). He passed second screen and started BKZ 320 every 4 weeks on (b) (6). At baseline, his ALT was 22, AST 18, AP 92, bilirubin less than 1 mg/dL. On (b) (6) dose interval was increased to every eight weeks, but on (b) (6) ALT was up at 58. Rifampicin held, but by (b) (6), ALT was 78 and AST 42. On (b) (6), his liver tests were significantly higher (Figure 15; 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; anti-smooth muscle antibody negative. On (b) (6), 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 (b) (6) (ALT 90, AST 49) raises the possibility of a non-DILI diagnoses such as autoimmune hepatitis, or gallstone disease. No further liver tests provided.

Figure 15



5.0 Summary: Bimekizumab (BKZ) is a humanized monoclonal antibody that binds and inhibits IL-17A and 17F. In this BLA, the sponsor seeks approval for treatment of plaque psoriasis (PSO). BKZ can cause liver injury, but severity is less clear. Non-clinical studies did not detect DILI, but lack of detection in such studies of biologics is common. Biologics probably cause injury by altering the immune response or new epitope formation with consequent immune mediated DILI.[9] This type of DILI is difficult to detect in animal and in vitro studies.[10]

In the pooled dataset (Pool S2), elevation of transaminases occurred more in the 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 (Section 4.6.3). 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 (Section 4.6.4).

[9] LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK548579/) Accessed May 25, 2021.
[10] Tasmim F, et al. Frontiers in Toxicology. https://doi.org/10.3389/ftox.2021.605392 April 2021.

Pool S2 had 8-9 BKZ patients for every 1 placebo, so 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[11] (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.[12] 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, 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 (see Section 4.1 for details and references). 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.[13]

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.

5.1 Recommendations, if you approve BKZ.

a) Labeling recommendations for liver biochemical abnormalities:

[11] Robles-Diaz M, et al. Gastroenterology (2014)
[12] Ghabril, M., et al. Clinical Gastroenterology and Hepatology (2013)
[13] Loomba R, Liang JT. Gastroenterology (2017)

Warnings or Adverse Events sections

Liver biochemical abnormalities - In a pooled safety dataset of randomized clinical trials a higher percentage of the 1789 patients treated with BKZ developed asymptomatic serum transaminase elevations (2-5X ULN), compared with placebo (7.5% vs 4.5%). In addition, a few patients treated with BKZ developed acute cholestatic liver injury with combined elevations of transaminases, alkaline phosphatase and total bilirubin which resolved after discontinuation of BKZ. The time to onset of the liver injury varied between 28 and 198 days after starting BKZ treatment. Test liver enzymes and bilirubin at baseline and evaluate patients once BKZ has been started if drug-induced liver injury is suspected. If treatment-related increases in liver enzymes occur and DILI is suspected, BKZ should be interrupted until a diagnosis of liver injury is excluded. Permanently discontinue use of BKZ in patients with causally associated elevations of transaminases and bilirubin. Since patients with active liver disease, cirrhosis, or moderate to heavy alcohol use may be at increased risk for worse outcome from liver injury associated with BKZ, routine use of this product in these patients is discouraged.

b) Hepatitis B reactivation risk: Screening patients for hepatitis B infection and monitoring for reactivation or prophylactic treatment should be considered for labeling. Otherwise, monitoring for reactivation should be included in post-market requirements as BKZ may be used in patients with inactive hepatitis B infection.

Paul H. Hayashi -S

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Paul H. Hayashi, MD, MPH
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Joseph Toerner, MD, MPH
Director, Division of Hepatology and Nutrition
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PAUL H HAYASHI
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Clinical Inspection Summary

Date	7/15/2021
From	Phuc (Phil) Nguyen M.D., Medical Officer Karen Bleich, M.D., Team Leader Kassa Ayalew, M.D., M.P.H., Branch Chief/ Interim Division Director Good Clinical Practice Assessment Branch (GCPAB) Division of Clinical Compliance Evaluation (DCCE) Office of Scientific Investigations (OSI)
To	Kevin Clark M.D., Medical Officer Gordana Diglisic, M.D., Team Lead Kendall Marcus, M.D., Division Director Division of Dermatology and Dentistry
BLA	761151
Applicant	UCB, Inc.
Drug	Bimekizumab
NME	Yes
Therapeutic Classification	Monoclonal antibody
Proposed Indication	Treatment of plaque psoriasis
Consultation Request Date	7/15/2020
Summary Goal Date	7/15/2021
Action Goal Date	7/15/2021
PDUFA Date	10/15/2021

I. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

Three phase-3 studies: PS008, PS009, and PS0013 were submitted to the Agency in support of a Biologics License Application (BLA 761151) for bimekizumab injections (BKZ) for the above proposed indication. Two clinical investigators (Drs. Andrew Blauvelt and Abel Jarell) who contributed to the data were selected for surveillance clinical inspections.

The inspections revealed no significant findings at the audited clinical investigator sites. Based on the results of these inspections, studies PS0013, PS0009, and PS0008 overall appear to have been adequately conducted, and the study data generated appear acceptable in support of the indication for this BLA.

II. BACKGROUND

UCB, Inc. seeks approval of bimekizumab for the treatment of adults with moderate to severe chronic plaque psoriasis. Bimekizumab, an engineered, humanized, full-length anti-IL-17

monoclonal antibody (mAb) of immunoglobulin (Ig) G1 subclass, is the first therapeutic approach to plaque psoriasis that selectively inhibits the activity of both interleukin (IL)-17A and IL- 17F subtypes of IL-17. IL-17A and IL-17F are key proinflammatory cytokines believed to play important roles in autoimmune and inflammatory diseases. Per the sponsor, broader IL-17 blockade may be more beneficial in the treatment of plaque psoriasis.

Data from three phase-3 clinical studies (PS0008, PS0009, and PS0013) were submitted for this BLA.

Study PS0008
Title of Study: *A Phase 3, Multicenter, Randomized, Double-Blind Study with an Active-Controlled Initial Treatment Period Followed by a Dose-Blind Maintenance Treatment Period to Evaluate the Efficacy and Safety of Bimekizumab In Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis"*

Per the protocol, this study was planned as an international, phase III, multicenter, randomized, double-blind, parallel-group, active-comparator-controlled study to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis.
The primary objective of the study was to compare the efficacy of bimekizumab administered subcutaneously (sc) for 16 weeks versus adalimumab in the treatment of subjects with moderate to severe chronic plaque psoriasis.

The study was planned to last a maximum of 77 weeks, to include a 2-5 week screening period, a 16 week double-blind, active-controlled initial treatment period, and a 40 week maintenance period, with a Safety Follow-Up (SFU) visit planned for 20 weeks after the final dose of study drug.

Eligible subjects were to be adults >18 years of age with a diagnosis of moderate to severe plaque psoriasis defined by a Baseline Psoriasis Area Severity Index (PASI) score equal or greater than 12, and a body surface area affected (BSA) equal or greater than 10%, with an Investigator's Global Assessment Score (IGA) equal or greater than 3, who were candidates for systemic therapy/phototherapy.

During the Initial Treatment Period study participants were to be randomly assigned to receive either bimekizumab 320mg administered every 4 weeks (Q4W) throughout the study; bimekizumab 320mg administered Q4W until Week 16 and subsequently bimekizumab Q8W from Week 16 through Week 52; or adalimumab 80mg administered as an initial dose, followed by 40mg Q2W starting 1 week after the initial dose until Week 24.

After the 16-week Initial Treatment Period, study participants were to enter the 40-week Maintenance Treatment Period. Treatment during the Maintenance Treatment Period was based on initial treatment: study participants in the bimekizumab 320mg Q4W treatment arm were to continue to receive bimekizumab 320mg Q4W, study participants in the bimekizumab 320mg Q4W/Q8W treatment arm were to receive bimekizumab Q8W from Week 16 through Week 52, and study participants in the adalimumab treatment arm were to receive bimekizumab 320mg Q4W from Week 24 through Week 52.

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

The PASI and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. Per the study protocol, the same assessor should evaluate the subject at each assessment.

Per the study report, the study was conducted at 77 sites in 9 countries. A total of 478 subjects were enrolled into the study. The first subject enrolled 26 January 2018, and the last subject completed 28 October 2019, based on a clinical cutoff date for the interim Clinical Study Report.

Study PS0009
Title of study: *A Phase 3, Multicenter, Randomized, Double-Blind, Placebo- and Active Comparator-Controlled, Parallel-Group Study to Evaluate the Efficacy and Safety of Bimekizumab In Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis*

Per the protocol, this was planned as an international, multicenter, randomized, double-blind placebo- and active comparator-controlled to evaluate the efficacy and safety of bimekizumab in adults with moderate to severe chronic plaque psoriasis. The primary objective of the study was to compare the efficacy of bimekizumab administered SC for 16 weeks versus placebo in the treatment of subjects with moderate to severe chronic plaque psoriasis.

The study was planned to last 73 weeks, with a 2-5 weeks screening period, a 16 weeks double-blind, active controlled initial treatment period, a 36 weeks maintenance treatment period, and an SFU visit planned at 20 weeks after the final dose of the study drug. Eligibility criteria were to be the same as PS0008.

Approximately 560 study participants were planned to be randomized 4:2:1 to receive the following blinded regimens: bimekizumab 320mg administered subcutaneously (sc) every 4 weeks (Q4W); ustekinumab; or placebo administered sc Q4W. After the 16-week Initial Treatment Period, study participants were to enter the 36-week Maintenance Treatment Period. The Maintenance Treatment Period started at Week 16 and study participants were to return to the clinic Q4W through Week 52.

During the Maintenance Treatment Period study participants in the bimekizumab 320mg Q4W and ustekinumab treatment arms were to continue to receive bimekizumab 320mg Q4W and ustekinumab, respectively, and study participants in the placebo arm were to receive bimekizumab 320mg Q4W starting at Week 16.

The co-primary efficacy endpoints are the PASI90 response (defined as a study participant that achieved 90% reduction from Baseline in the PASI score) at Week 16 and the IGA response

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

Similar to PS0008, the PASI and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. The same assessor should evaluate the subject at each assessment.

Per the study report, the study was conducted at 105 sites in11 countries. A total of 567 subjects were enrolled into the study. The first subject enrolled 06 December 2017, and the last subject completed 04 September 2019, based on a clinical cutoff date for the interim Clinical Study Report.

Study PS0013
Title of Study: *A Phase 3, Multicenter, Double-Blind, Placebo-Controlled Study with an Initial Treatment Period Followed by a Randomized-Withdrawal Period to Evaluate the Efficacy and Safety of Bimekizumab in Adult Subjects with Moderate to Severe Chronic Plaque Psoriasis"*

Per the Protocol, this was an international, randomized, double-blind placebo-controlled study to evaluate the efficacy and safety of bimekizumab in adult subjects with moderate to severe chronic plaque psoriasis. The primary objective of the study was to compare the efficacy of bimekizumab administered subcutaneously (sc) for 16 weeks versus placebo in the treatment of study participants with moderate to severe chronic plaque psoriasis (PSO).

The study was planned to last a maximum of 89 weeks, with a 2-5 week screening period, a 16 week placebo-controlled initial treatment period, a 40 week placebo-controlled randomized-withdrawal period, and a SFU visit at 20 weeks after the final dose of the study drug. Eligibility criteria were the same as PS0008 and PS0009.

A total of 400 study participants were planned to be randomized 4:1 to receive: bimekizumab 320mg administered Q4W or placebo administered Q4W. At the Week 16 study visit, study participants who achieved a 90% improvement or more from baseline on PASI score (PASI 90) were to be entered into the Randomized-Withdrawal Period. Study participants initially randomized to bimekizumab 320mg Q4W were to be re-randomized 1:1:1 to bimekizumab 320mg Q4W, bimekizumab 320mg Q8W, or placebo (ie, treatment withdrawal). All study participants initially randomized to placebo who achieved a PASI90 response at Week 16 would continue to receive placebo Q4W.

Study participants who did not achieve a PASI90 response at the Week 16 study visit and all study participants who relapsed at Week 20 or later during the Randomized-Withdrawal Period (up to Week 56) were to be allocated to the escape arm until the clinical cutoff date.

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

Similar to PS0008 and PS0009, the PASI, BSA, IGA, scalp IGA, mNAPSI, and pp-IGA should be performed by the Investigator, another delegated physician, or an appropriately qualified medical professional (based on local requirements) who has had documented training on how to perform these assessments correctly. The same assessor should evaluate the subject at each assessment.

Per the study report, the study was conducted at 77 sites in 9 countries. A total of 576 subjects were enrolled into the study. The first subject enrolled 05 February 2018, and the last subject completed 18 October 2019, based on a clinical cutoff date for the interim Clinical Study Report.

III. RESULTS (by Site)

1. Andrew Blauvelt, M.D.
Oregon Medical Research Center, 9495 SW Locust St. Suite G Portland, OR 97223
Study: PS0008, PS0013
Site: 929
Dates of inspection: 11/30/2020 to 12/08/2020

This inspection was conducted on-site. For PS0008, the site screened 22 subjects and enrolled and dosed 18 subjects. For PS0013, the site screened 25 subjects and enrolled and dosed 20 subjects.

For all enrolled subjects, the source documentation matched the data listings regarding eligibility, primary efficacy endpoint data (PASI and IGA raw scores at baseline and week 16), randomization treatment assignment, and discontinuations. The inspection revealed no deficiencies with maintenance of the blind. There were no major concerns with informed consent process and records.

Per the inspection report, the site used different assessors for PASI and IGA scores at the baseline and week 16 visits, for 9 out of the 15 subjects for whom the site had collected this data in the PS0008 study, and for 7 out of the 20 subjects for whom the site had collected this data in the PS0013 study. The two different assessors were the CI and his Co-Clinical Investigator, Dr. Ehst, who were trained on the administration of assessments.

Reviewer comments: Both protocols recommend that "the same assessor should evaluate the subject at each assessment." The introduction of variability in intra-subject PASI and IGA scores related to differences between assessors cannot be excluded.

Dr. Blauvelt explained he plans to schedule subjects' study visits in the future in a manner that ensures the same investigator assesses respective subjects, if possible, at visits where primary efficacy data is collected, if this is required by the protocol.

The following concomitant medications were not reported in the subject level data line listings:

Study	Subject #/Arm	Medication	Date
PS0008	(b) (6) /BKZ	Fluconazole	(b) (6)

	(b) (6)	Hydrocortizone topical	(b) (6)
PS0008	/BKZ	Baclofen	
		Acetaminophen + Codeine	
PS0008	/BKZ	Ondansetron	
PS0008	/BKZ	Augmentin	
		Mucinex	
		Amoxicillin	
PS0008	/adalimumab-BKZ	Losartan	
PS0013	/placebo-NA-BKZ	Lisinopril	

Review comments: The CI did inform the sponsor of these medications to update the data listings. The unreported concomitant medications are not protocol-prohibited, and all AEs associated with these medications are appropriately reported in the data listings. The list of medications is provided for consideration by the review team in case they are relevant to their review.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. Data from this site appear acceptable in support of this BLA.

2. Abel Jarell, M.D.
ActivMed Practices & Research, Inc., 110 Corporate Drive Suite 2 Portsmouth, NH 03801
Study: PS0009, PS0013
Site: 901
Date of Remote Regulatory Assessment: 1/11/2021 to 1/15/2021

This inspection was conducted on-site. For PS0009, the site screened 13 subjects and enrolled and dosed 12 subjects. For PS0013, the site screened 7 subjects and enrolled and dosed 6 subjects. All subject records were reviewed. The PASI score and IGA score were verified at baseline and week 16 using source records. There was no evidence of underreporting of adverse events. There were no major protocol deviations or any significant concern with maintenance of the blind.

For Subject (b) (6) (Study PS0013/Placebo-NA-BKZ), a minor discrepancy was noted: the medication Ondansetron was listed as 4 mg in source records but was noted to be 25 mg in the data listing.

For PS0009 primary endpoint visits, a sub investigator trained in assessments conducted PASI scores assessments instead of Dr. Jarell for one out of 12 baseline patient visits, and for 2 out of 12 week-16 visits. All other PASI and IGA scores collected during the baseline and week-16 visits were done by Dr. Jarell. For PS00013, 2 other sub investigators conducted assessments at 2 out of the 6 week-16 visits, while Dr. Jarell conducted all other assessments at the baseline and week-16 visits.

Reviewer comments: The protocol recommends that the same assessor should evaluate the subject at each assessment. A small portion of visits were conducted by a different assessor than Dr. Jarell. The

introduction of variability in intra-subject PASI and IGA scores related to differences between assessors cannot be excluded.

Overall, the inspection revealed adequate adherence to the regulations and the investigational plan. The observations above are unlikely to affect primary safety and efficacy analyses, or impact suggested labeling. Therefore, data from this site appear acceptable in support of this BLA.

{See appended electronic signature page}
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Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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cc:
DDD/Division Director/ Kendall Marcus
DDD /Team Lead/ Gordana Diglisic
DDD /Clinical Reviewer/ Kevin Clark
DRO /Regulatory Project Manager/ Strother Dixon

OSI/DCCE/Acting Division Director/Branch Chief/Kassa Ayalew
OSI/DCCE/GCPAB/Team Leader/Karen Bleich
OSI/DCCE/GCPAB Reviewer/Phillip Phuc Nguyen
OSI/DCCE/GCPAB/Program Analyst/Yolanda Patague
OSI/DCCE/Database Project Manager/Dana Walters

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 7, 2021

TO: Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation

FROM: Kara A. Scheibner, Ph.D.
Pharmacologist
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance

THROUGH: Kimberly A. Benson, Ph.D.
Deputy Director
Division of Generic Drug Study Integrity
Office of Study Integrity and Surveillance

SUBJECT: Remote Record Review of (b) (4) (b) (4)

1. RRR Summary

The Office of Study Integrity and Surveillance (OSIS) conducted a remote record review (RRR) of the analytical portion of study UP0033 (BLA 761151, Bimekizumab) conducted at (b) (4) (b) (4)

I observed objectionable conditions in the anti-drug antibody method validation and study during the RRR including 1) use of inconsistent acceptance criteria, 2) use of a sub-optimal low positive control, and 3) an absence of established criteria to investigate non-monotonic assay signals in the titer assay.

1.1. Recommendation

Based on my review of the RRR observations and the firm's response, I conclude that the observations do not impact the reliability of data from the audited study. Data from Study UP0033 are reliable to support a regulatory decision.

2. Reviewed Studies

Study UP0033 (BLA 761151)

"Single-dose BE study comparing the proposed commercial device presentations and drug substance manufacturing process with those used in Phase 3 (SS-1mL, [redacted], AI-1mL)"
Sample Analysis Period:
PK Assay – 05/08/2018 to 07/22/2019
ADA Assay – 05/30/2019 to 07/03/2019

3. Scope of RRR

OSIS scientist Kara A. Scheibner, Ph.D. audited the analytical portion of the above study conducted at [redacted]

The RRR included an examination of study records for the pharmacokinetic (PK) assay method validation and sample analysis, and for the anti-drug antibody (ADA) assay method validation and sample analysis. The RRR also included a virtual tour of the facility; a review of relevant SOPs; a review of equipment and maintenance records; a review of sample receipt and storage operations and documentation; a review of study correspondence; and interviews with the firm's management and staff.

4. RRR Observations

At the conclusion of the RRR, I observed objectionable conditions. The following items were discussed with the firm's management during the RRR close-out meeting.

My evaluation of the observations that were discussed and the firm's response dated 05/07/2021 (**Attachment 01**) are presented below.

4.1. Observations discussed at the RRR close-out

4.1.1. Item 1

[redacted]

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5. Conclusion

After review of the RRR observations, I conclude that PK and ADA data from Study UP0033 are reliable.

cc: OTS/OSIS/Kassim/Folian/Mitchell/Fenty-Stewart/Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Lewin/Scheibner

Drafts: KAS 5/6/2021; 5/25/2021
Edit: MFS 5/6/2021; KAB 06/03/2021

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06/07/2021 01:31:38 PM

MEMORANDUM

REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	May 27, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761151
Product Name and Strength:	Bimzelx (bimekizumab-bkzx) injection, 160 mg/mL single-dose safety syringe and 160 mg/mL single-dose auto-injector
Applicant/Sponsor Name:	UCB, Inc.
OSE RCM #:	2020-1496-1 and 2020-1506-1
DMEPA Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader (Acting):	Ebony Whaley, PharmD, BCPPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU) and carton labeling received on May 19, 2021 for Bimzelx. The Division of Dermatology and Dentistry (DDD) requested that we review the revised IFU and carton labeling for Bimzelx (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

The IFU and prefilled syringe carton labeling are acceptable from a medication error perspective. However, the revised autoinjector carton labeling is unacceptable from a medication error perspective. As presented, the image of the second autoinjector will not fully

[a] Owens, L. Human Factors Results and Label and Labeling Review for Bimzelx (BLA 761151). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2021 MAY 04. RCM No.: 2020-1496 and 2020-1506.

appear on the principal display panel (PDP), which may confuse users and lead to wrong dose medication errors.

3 RECOMMENDATIONS FOR UCB, INC.

We recommend the following be implemented prior to approval of this BLA:

A. Autoinjector Carton Labeling

1. The carton labeling appears to show the images of the autoinjectors on two separate areas of the carton (i.e. one on the principal display panel [PDP] and (b) (4)). Ensure that the image of both autoinjectors appear on the PDP to maintain consistency and avoid confusion with the presentation of the number of autoinjectors inside of the carton. Please see image on the PDP below for illustration.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON MAY 19, 2021

FDA Request and UCB Response:

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IFU - PFS

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IFU - AI

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Carton labeling

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05/27/2021 11:31:02 AM

HUMAN FACTORS STUDY REPORT AND LABELS AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	May 4, 2021
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761151
Product Type:	Combination Product
Drug Constituent Name and Strength	Bimzelx (bimekizumab-bkzx) injection, 160 mg/mL single-dose safety syringe and 160 mg/mL single-dose auto-injector
Rx or OTC:	Rx
Applicant/Sponsor Name:	UCB, Inc
Submission Date:	7/15/2020
OSE RCM #:	2020-1496 and 2020-1506
DMEPA Human Factors Evaluator:	Lissa C. Owens, PharmD
DMEPA Team Leader:	Millie Shah, PharmD, BCPS
DMEPA Associate Director for Human Factors (Acting):	Lolita White, PharmD
DMEPA Associate Director of Nomenclature and Labeling	Mishale Mistry, PharmD, MPH

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under BLA 761151 for Bimzelx (bimekizumab-bkzx) injection.

1.1 PRODUCT DESCRIPTION

This is combination product with a proposed single-dose prefilled safety syringe (PFS) containing 160 mg/mL of bimekizumab and a single-dose autoinjector (AI) containing 160 mg/mL of bimekizumab that are intended to treat moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

1.2 REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

We provided recommendations to the applicant in our review of the human factors validation study protocol on June 19, 2018[1].

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

[1] Mena-Grillasca C. Label and Labeling Review for Bimekizumab IND 128707. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 19. RCM No.: 2018-671

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide a summary of the HF validation study design, errors/close calls/use difficulties observed (Table 2), and our analysis to determine if the results support the safe and effective use of the proposed product.

3.1 SUMMARY OF STUDY DESIGN

The PFS and AI studies each contained a total of seventy-five (n=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 proved in the HF validation study. A simulated use methodology was used 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.

3.2 RESULTS AND ANALYSES

Tables 2 (PFS) and 3 (AI) describes the study results, UCB, Inc's analyses of the results, and DMEPA's analyses and recommendations.

Table 2: Prefilled Syringe Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and NC for Non-Critical)	Number of Use Errors and Description of Use Errors	Number and Description of Close Calls and Use Difficulties	Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties[2]	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations

[2] AX: Patients with axial spondyloarthritis; PS: Patients with psoriatic arthritis; CG: Caregivers; H: Health Care Provider

Remove bimekizumab-SS-1mL carton from refrigerator [C] This was evaluated by asking participants how the bimekizumab-SS-1mL should be stored	Failures: n=2	N/A	PA09 originally stated to store the bimekizumab-SS-1mL in a closet, to not freeze them and to protect the devices from light. In the post-test interview PA09 found the information on the carton to refrigerate the syringes. H07 stated room temperature.	The root cause of the errors was perception, due to the participants not seeing the relevant information on the carton. After reading the carton in the post-test interview, both participants found the correct information about storing the syringes in the carton in the fridge.	No mitigation required.	Based on the Applicant's use-related risk analysis (URRA), the failure to properly store this product will result in degraded drug medication error which may lead to ineffective therapy. Our review of the subjective feedback does not provide information that the participants referred to the labeling prior to answering the storage question. However, our review of the RCA supports that both participants were able to read the carton labeling as part of the post-test assessment and provide correct storage information. The RCA also provides that the participants did not see the storage information initially but upon second look did find it. Our review of the user interface finds that there are acceptable mitigation strategies currently in place, including storage information in the IFU and prominently placed on the carton. We did not identify additional mitigations to further reduce the occurrence of these storage errors and note that the participants were able to independently identify the information regarding storage in the post-test interview. Therefore,

						we agree with the Applicant and find no additional mitigation is needed and find the residual risk acceptable. We have no recommendations at this time.

Remove bimekizumab-SS-1mL carton from refrigerator [C] This was evaluated by asking participants how many bimekizumab-SS-1mLs they would need to use if their prescription was 160mg or 320mg.	Failures: n=3	N/A	PS12 initially said 80 mg. Thought there was 160 mg between the two syringes. Participant reread the carton and realized their error when probed by the moderator. They corrected their answer to 160 mg in one syringe. H01 and H15 thought 2 syringes were needed for a 160 mg dose. After using syringe both corrected their answers to 160 mg in one syringe.	The root cause of the errors were cognition perception and negative experience transfer, due to the participants not seeing or understanding the information on the carton and previous experiences with medication. The low occurrence of confusion about dosing was not unexpected due to the participants having no prior experience of the bimekizumab-SS-1mL. The syringe labelling and instructions for use (IFU) described the dosing clearly and correctly; all three participants realized their mistakes and	No mitigation required.	Based on the Applicant's URRA, the potential harm associated with this use risk is a single missed dose or under dose leading to possible compromised care. Based on the participant subjective feedback, the participants found it unclear how much drug product is in one syringe. We disagree with the Applicants RCA that the failures were due to the participants not seeing or understanding the information on the carton and previous experiences with medication. The Applicant did not provide mitigation to address these failures. Our review of the mitigation strategies currently in place identified additional labeling recommendations that may further reduce the occurrence of these use errors and minimize the risk of confusion related to this task. Therefore, we provide carton labeling recommendation #2 to increase the prominence of the instructions and provide IFU recommendation #2 to revise the instruction in the IFU to decrease confusion (see Table 4).

				understood each syringe contained 160 mg of bimekizumab		
Check bimekizumab-SS-1mL carton [C] This was evaluated by participants what they would do if the pack was tampered with	Failures: n=2	N/A	PA09 and PA13 stated they would use the syringes even if the seal was broken. Both found the information in the instruction for use not to use if the tamper seal is broken.	The root cause of the errors was either cognition or action, due to either thinking the product would be safe to use if pharmacy had provided it with the seal broken, or that they would use the syringe even if the tamper seal was broken. Both participants found the correct information in the post-test interview.	No mitigation required.	Based on the Applicant's URRA, if the packaging is tampered with, it may result in the wrong drug being injected leading to a medication error. The participant subjective feedback did not provide information for the incorrect answers for this task. The Applicant's RCA attributes the error to the participant thinking the product would be safe to use if pharmacy had provided it with the seal broken. (i.e. mental model) Our review of the user interface finds that there are mitigation strategies currently in place, including information in the IFU. We did not identify additional risk mitigations to further reduce the occurrence of these errors and note that the participants found the correct information in the post-test interview. Therefore, we agree with the Applicant and find their conclusion and residual risk acceptable. We have no recommendations at this time

Check medicine for coloration and particles [C]	Failures: n=11	N/A	AX07, PS05: trusting, looked full, date on box. AX09: Would check when received at home. AX11, CG02: Does not generally, check. PA02: glossed over as too busy thinking about giving a shot. PA13, PS03, CG06: Would do usually. PS15: "I didn't. I saw that it was clear so [it was safe to use]." CG01: would probably check. In a hurry. Thought did not have to as a sugar solution.	Cognition – AX07, AX11, PS05: Would not necessarily think to check, trust that all fine unless something unexpected. PA02, PA13. PA02: was thinking ahead and thinking of shot. Action – AX09, PS03, AX09: knows that should have done. PS03: forgot.	N/A- Information found in IFU and the likelihood of this occurring is extremely low.	Based on the Applicant's URRA, the potential harm associated with this use risk is a possible infection. The participant subjective feedback indicates that they would have checked at home, does not check in general, test artifact since using a placebo, forgot or were preoccupied with giving the injection. The RCA is in alignment with the subjective feedback. The Applicant did not suggest any mitigation. Our review of the Quick Start Guide (QSG) located on the carton determined that the task of checking the medicine for the coloration and particles is not present. Although the QSG includes a statement, "See enclosed full Instructions for Use booklet," which does include the critical task of checking the medication. Thus, we recommend increasing the prominence of this statement on QSG and adding a statement to check for coloration and particles. We provide QSG – Prefilled Syringe and Autoinjector recommendation #3 in Table 4 address this use risk.

Allow medicine to warm up by leaving it at room temperature until medicine temperature reaches ambient [C] This was evaluated by asking participant to state the requirement and method for allowing drug to warm.	Failures: n=1	N/A	CG03 misread the instructions for use and stated 30-40 minutes. In post-test interview correctly read instructions.	Not listed	No mitigation required.	Based on the Applicant's URRA, the potential harm associated with this use risk is the potential for degraded drug medication error. The participant subjective feedback indicates they misread the IFU. However; in the post-test interview, they correctly read the instructions. Our review of the user interface finds that there are mitigation strategies currently in place, including information in the IFU. We did not identify additional risk mitigations to further reduce the occurrence of this error as it is in alignment with current best practices we would recommend. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no recommendations at this time.

Check medicine for coloration and particles [C] This was evaluated by asking participants how they can tell if a drug product is safe to use. Success: Participant states that the medicine should be checked for coloration and particles	Failures: n=3	N/A	PA04, PA09, PS15 did not state the correct color of the liquid and did not use the instruction for use to answer the question. In the post-test interview all three found the correct color in the instruction for use.	Not listed	No mitigation required.	Based on the Applicant's URRA, the potential harm associated with this use risk is an infection. The participant subjective feedback indicates the participants did not refer to the IFU to determine what color the liquid should be, thus they answered incorrectly. The Applicant did not suggest any mitigations. Our review of the user interface finds that there are mitigation strategies currently in place, including information in the IFU. We did not identify additional risk mitigations to further reduce the occurrence of this error as it is in alignment with current best practices we would recommend. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no recommendations at this time.

Check medicine for coloration and particles [C] This was evaluated by asking participants how they can tell if a drug product is safe to use. Success: Participant states that they can see the liquid inside	Failures: n=5	N/A	PA04, PA07, PS08 could not see the liquid due to an air bubble when given a syringe in the post-test interview. PS16 was expecting the liquid to be colored and so was looking for a yellow colored liquid. CG11 could not determine if there was liquid in the syringe. They could see the liquid due to an air bubble when given a syringe in the post-test interview.	Not listed	No mitigation required.	Based on the Applicant's URRA the potential harm associated with this use risk is an infection. The participants' subjective feedback attributed use error to the presence of an air bubble in the syringe and mental model where they expected the liquid to be yellow in color. The Applicant did not suggest any mitigations. Our review of the user interface finds that there are mitigation strategies currently in place, including information in the IFU. We did not identify additional risk mitigations to further reduce the occurrence of this error as it is in alignment with current best practices we would recommend. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no recommendations at this time.

Dispose of used bimekizumab-SS - 1mL in sharps container [C]	Failures: n=3	N/A	AX11: assumed no one had used the sharps in sessions so thought was for show [empty sharps]. PS09: Knows said to use special container. Probably would not. If provided one, would use a sharps container. PS15: Usually leaves used device on table. Would throw it in the sharps container next time.	Perception – AX11: saw the sharps bin but assumed it was for show as could not see devices from previous participants. Action – PS09 knew the correct place to dispose but would still probably dispose of in trash. PS15 knew to throw away in sharps but would usually not do so.	No further risk control measures proposed for the following reasons: -Needle guard prevents needle sticks after use. - The same problems are inherent with most self-administered drugs.	Based on the Applicant's URRA, the potential harm associated with this use risk is needle stick injury. The participants' subjective feedback attributed use error to assumptions that no one else used the sharps container, prior knowledge of utilizing the container and acknowledgement that they would use one the next time. We find that the prefilled syringe has a needle guard which would decrease the potential harm associated with the risk/error of infection from cross-contamination and a needle stick injury. In addition, our review of the labeling finds that the mitigation strategies currently in place to address this risk, include: textual and visual descriptions in the IFU instructing users how to dispose of the prefilled syringe and we did not identify additional risk mitigations to further reduce the occurrence of these errors. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

Table 3: Autoinjector Summary and Analyses of Study Results						
Tasks Evaluated (C for Critical and NC for Non-Critical)	Number of Use Errors and Description of Use Errors	Number and Description of Close Calls and Use Difficulties	Participant's Subjective Feedback on Use Errors, Close Calls, and Use Difficulties[3]	Applicant's Root Cause Analysis	Applicant's Discussion of Mitigation Strategies	DMEPA's Analysis and Recommendations

[3] AX: Patients with axial spondyloarthritis; PS: Patients with psoriatic arthritis; CG: Caregivers; H: Health Care Provider

Remove bimekizumab-AI-1mL carton from refrigerator [C] This was evaluated by a knowledge test by asking participants how many bimekizumab-AI-1mLs they would need to use if their prescription was 160 mg or 320 mg	Failures: n=4	N/A	AX03, AX15 and PA07 thought that 160 mg required two AIs, and 320 mg required four AIs. AX03 and AX15 did not think that one AI would be capable of holding 160 mg and that '2x' meant use two AIs to administer 160 mg. PA07 found the wording confusing. None of the participants attempted to use two AIs to complete their dose of 160 mg and confirmed after opening the pack and seeing the label they understood that each AI contained 160 mg. H15 answered that they would use two AIs. H15 thought the box contained one device that had changeable cartridges and that each cartridge had 2x160 mg inside.	The root cause of the errors was cognition and/or perception. The low occurrence of confusion about dosing was not unexpected due to the participants having no prior experience of the bimekizumab-AI-1mL. The AI labeling communicated the dosing correctly to participants and during the simulated use part of the study all participants correctly only used one AI to complete the 160mg dose. For the knowledge task, after reading the instructions for use (IFU) all users realized the mistake and understood each AI contained 160mg of bimekizumab	No mitigation required. No mitigation required as they understood once they opened the pack.	Based on the Applicant's URRA, the potential harm associated with this use risk is a single missed dose or under dose. Based on the subjective feedback, we note that some participants found the wording regarding the strength and net quantity confusing. We further note the mitigation strategies currently in place to address this risk include information on both the carton and in the IFU. However, we identified additional labeling recommendations that may further reduce the occurrence of these use errors and minimize the risk of confusion related to this task. Therefore, we provide carton labeling recommendation #3 in Table 4 below to address this concern.

Inspect AI Contents (through Viewing window) [C]	Failures: n=8	N/A	AX02: did not read the IFU because administering injections to themselves is 'something [they] have done so much of before' when asked, they stated they would have read the IFU if they were doing it for real. They did not know why they had not treated the session as if it was for real. AX15 thought that they did not need to check because it was an AI (as opposed to a syringe). Felt it was similar to instructions they had read in the past so glanced over step 1d in the IFU. Suggested making the frame around Figure B bolder to pop out. PS03 felt they missed the instruction to check the medication because they 'read on the faster side' but the information itself was clear.	Abnormal use – AX02 chose not to read the instructions because they thought it would be self-explanatory and despite knowing in real use they would read the instructions. Negative experience transfer – As an experienced user, AX15 did not read the instructions thoroughly. Perception – PS03 reads fast and missed the step. Perception – PS06 skipped the information in the IFU. Negative experience transfer – PSO9 assumed that they did not need to check. Negative experience transfer – PS10 would expect the	No further risk Control measures proposed for the following reasons: -Drug manufacture and PFS filling is performed under GMP and quality is carefully controlled. The likelihood Of contaminated drug is extremely low. -The same problems are inherent with most self-administered drugs. -Although some participants the syringe contents during the study, they would normally check if they were at home injecting their drug. All participants	Based on the Applicant's URRA, the potential harm associated with this use risk is an infection. The participant subjective feedback attributed use error to lack of prominence of the instructionor test artifact due to the simulated use test environment. The Applicant also stated negative transfer contributed to use errors with this task. The Applicant did not suggest any mitigation. Our review of the labeling finds the instruction is present in the IFU; however, our review of the Quick Start Guide (QSG) located on the carton determined that the task of checking the medicine for the coloration and particles is not present. Although the QSG includes a statement, "See enclosed full Instructions for Use booklet," which does include the task of checking the medication, the statement lacks prominence on the QSG. Thus, we provide QSG – Prefilled Syringe and Autoinjector recommendation #3 in Table 4 to address this concern.

			PS06 skimmed from step 1 to step 2 and missed the page in-between. PS09 Assumed with a device like the bimekizumab- AI-1mL that they wouldn't need to check the medication. Found the correct information in the IFU but suggested it could be made bold to stand out. PS10 did not feel that the instructions contributed to the use error, that they had missed the information due to concentrating more on how to administer the dose. They would trust the doctor to give them something safe to use. PS13 knew they were supposed to check as per the instructions. They suggested that they may have been rushing and felt the pressure due to the test environment. CG04 could find the	medication to be safe if given to them by a Doctor. Test artifact – PS13 was aware of the session being a simulated scenario. Action – CG04 did not follow the information during the session.	found and understood the information in the IFU. Container Closure Integrity Testing demonstrated that the device, the assembly process and the shipment are not impacting the integrity of the syringe content.	

			information in the IFU, but during the simulation they had concentrated on how to administer the dose. They felt that the instructions should come after figure B, as they noticed the graphic and then moved on to the information following.			

Check medicine for coloration and particles [C] This was evaluated by asking participants how they can tell if a drug product is safe to use	Failures: n=10	N/A	AX04 said that colorless suggested clear of particles. Suggested putting color in one sentence and free of particles in second sentence. AX14 became confused with yellow filling the viewing window. Suggested giving guidance pre- and post-administration and say what the actual steps are in the instructions for use. AX12 said they did not have an opinion about the color. AX15 said that had not noticed and suggested making eye symbol bigger to draw attention to the information. PA06, PA11, PA12, PA13, PS06 said that previous/own medication was clear.	A factor in the root cause of this error was a test artifact, as the human factors validation study used sorbitol filled syringes which were colorless. After reading the IFU in the post-test interview all users found the correct information on the color of the medicine.	No mitigation required as all participants found the correct answer in the post-test interview.	Based on the Applicant's URRA the potential harm associated with this use risk is an infection. The participant subjective feedback attributed use error to lack of clarity in the IFU, test artifact due to the simulated use test environment or negative transfer based on experience with other products. The Applicant did not suggest any mitigation. Our review of the labeling finds the instruction is present in the IFU; however, our review of the Quick Start Guide (QSG) located on the carton determined that the task of checking the medicine for the coloration and particles is not present. Although the QSG includes a statement, "See enclosed full Instructions for Use booklet," which does include the task of checking the medication, the statement lacks prominence on the QSG. Thus, we provide QSG – Prefilled Syringe and Autoinjector recommendation #3 in Table 4 to address this concern.

			PA13 suggested medication color text made bold. PS03 thought color transitioned from clear to yellow but now understood.			

Check medicine for coloration and particles [C] This was evaluated by asking participants how they can tell if a drug product is safe to use.	Failures: n=4	N/A	CG07 said that they had based their answer on the fact that it was not real medication. Information is clear in the instructions for use. CG09 said had read that should be free of particles and not cloudy so thought it should be clear. Said that in their experience medication is not colored. Suggested a label on instructions for use that drug is colored to draw attention to it. CG11 said had read not cloudy so thought it should be clear. Suggested an almost photographic image in the instructions for use for clarity. CG15 said that had not read in instructions for use initially and based on what they saw in	A factor in the root cause of this error was a test artifact, as the human factors validation study used sorbitol filled syringes which were colorless. After reading the IFU in the post-test interview all users found the correct information on the color of the medicine.	No mitigation required as all participants found the correct answer in the post-test interview.	Based on the Applicant's URRA, the potential harm associated with this use risk is an infection. The participant subjective feedback attributed the use errors to test artifact, mental model and lack of prominence in the IFU. The Applicant attributed the errors to test artifact since colorless sorbitol was used in the simulated use study and is not representative of the color of the intend to market product. The Applicant did not suggest any mitigation. We disagree and find that based on our review of the participant subjective feedback, additional mitigations should be implemented. Our review of the Quick Start Guide (QSG) located on the carton determined that the task of checking the medicine for the coloration and particles is not present. Although the QSG includes a statement, "See enclosed full Instructions for Use booklet," which does include the task of checking the medication, the statement lacks prominence on the QSG. Thus, we provide QSG – Prefilled Syringe and Autoinjector #3 in Table 4 to address this concern.

			the AI. Suggested writing medication information in bold			

Check medicine for coloration and particles [C] This was evaluated by asking participants to look at bimekizumab-AI-1mL and state whether they can see the liquid inside	Failures: n=3	N/A	H05 said clear because of what they saw in AI. Said that thought had not been paying enough attention when reading instructions for use and information was plain. H13 said that associates yellow with the drug not being good. Said information had not stood out and to highlight the information as would be concerned with drug the color it should be. H15 said that trusted what was in the package. Suggested bullet pointing information to check and to stand out more at the start.	A factor in the root cause of this error was a test artifact, as the human factors validation study used sorbitol filled syringes which were colorless. After reading the IFU in the post-test interview all users found the correct information on the color of the medicine.	No mitigation required as all participants found the correct answer in the post-test interview.	Based on the Applicant's URRA, the potential harm associated with this use risk is an infection. The subjective feedback indicates mental model of the correct color of "good" medicine and lack of prominence in the IFU. The Applicant states test artifact also contributed to the use error since colorless sorbitol was used in the simulated use study and is not representative of the color of the intend to market product. The Applicant did not suggest any mitigation. Our review of the labeling finds the instruction is present in the IFU; however, our review of the Quick Start Guide (QSG) located on the carton determined that the task of checking the medicine for the coloration and particles is not present. Although the QSG includes a statement, "See enclosed full Instructions for Use booklet," which does include the task of checking the medication, the statement lacks prominence on the QSG. Thus, we provide QSG – Prefilled Syringe and Autoinjector recommendation #3 in Table 4 to address this concern.

Push AI against injection site to start injection (start click Occurs) [C]	Failures: n=1	Close Calls: n=1	Failure: AX02 did not read the IFU before performing the injection. Recapped AI as though had to check the needle before use. Recapping caused the bimekizumab- AI-1mL to actuate and therefore, did not actuate at the site. Finds in IFU to not put the cap back on. AX02 repeatedly states how you know when the injection is underway, but not that it will click when the injection starts. Understands yellow bar will move through the viewing window. Successfully activates the AI at the site in their second attempt. Close Calls: States it doesn't seem like an injection pen anymore and instinctively started using it like current PFS and past AIs. Thinks the cap makes it seem like the	Cognition/Negative experience transfer – the cap design was unfamiliar to AX07; therefore, they did not recognize initially that it needed to be removed. This was coupled with a reduction of concentration as they progressed through the instructions. AX07 critical task	No further risk control measures proposed for the following reasons: -The cap is preventing access to the needle tip and to the actuation mechanism. -Resistance to Drop Test and to shipping simulation provides evidence to that resistance. - By design, once cap has been removed, the AI mitigates the risk of an inverted grasp because the device only has one hole, on the injection area. The risk of misinterpreting the bore from where the needle will protrude is reduced	Based on the Applicant's URRA, the potential harm associated with this use risk is a single missed dose, delayed dose, under dose, needle stick injury, laceration/pain. We acknowledge that the participants who failed, recapped the device (error), read the IFU and eventually self-corrected on their own and activated the injection. Based on our review, we agree negative transfer played a role in the failure and close call. Further, we consulted with CDRH who confirmed the activation force is 2- 10 N which is standard (not too high or low) for AI. Our review of the user interface finds there are mitigation strategies currently in place to address this risk, including: textual and visual descriptions instructing users how to activate the injection in the IFU, the design mitigation where the dose will not be delivered without removing the cap. We did not identify additional risk mitigations to further reduce the occurrence of these use issues. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no recommendations at this time

			opposite end of the injection end. Realized needed to remove the cap when they tried to push it against the skin.		compared to alternative designed AIs with two bores, one at each end. Also, the handle and tapering front end of the device provide visual cues on the correct orientation of the device. These design features make the handling and positioning of the device intuitive.	

Hold the AI Pressed on the Injection site until the second click (end click) occurs [E*] * The Applicant defined this task as "Necessary" but not critical; however, we consider this task to be critical because failure to hold the AI at the injection site until the second click may result in single missed dose, under dose, and irritation due to drug contact.	Failures: n=6	N/A	AX01 usually only holds for 5 seconds. Found in IFU to wait until see yellow in window and 15 seconds has gone. AX02 Due to previous task failures did not successfully perform task. In second injection performed successfully. AX15 States pushed it down and counted for 15 seconds. Knew the yellow goes all the way to the end of the window but did not check during injection. Reads IFU and finds the second click. States glanced over IFU and missed part about second click. PA07 Saw there was liquid after the injection. Looks in IFU to find if that is normal. Cannot find and thinks that information should be in the IFU that there	AX01 due to previous knowledge participant performed injection how they would have expected Cognition, AX02 did not read the IFU prior to starting task. Did not understand that recapping caused the device to actuate. Cognition, AX15 had not properly read the IFU so was not expecting a second click, they had read about waiting 15 seconds and that the yellow bar fills the window, but as they were not expecting a second click they did not wait for it. Cognition, PA07 did not understand the implication of liquid on pad due to removing too quickly. Perception, PA15 did not hear the second click. However, read IFU instruction to wait for the second click and said that if did	No further risk control measures proposed. All participants who experienced use problems acknowledged that the information was clear and easy to understand in the IFU	Based on the Applicant's URRA, the potential harm associated with this use risk is a single missed dose, under dose, and irritation due to drug contact. The Applicant did not consider this task to be critical and did not provide data for this task in the HF validation study report. Thus, we sent an information request (IR) to obtain this data. Additionally, we sent an IR to obtain data on the actual time participants held the AI at the injection site and the injection completion time (See Appendix E). Participant subjective feedback included usually only holds for 5 seconds (negative transfer), counted for 15 seconds and knowledgeable that they yellow should go to the end of the window but did not check, noticed liquid remaining after the injection, and read the IFU and heard both audible clicks but was unsure if the yellow appeared. It was stated that participants went back and read it and were then able to administer a successful dose. Based on the Applicant's IR response, we find that all participants who lifted the AI prior to the second click, held the AI at the injection site long enough for the injection to complete. Thus, these use errors would not have

			will be splash back. Believes gave full dose. Finds in IFU 'You will hear a second click after 15 seconds.' PA15 Reads IFU how to identify if the dose has been completed, reads verbatim correctly. Thinks put AI against skin, heard first click, and heard the second click but not sure if saw the yellow. Knows to remove from skin after you hear the second click. Did not hear the second click during the simulation just counted 15 seconds. States didn't remember if there was a second click after reading the IFU. Said maybe did not notice as it wasn't in bold. If it was in bold 'you'd notice it more.' CG14 Finds in IFU to hear a second click after 15 seconds after the first click.	again would wait for the second click and the yellow filling the window. Action, CG14 stated they were nervous, they read the instruction to wait for the second click, but they stated that their mind 'went blank' when they were performing the injection and it was not a fault of the IFU, as the IFU was very clear.		resulted in a wet injection/underdose. We note that PA07 experienced a wet injection with simulated injection. However, we find the mitigation strategies currently in place to address this risk, including: audio and haptic feedback, viewing window showing yellow plunger when complete, and textual and visual cues instructing users on the start and end of an injection and how to confirm a complete dose was delivered. However, we identified additional labeling recommendations that may further reduce the occurrence of these use errors and minimize the risk of confusion related to this task. Thus, we provide instructions for use recommendation #1 in Table 4 to address this concern.

			Performed successfully in second injection.			

Dispose of used AI in sharps [C]	Failures: n=6	Close Calls: n=1	Failure: AX13 states normally throws in trash. Had not checked the IFU how to dispose of the AI. Did not notice the sharps container on the table. Reads only the last page of the IFU and finds to check local guidelines for correct disposal method and would follow those. States at home would throw in trash. After the second Injection AX15 Correctly disposes of the used AI in a sharps container. Did not know where to throw and did not notice the sharps container on the table. Finds in IFU to dispose of the AI in a sharps container. States did not dispose of the AI as thought was going to do the second injection. Then realized 1 AI is 160mg and did not need to. Found correct disposal instruction in	Perception – AX13 did not see the sharps container at the time of disposal. Action – AX15 knew the correct place to dispose but would still probably dispose of in trash at home. Perception – PA06 did not initially see the sharps container at the time of disposal. Cognition – PS06 did not understand how much was in the AI and so was focused on the second injection rather than disposal. Perception – PS13 was rushing and not focused on disposal. Action – H15 is used to an assistant disposing of the AI and so did not	No further risk control measures proposed for the following reasons: - The AI, by design, is single use and the syringe is not accessible, so it cannot be re-used - Needle guard prevents needle sticks after use. - The same problems are inherent with most self-administered drugs. After reading Instructions users realized the mistake and did not made it twice.	Based on the Applicant's URRA, the potential harm associated with this use risk is an infection from cross-contamination and a needle stick injury. The participant subjective feedback included a participant following their typical pattern of disposing devices into the trash, participants inadvertently overlooking the sharps container on the table or due to normally having an HCP dispose of their usual devices. Some participants referred to the IFU and then disposed of the AI correctly. The Applicant did not provide mitigation strategies stating that the design of the AI includes a needle guard which prevents needle stick injury and no additional mitigation is needed. We find that the mitigation strategies currently in place to address this risk, including: textual and visual descriptions in the IFU instructing users how to dispose of the AI as well as the needle guard included in the device physical design and we did not identify additional risk mitigations to further reduce the occurrence of these use issues. Therefore, we find the Applicant's conclusion and residual risk acceptable. We have no further recommendations at this time.

			IFU. Was rushing and forgot the step. States was maybe feeling some pressure. Knew had not properly finished. Finds in IFU correct disposal instruction. States has a nurse who sets up the injection on the tray, H07 performs the injection then leaves the room with the patient to continue their appointment whilst the nurse throws everything away. Correctly states to dispose of AI in a sharps container. AX03 was about to put the bimekizumab- AI-1mL in the general waste then realized and puts in sharps. Close Call: AX03 saw the sharps bin at the start	perform task. Perception – AX03 did not initially see the sharps container at the time of disposal.		

			missed it during the session. Found correct instruction in knowledge task.			

3.3 ANALYSIS OF OTHER TASK ERRORS

The HF validation studies showed use errors (e.g. failures, difficulties, and close calls) with the following 1 critical task and 1 non-critical task; however our assessment of these user errors finds the residual risk is acceptable and thus are not the focus of this review. We reviewed the available participants' subjective feedback, the Applicant's root cause analysis and Applicant's proposed risk mitigation strategy to determine acceptability. In addition, we considered the use tasks of the proposed product with the use tasks in similar marketed products with the same user groups to determine if there are any current concerns of vulnerability to use error. Subsequently, our assessment of the aforementioned considerations in totality finds the residual risk is acceptable for the use tasks below; thus, we find no recommendations to further address the use errors or mitigations are necessary at this time to address the use errors related to the following use tasks:

- Failure to swab injection site
- Failure to remove cap

3.4 LABELS AND LABELING

Tables 3 and 4 below include the identified medication error issues with the submitted packaging, label and labeling, our rationale for concern, and the proposed recommendation to minimize the risk for medication error.

4. CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study identified failures, close calls, and use difficulties with critical tasks. In addition, our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. Below, we have provided recommendations in Table 3 for the Division and Table 4 for UCB, Inc. We ask that the Division convey Table 4 in its entirety to UCB, Inc so that recommendations are implemented prior to approval of this BLA. We find these revisions can be implemented without submission of additional HF validation testing data for the Agency's review in this instance.

4.1 RECOMMENDATIONS FOR UCB, INC

We found the results of your human factors (HF) validation study acceptable. However, based on our evaluation of the human factors validation study results and proposed packaging, label and labeling, we have identified areas of vulnerability that may lead to medication errors. We have provided recommendations in Table 4 and we recommend that you implement these recommendations prior to approval of this BLA. We find these revisions can be implemented without submission of additional HF validation testing data for the Agency's review.

Table 3: Identified Issues and Recommendations for Division of Dermatology and Dentistry (DDD)			
	Identified Issue	Rationale for Concern	Recommendation
Full Prescribing Information– Section 16 How Supplied/Storage and Handling			
1.	The first temperature numerical is missing the degree abbreviation (i.e., C and F).	Lack of clarity may result in confusion.	Revise the sentence to read “Store cartons with BIMZELX refrigerated between at 2°C to 8°C (36°F to 46°F)”

Table 4: Identified Issues and Recommendations for UCB, Inc (entire table to be conveyed to Applicant)			
	Identified Issue	Rationale for Concern	Recommendation
Instructions for Use (IFU) – Autoinjector			
1.	The human factors validation study identified use errors with the critical task of holding the autoinjector pressed on the injection site until the second click occurs. Our review of the IFU and participants' subjective feedback identified that the instruction "You will hear a second "click" in about 15 seconds after you hear the first click" lacks prominence.	Based on the use-related risk analysis (URRA), the potential harm associated with this error is a missed dose, underdose and irritation due to drug contact. This instruction may be overlooked.	Based on the use errors and participants' subjective feedback, we recommend you consider increasing the prominence of the statement, "You will hear a second "click" in about 15 seconds after you hear the first click" under Step 10 in the Autoinjector IFU by using color, boxing, or some other means.
Instructions for Use (IFU) – Prefilled Syringe and Autoinjector			
2.	The knowledge based testing identified use errors with the critical tasks of administering a	Based on the use-related risk analysis (URRA), the potential harm associated with this error is a missed dose or underdose.	Revise the statement (b) (4) to "A complete dose (320 mg) is 2 prefilled syringes (or autoinjectors). Use a new prefilled syringe (or autoinjector) and repeat Step 1 to Step 12."

	second prefilled syringe or autoinjector to deliver a complete dose. Our review of the IFU identified that the statement in the IFU "If you need to give a second injection for your prescribed dose…" appears misleading as the prescribing information states that the recommended dose is 320 mg, which requires administration of two 160 mg prefilled syringes or autoinjectors.		
Container Label(s) and Carton Labeling – Prefilled Syringe and Autoinjector			
1.	The format for expiration date is not defined.	Clearly define the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to

			represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or a space be used to separate the portions of the expiration date.
Carton Labeling – Prefilled Syringe and Autoinjector			
1.	The usual dose statement on the carton is currently presented as: (b) (4)	The usual dosage statement should meet 21 CFR 201.55 and maintain consistency with the Prescribing Information.	Revise the statement (b) (4) to read "Recommended Dosage: See prescribing information"
2.	The dosing statement is included on the side panel with the quick guide but not included on the Principal Display Panel.	As currently presented, the statement, "2 Autoinjectors" or "2 Prefilled Syringes," may be overlooked, leading to under dose errors.	Consider adding the statement "For a 320 mg dose, two 160 mg autoinjectors (or two 160 mg syringes) are required" to the Principal Display Panel (PDP) and use color, boxing, or some other means to ensure the statement is prominent.
3.	The knowledge based testing identified confusion pertaining to the strength if 160 mg was for both syringes (autoinjectors)	Based on the use-related risk analysis (URRA), the potential harm associated with this error is a missed dose, underdose, or an overdose.	Based on participants' subjective feedback, we recommend you revise the strength statement on the PDP and side panels from '160 mg/mL' to '160 mg/mL per syringe (or per autoinjector)'

	combined or individually.		
QSG – Prefilled Syringe and Autoinjector			
1.	The human factors validation study identified use errors with the critical task of holding the autoinjector pressed on the injection site until the second click occurs. Our review of autoinjector quick start guide (QSG) identified that the instruction "Injection is complete at 2nd click" lacks prominence.	Based on the use-related risk analysis (URRA), the potential harm associated with this error is a missed dose, underdose and irritation due to drug contact. This instruction may be overlooked.	Based on the use errors and participants' subjective feedback, we recommend you consider increasing the prominence of the statement, "Injection is complete at 2nd click" on the autoinjector QSG by using bolding, boxing, or some other means.
2.	The knowledge based testing identified use errors with the critical tasks of administering a second prefilled syringe or autoinjector, thereby delivering a complete dose. Our review of the carton	Based on the use-related risk analysis (URRA), the potential harm associated with this error is a missed dose or underdose. This instruction may be overlooked or omitted.	Increase the prominence of the statement ""For a 320 mg dose, two 160 mg autoinjectors (or syringes) are required" on the QSG

	labeling identified that the statement on the QSG “For a 320 mg dose, two 160 mg autoinjectors (or syringes) are required” lacks prominence		
3.	Our review of the Quick Start Guide (QSG) located on the carton determined that the critical task of checking the medicine for the coloration and particles is not present.	As currently presented, checking the medication for coloration and particles may be overlooked leading to risk of infection should the product be injected.	Based on the use errors and participant feedback, we recommend you add a statement to the QSG to inform patients to check the medication for coloration and particles prior to use. Ensure this statement aligns with the statement in the IFU. You may also consider the use of color, boxing, or some other means to increase the prominence of the statement: “See enclosed full instructions for use booklet” on the side panel of the Carton above the Quick Start Guide.
4.	The statement, “See enclosed full Instructions for Use booklet,” on the QSG lacks prominence.	As currently presented, statement, “See enclosed full Instructions for Use booklet,” on the QSG may be overlooked, leading to medication errors.	Consider using color, boxing, or some other means to increase the prominence of the statement: “See enclosed full instructions for use booklet” on the side panel of the Carton above the Quick Start Guide.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Bimzelx that UCB, Inc submitted on 7/15/2020

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	Engineered, humanized, full-length IgG1 mAb
Active Ingredient (Drug or Biologic)	bimekizumab-bkzx
Indication	Treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy
Route of Administration	Subcutaneous
Dosage Form	injection
Strength	160 mg/mL
Dose and Frequency	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.
How Supplied	• Carton of two 160 mg/mL single-use autoinjectors • Carton of two 160 mg/mL single-use prefilled syringes
Storage	Refrigerated between at 2°C to 8°C (36°F to 46°F)”
Intended Users	Adult patients with plaque psoriasis, Caregivers, HCP
Intended Use Environment	Home and Office

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On December 9, 2020, we searched the L:drive and AIMS using the terms, Bimekizumab to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified one previous reviews[4], and we confirmed that our previous recommendations were considered.

[4] Mena-Grillasca C. Label and Labeling Review for Bimekizumab IND 128707. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2018 JUN 19. RCM No.: 2018-671

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS-
N/A

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:
\\CDSESUB1\evsprod\bla761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5354-other-stud-rep\md-q-101725\md-q-101725.pdf

\\CDSESUB1\evsprod\bla761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5354-other-stud-rep\md-q-101724\md-q-101724.pdf

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On November 19, 2020 we issued an information request[5] (IR) to the applicant for further clarification regarding the timing surrounding the 2nd click, patient feedback during the 2nd click and the FMEA during this task. The response provided by applicant[6] on November 25, 2020 was acceptable.

On January 13, 2021 we issued an information request[7] (IR) to the applicant for further clarification regarding the results of the knowledge based tasks and the FMEA during these tasks. The response provided by the applicant[8] on January 21, 2021 was acceptable.

On February 8, 2021 we issued an information request[9] (IR) to the applicant for further clarification regarding the root cause analysis during the knowledge based tasks. The response provided by the applicant[10] on February 10, 2021 was not acceptable and therefore we issued

[5] https://darrts fda.gov//darrts/faces/ViewDocument?documentId=090140af805aee78&_afrRedirect=822215851353556

[6] \\CDSESUB1\evsprod\bla761151\0020\m1\us\111-information-amendment\response-1-19nov20.pdf and \\CDSESUB1\evsprod\bla761151\0020\m1\us\111-information-amendment\response-2-19nov20.pdf

[7] https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af805c5fb0&_afrRedirect=1446781522978331

[8] \\CDSESUB1\evsprod\bla761151\0028\m1\us\111-information-amendment\fda-response-1-13jan21.pdf

[9] https://darrts fda.gov/darrts/faces/ViewDocument?documentId=090140af805cffb2&_afrRedirect=11796031872990025

[10] \\CDSESUB1\evsprod\bla761151\0036\m1\us\111-information-amendment\response-1-05feb21.pdf

another information request[11] on February 16, 2021. The response provided by the applicant[12] on February 19, 2021 was acceptable.

[11] https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af805d288a&_afrRedirect=1795739714421314

[12] \\CDSESUB1\evsprod\bla761151\0040\m1\us\111-information-amendment\fda-response-1-16feb21.pdf

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[13] along with postmarket medication error data, we reviewed the following Bimzelx labels and labeling submitted by UCB Inc.

- Container label received on July 15, 2020
- Carton labeling received on July 15, 2020
- Professional Sample Container label received on July 15, 2020
- Professional Sample Carton Labeling received on July 15, 2020
- Instructions for Use (Image not shown) received on July 15, 2020:
  Prefilled syringe:
  \\CDSESUB1\evsprod\bla761151\0001\m1\us\114-labeling\draft\labeling\ifu_pfs_202008-sub.pdf
  Autoinjector:
  \\CDSESUB1\evsprod\bla761151\0001\m1\us\114-labeling\draft\labeling\ifu_ai_202008-sub.pdf
- Medication Guide received on July 15, 2020:
  \\CDSESUB1\evsprod\bla761151\0001\m1\us\114-labeling\draft\labeling\medguide-202008-sub.pdf
- Prescribing Information (Image not shown) received on July 15, 2020:
  \\CDSESUB1\evsprod\bla761151\0001\m1\us\114-labeling\draft\labeling\pi-202008-sub.pdf

6 Pages of Draft Labeling have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

[13] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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.

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CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA tracking number	C2020335
NDA#/Referenced IND for NDA	BLA 761151/ IND 128707
Applicant:	UCB, Inc.
Established Name/Trade Name:	BIMZELX/Bimekizumab (UCB4940) solution for subcutaneous injection
Indication:	Treatment of moderate to severe plaque psoriasis
PDUFA Goal Date:	July 15, 2021
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer	Kevin Clark
Clinical Team Leader (TL)	Gordana Diglisic
Regulatory Project Manager:	Strother D. Dixon
COA Reviewer:	Mira Patel
COA TL:	Selena Daniels
COA Deputy Director:	Elektra Papadopoulos
Instruments reviewed:	Patient Symptom Diary (PSD) ☒ Patient-reported outcome (PRO)

Table of Contents

1 EXECUTIVE SUMMARY

In this submission, the applicant is seeking approval of bimekizumab solution for subcutaneous injection for the treatment of adult patients with moderate to severe chronic plaque psoriasis[1] who are candidates for systemic therapy and/or phototherapy (b) (4)

The applicant proposes specific targeted clinical outcome assessment (COA)-related labeling claims from two phase 3 clinical trials (Studies PS0009 and PS0013):

- Study PS0009 is a multicenter, randomized, double-blind, placebo- and active comparator- controlled parallel-group study.
- Study PS0013 is a multicenter, randomized withdrawal, double-blind, placebo-controlled study.

To support these claims, the applicant submitted a patient-reported outcome (PRO) evidence dossier for the Patient Symptom Diary (PSD). A copy of the instrument can be found in Appendix A. The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the PRO-related labeling claims.

The ranked secondary efficacy PRO endpoints proposed for labeling (for Studies PS0009 and PS0013) are:

- Proportion of subjects achieving a clinically meaningful change in PSD Item 3 (skin pain) score (≥1.98 improvement) at Week 16.
- Proportion of subjects achieving a clinically meaningful change in PSD Item 1 (skin itching) score (≥2.39 improvement) at Week 16.
- Proportion of subjects achieving a clinically meaningful change in PSD Item 5 (skin scaling) score (≥2.86 improvement) at Week 16.

The data from Studies PS0009 and PS0013 did demonstrate that bimekizumab solution had statistically significant improvement in the selected secondary efficacy endpoints compared with placebo.

From a COA perspective, items 1, 3, and 5 of the PSD appear fit-for-purpose in this context of use.

2 REVIEW CONCLUSIONS

PSD Item 1 (skin itching), Item 3 (skin pain), and Item 5 (skin scaling) were reviewed for content validity and other measurement properties, as well as the applicant's proposed thresholds for meaningful within-patient score change for each item. These 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. It is unknown whether the patients observed clinically meaningful within-patient score changes in each of the items due to the following limitations of the external anchors:

[1] characterized by baseline Psoriasis Area Severity Index (PASI) ≥12, body surface area (BSA) affected by psoriasis ≥10%, and IGA score ≥3 [on a 5-point scale])

- The recall period of the Patient Global Assessment of Psoriasis was not consistent with the assessment time period of the prespecified endpoints. Additionally, there was substantial missing data at Week 16.
- The alternative external anchor, the Dermatology Life Quality Index item 1 was not an appropriate anchor as it is a multi-barreled item (i.e., assesses pain, itching, and stinging in one item) which is problematic for data interpretation.

The described deficiencies limit the utility for anchor-based analyses as it does not fully address the question of clinical meaningfulness of the target COA endpoint (i.e., the endpoint is measuring psoriasis-related pain, itching, and scaling). We do note that change from baseline in the 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 studies. Input from Clinical and Biostatistics was sought to determine whether the clinical trial data are supportive to include in the label. Biostatistics confirmed that the data from the Studies PS0009 and PS0013 demonstrate that bimekizumab solution has statistically significant improvement in the secondary efficacy endpoints for the three PSD items compared with placebo. In addition to achieving statistical significance, additional analyses evaluating the proportion of patients achieving a score of 0 in all three symptoms (skin pain, skin itching, skin scaling) showed that bimekizumab solution had greater improvements than the placebo arm. Based on this, DCOA and the Division are in agreement to include a descriptive labeling claim for all three PSD items.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, we recommend sponsors consider the following when selecting appropriate anchors scales for use in anchor-based methods:

- Selected anchor scales should be associated with the target COA endpoint in a way that addresses the question of clinical meaningfulness of the target COA endpoint.

- The anchor scale should be easier to interpret than the COA endpoint itself and meaningful to patients. The anchor scale's response categories should be distinct and non-overlapping and should represent meaningful differences among adjacent response categories.

- The anchor scale's recall period should be consistent with the assessment time period of the prespecified endpoint to the extent possible. Additionally, the selected anchors should be assessed at comparable time points as the target COA endpoint but completed by the respondent after the target COA in the order of assessments.

- The anchor scale should be plainly understood by respondents in the context of use; you should consider testing the draft anchor item(s) including their response categories in cognitive interviews.

Early engagement with FDA during drug development on COA is highly encouraged. Qualitative research can also provide useful data in interpreting clinically meaningful within-

patient change and can supplement quantitative methods, such as anchor-based analyses. We recommend that sponsors review the Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims[2] and FDA Discussion Document: Incorporating Clinical Outcome Assessments into Endpoints for Regulatory Decision-Making[3].

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:
The applicant was provided the following key COA-related comments under IND 128707:

- In Advice Letter dated April 18, 2017 (DARRTS Reference ID: 4085816), it was communicated to the applicant that content relevance was established for the PSD. The sponsor planned to evaluate the psychometric properties of the instrument during their phase 2 and 3 studies.
- In Advice Letter dated February 2, 2018 (DARRTS Reference ID: 4216363), the Division recommended that symptoms such as pain, itch, and scaling be assessed separately. Also, recommendation was given to consider subjects who have a baseline score in these items in order to observe a meaningful response (e.g., ≥4-point change from baseline) among those subjects who had ≥4-point NRS at baseline. Additionally, it was suggested that the applicant evaluate pruritus on an 11-point numerical rating scale (NRS) and that a reduction of 4 or more points on the NRS is generally considered clinically significant.

Previous COA Reviews:

- AT 2016-06_IND 128707_Kovacs dated August 3, 2016 (DARRTS Reference ID: 3956800)
- C2017036_IND 128707_Choudhry dated May 27, 2017 (DARRTS Reference ID: 4093773)
- C2017191_IND 128707_Choudhry dated September 15, 2017 (DARRTS Reference ID: 4143194)
- C2017379_IND 128707_ Choudhry dated January 11, 2018 (DARRTS Reference ID: 4204845)

Disease Background:
Psoriasis is a common, chronic inflammatory disease characterized by a series of linked cellular changes in the skin: hyperplasia of epidermal keratinocytes, vascular hyperplasia and ectasia, and infiltration of T lymphocytes, neutrophils, and other types of leukocytes in affected skin. Psoriasis-related symptoms include, but or not limited to, itch, pain, and scaling.

[2] https://www.fda.gov/media/77832/download
[3] https://www.fda.gov/media/132505/download

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

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies PS0009 and PS0013 are adults (18 years and older) with a diagnosis of moderate to severe plaque psoriasis (PASI ≥12 and BSA affected by PSO ≥10% and Investigator's Global Assessment [IGA] score ≥3) who were candidates for systemic psoriasis therapy and/or phototherapy.

A complete list of the inclusion and exclusion criteria is summarized in the clinical study reports for Studies PS0009 and PS0013.

Reviewer's comment(s): *The eligibility criteria for Studies PS0009 and PS0013 are the same, except that no previous exposure to ustekinumab was allowed in Study PS0009.*

5.2 Clinical Trial Design

The applicant conducted two phase 3 clinical trials:

- Study PS0009 is a multicenter, randomized, double-blind and placebo- and active controlled parallel-group study.
- Study PS0013 is a multicenter, randomized withdrawal, double-blind and placebo-controlled study.

Refer to the clinical study reports for more details on the clinical trial design.

Reviewer's comment(s):
For Study PS0009, during the 16-week initial treatment period, a total of 567 study participants were randomized in a 4:2:1 ratio to receive either bimekizumab 320mg Q4W (321 participants), ustekinumab (163 participants), or placebo (83 participants). After the 16-week initial treatment period, study participants entered the 36-week maintenance treatment period.

For Study PS0013, during the placebo-controlled initial treatment period, a total of 435 study participants were randomized in a 4:1 ratio to receive bimekizumab 320mg Q4W (349 participants) or placebo (86 study participants). At the Week 16 study visit, study participants who achieved a PASI90 response entered into a double-blind, placebo-controlled randomized-withdrawal period (randomized to bimekizumab 320mg Q4W were re-randomized 1:1:1 to bimekizumab 320mg Q4W, bimekizumab 320mg Q8W, or placebo [i.e., treatment withdrawal]) lasting 40 weeks. Study participants who did not achieve a PASI90 response at the Week 16 study visit were allocated to the escape arm (i.e., received open-label bimekizumab 320mg Q4W).

5.3 Endpoint Position, Definition, and Assessment Schedule

Table 1 describes the intended placement of the COAs in the endpoint hierarchy for Studies PS0009 and PS0013.

Table 1. Endpoint Position and Definition for Studies PS0009 and PS0013

Concept		Endpoints	Analysis time point	COA name (type of COA)
Co-primary				
Severity and extent of psoriasis (ie, redness, thickness, and scaling of lesions on body)	→	Achievement of 90% reduction from Baseline as evaluated by the PASI 90 at Week 16	Week 16	PASI (ClinRO)
Overall severity of psoriasis	→	*Clear* or *Almost Clear* with at least a two-category improvement relative to Baseline as evaluated by the IGA at Week 16	Week 16	IGA (ClinRO)
Secondary				
Severity and extent of psoriasis (ie, redness, thickness, and scaling of lesions on body)	→	Achievement of complete clearance (100% reduction) as evaluated by the PASI100 at Week 16	Week 16	PASI (ClinRO)
Overall severity of psoriasis	→	*Clear* with at least a two-category improvement relative to Baseline as evaluated by the IGA at Week 16	Week 16	IGA (ClinRO)
Severity and extent of psoriasis (ie, redness, thickness, and scaling of lesions on body)	→	Achievement of 75% reduction from Baseline as evaluated by the PASI75 at Week 4	Week 4	PASI (ClinRO)
Severity of skin pain	→	Response in skin pain as evaluated by clinically meaningful change in PSD skin pain item score (≥ 1.98 improvement) at Week 16	Week 16	PSD (PRO)
Severity of skin itching	→	Response in skin itching as evaluated by clinically meaningful change in PSD skin itching item score (≥ 2.39 improvement) at Week 16	Week 16	PSD (PRO)

Severity of skin scaling	→	Response in skin scaling as evaluated by clinically meaningful change in PSD skin scaling item score (≥ 2.86 improvement) at Week 16	Week 16	PSD (PRO)
Overall severity of psoriasis on the scalp	→	*Clear* or *Almost Clear* with at least a two-category improvement relative to Baseline as evaluated by the Scalp IGA at Week 16 for patients with scalp psoriasis at Baseline	Week 16	Scalp IGA (ClinRO)
Maintenance of clearance of psoriasis signs on the body	→	Achievement of 90% reduction from Baseline as evaluated by the PASI90 at Week 56 among Week 16 PASI90 responders[a]	Week 56	PASI (ClinRO)
		Maintenance of clearance of psoriasis signs on the body: PASI90 at Week 52[b]		
		Maintenance of clearance of psoriasis signs on the body: IGA at Week 52[b]		

Abbreviations: ClinRO= clinician-reported outcome; COA=clinical outcome assessment; IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; PSD=Patient Symptom Diary

[a] This is included in the sequence of testing for PS0013 only (ie, it is not included for PS0009)

[b] These endpoints are included in the sequence of testing for PS0009 only (ie, it is not included for PS0013)

The PSD was administered daily for 16 weeks in Studies PS0009 and PS0013. The administration schedule of all other COAs can be found in in the clinical study reports for Studies PS0009 and PS0013.

Reviewer's comment(s):

- *PSD data were captured electronically.*
- *Other COAs utilized in the clinical trials includes the following:*
  - *Psoriasis Area and Severity Index (PASI)*
  - *Investigator Global Assessment (IGA)*
  - *Scalp IGA (ClinRO)*
  - *Dermatology Life Quality Index (DLQI)*
  - *Patient Global Assessment of Psoriasis (PGAP)*
  - *Short Form-36 item (SF-36)*
  - *Patient Health Questionnaire-9 (PHQ-9)*
  - *Patient's Global Assessment of Disease Activity (PGADA)*
  - *Modified Nail Psoriasis Severity Index Score (mNAPSI)*
  - *EuroQoL 5-Dimensions-3-Levels (EQ-5D-3L)*
  - *palmoplantar Investigator's Global Assessment (pp-IGA)*
  - *Body Surface Area (BSA)*

For details on the exact COAs that were administered in each of the trials, refer to the associated study protocols.

5.4 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The sponsor has proposed the following specific targeted COA-related labeling claims (in blue text):

The applicant proposed a specific targeted PRO-related labeling claim for the PSD as follows:

Reviewer's comment(s): *While the PSD Item 1 (skin itching), Item 3 (skin pain), and Item 5 (skin scaling) appear fit-for-purpose for the context of use of this drug development program, there were concerns regarding the evaluation and interpretation of clinically meaningful within-patient thresholds for each item (see Section 5.5.6). However, based on additional analyses evaluating the proportion of patients achieving a score of 0 in all three symptoms (skin pain, skin itching, skin scaling) the treatment arm had greater improvements than the placebo arm, in addition, to achieving statistical significance. Based on this, the Division has recommended a descriptive claim for the three PSD items.*

5.5 Clinical Outcome Assessment(s)

5.5.1 Clinical Outcome Assessment Description(s)

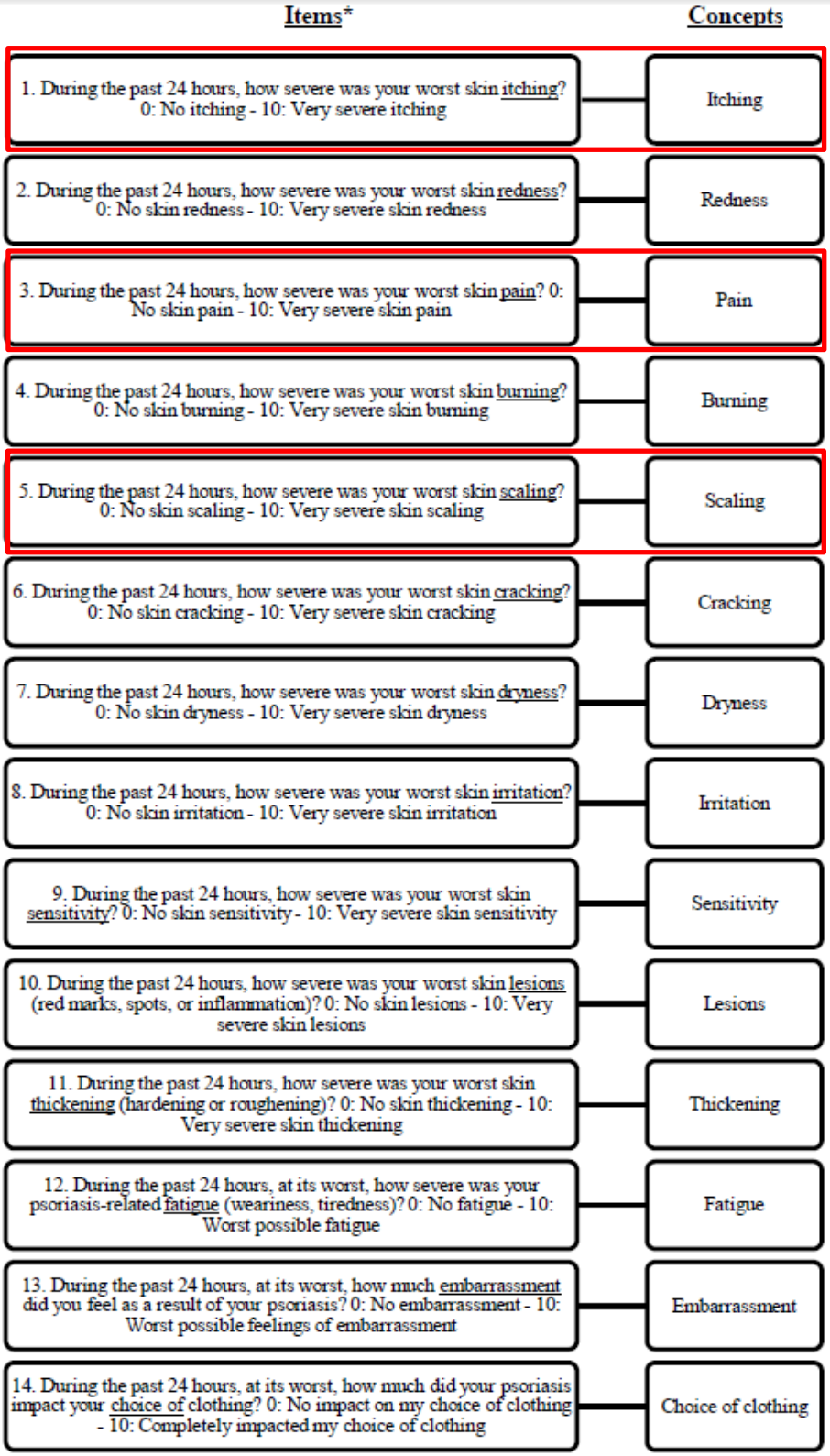
Patient Symptom Diary (PSD) Items 1, 3, and 5

PSD Item 1 (skin itching), Item 3 (skin pain), and Item 5 (skin scaling) are a part of a 14-item PRO instrument designed to assess plaque psoriasis-related symptoms and impacts. Each item is rated on an 11-point numeric rating scale (NRS), ranging from 0 ("No [symptom or sign or impact]" to 10 ("Very severe [symptom or sign]" or "Worst possible [impact]"). The recall period is the previous 24 hours.

5.5.2 Conceptual Framework(s)

The conceptual framework for the PSD is shown in Figure 1 (items highlighted in red are the applicant's proposed items for labeling claims).

Figure 1. Conceptual Framework for PSD



Reviewer's comment(s): *The PSD does not have domain-level concepts or an overall concept.*

5.5.3 Scoring Algorithm

PSD Items 1, 3, and 5

The PSD Item 1 (skin itching), Item 3 (skin pain), and Item 5 (skin scaling) generates individual item scores, which range from 0 to 10, where higher scores indicate greater symptom severity or worst possible impact. Per the NRS of each item, 0 indicates that no sign, symptom, or impact was present, and 10 indicates experience of a very severe sign or symptom or worst possible impact.

Reviewer's comment(s): *Weekly average scores were derived for each item of the PSD. A weekly average score is the sum of the scored item over the course of the study week (up to the actual visit date) divided by the number of days the item was completed.*

Since the PSD was administered on an electronic device and the patient had to select a response before advancing to the following item (i.e., patients could not skip items), no item-level missing data occurred during the clinical trials. However, form-level missing data was possible where daily PSD item scores were not collected by study participants. If missing data at the form-level occurred, then data scoring were handled as described below:

- *If a study participant had missing valid responses for ≥ 4 days in any week (irrespective of whether they were consecutive or not), the average weekly score for that item was set to missing.*

If a study participant had missing valid responses for < 4 days in any week, the weekly score for that item was the arithmetic average of available daily scores.

5.5.4 Content Validity

The applicant completed the following instrument development activities to evaluate the content validity of the PSD, which included Items 1, 3, and 5:

- Literature review,
- Expert input (clinician interviews), and
- Patient input (concept elicitation and cognitive interviews).

A summary of the findings from the qualitative research is shown below. For more details on the methodology and results of these activities, see the PRO Dossier.

Literature review:

- A total of 24 articles were reviewed regarding concepts related to plaque psoriasis. The conceptual review findings indicated that plaque psoriasis is commonly characterized by:
    - Itching (pruritus),
    - Erythema (redness, irritation),
    - Flaking (shedding, scaling, shedding),
    - Burning/stinging,
    - Lesions,
    - Pain (due to psoriasis or cracking)

- Other symptom/sign-related concepts were thickening of the skin, bleeding, cracking (tearing), soreness (tenderness), and dry skin. The most commonly identified impact-related concepts were interferences with relationships, sexual difficulty, and depression.

- A total of 56 articles were reviewed, which identified 48 PRO instruments that measure signs, symptoms, or impacts in plaque psoriasis populations. No instruments that evaluated psoriasis signs and symptoms and that were used to support approval and label claims for psoriasis products were available for public use.

- The applicant concluded that a novel PRO instrument needed to be developed to evaluate patients' experiences of signs, symptoms, and impacts of plaque psoriasis in the context of use for this drug development program.

Expert input:

- Five clinicians described plaque psoriasis as a visible chronic skin condition caused by a dysfunction in the immune system that is commonly characterized by:
    - Redness
    - Scaling
    - Itching
    - Flaking
    - Bleeding
    - Pain

- As for the impacts of psoriasis, clinicians most commonly endorsed depression, interference with relationships, and appearance.

Patient input:

- The total sample for the concept elicitation interviews consisted of 15 subjects with plaque psoriasis.
    - The signs and symptoms of psoriasis that were most commonly (spontaneously) reported by the participants were itching (100%), redness (100%), dryness (86.7%), and flaking (80%).
    - Pain and scaling were spontaneously reported by 40% of the participants.
    - The most bothersome symptoms and signs were itching (100%), redness (86%), dryness (80%) and flaking (80%).
    - Bothersome of pain was reported by 53.3% and scaling was reported by 66.7%.
    - The symptoms that were the most frequently rated for severity at its worst (on an NRS scale of 0-10) included skin itching (80.0%; mean [SD]=8.3 [3.8]), skin flaking (60.0%; mean [SD]=7.8 [4.2]), and skin redness (60.0%; 5.9 [3.4]).
    - Pain severity at its worst was reported by 46% (mean [SD]=7.3 [4.1]) and scaling severity by 33% (mean [SD]=6.6 [3.5]) of the participants.
    - The most frequently reported impacts of psoriasis were an impact on clothing choice (100%), skin damage due to scratching or picking at the skin (100%), an emotional impact of feeling self-conscious due to the psoriasis (93.3%), an impact on appearance (86.7%), and an impact on sleep (80%).

  - Clothing choice (93.3%), appearance, skin damage and unwanted attention (60% for each impact) were most bothersome to participants.

- The total sample for the cognitive interviews consisted of 15 subjects with plaque psoriasis. For the items of itching, pain and scaling, patient input is as follows:
  - Item 1 (skin itching) and response option was interpreted as intended by 100% of the participants. With regard to the recall period, 4 subjects (26%) had difficulty adhering to the 24-hour recall period and used a different recall period instead.
  - Item 3 (skin pain) was interpreted as intended by 90% of the participants. Two subjects misinterpreted the item and response options (one subject attributed pain to arthritis and "when your bone hurts"; another subject reported that pain and burning were the same concept).
  - Item 5 (skin scaling) was interpreted as intended by 60% of the participants. Four subjects reported that scaling and flaking were the same concept; one subject reported that "it's not a time question" and the recall period of 24 hours did not apply; one subject attributed scaling to "scratching".

  Reviewer's comment(s): *For additional details on patient input for the other PSD items, refer to the PRO evidence Dossier (Appendix D3).*

  - For usability testing results of the PSD, on a scale of 1 (poor) to 5 (excellent), the majority of subjects rated the device as "excellent" for finger sensitivity, stylus sensitivity, and overall appearance (n=10, 66.7%; n=13, 86.7%; n=11, 73.3% respectively). On a similar scale of 1 (difficult) to 5 (easy), the majority of subjects rated selecting an answer, advancing to the next screen, readability of font size, and overall ease of use as "easy".
  - For the translation process of the PSD, the instrument was translated (or culturally adapted) in several languages (see PRO evidence Dossier (Appendix F) for list of languages) through the translation process identified in the Principles of Good Translation and Cultural Adaptation Practice as recommended by the International Society for Pharmacoeconomics and Outcomes Research (Wild et al, 2005).

Reviewer's comment(s): *Based on the applicant's qualitative evidence, it appears that the concepts of skin itching, skin pain, and skin scaling were clinically important and relevant concepts in this patient population. Overall, this reviewer does not have any critical concerns regarding the content validity of the PSD Item 1 (skin itching), Item 3 (skin pain), and Item 5 (skin scaling).*

5.5.5 Other Measurement Properties

The applicant evaluated the psychometric properties of the PSD using data from the phase 2b trial (Study PS00100[4,5]) and pooled data from the two phase 3 trials (Studies PS0009 and PS0013).

A summary of the findings is provided for each study, specifically for the PSD Item 1 (skin itching), Item 3 (skin pain), and Item 5 (skin scaling). For more details on the methodology and results of these analyses, refer to the PRO evidence Dossier (Appendix E1).

Study PS0010
A total of 180 subjects in Study PS0010 were included in the analysis population.

The results are summarized as follows:

- The mean (SD) PSD item scores at baseline were 4.6 (2.9) for itching, 3.4 (2.9) for pain, and 5.2 (2.7) for scaling. At Week 12, the mean (SD) scores were 2.0 (2.6) for itching, 1.3 (2.3) for pain, and 1.8 (2.6) for scaling.

- No floor effects (using a cutoff of >25%) were demonstrated for each of three items at baseline.

- For assessment of test-retest reliability, the intra-class coefficients (ICC) for participants who had the same score on the PGIS overall psoriasis item (i.e., no change in disease severity) at Weeks 2 and 4 (n=91) were 0.924 for itching, 0.925 for pain, and 0.916 for scaling. At Weeks 11 and 12 (n=103), the ICCs were 0.992 for itching, 0.987 for pain, and 0.991 for scaling.

- For assessment of convergent validity, moderate correlations (0.41-0.75) were observed between each of the three PSD items and assessments measuring similar concepts related to psoriasis symptoms (SF-36 pain domain, DLQI total, PGIS items) at baseline.

- For assessment of divergent validity, low correlations (0.10-0.42) were observed at between each of the three PSD items and assessments measuring more distal concepts of clinical signs and symptoms of psoriasis (other SF-36 domain scores[6]) at baseline.

[4] Study PS0010 is a phase 2b, multicenter, randomized, double-blind, placebo-controlled, parallel-group, dose-ranging study to evaluate the safety, efficacy, pharmacokinetic, and pharmacodynamic of bimekizumab in adult subjects with psoriasis.
[5] 19 PSD items were initially evaluated to finalize the PSD (item reduction, evaluation of reliability, validity and sensitivity to change) for inclusion in the phase 3 clinical trials.
[6] Physical functioning; role limitation physical; general health; emotional well-being, role limitation emotional; social functioning; energy/fatigue; mental health; physical health

- For the assessment of known-groups validity, the PSD items 1, 3, and 5 scores increased with the severity levels assessed by the PGIS symptom items[7], IGA[8], PASI[9], and DLQI[10].

- For the assessment of responsiveness, medium to large effect sizes were observed in the defined improvement groups based on the PASI, IGA, DLQI total score, and PGIC from baseline to Week 12.

Reviewer's comment(s):

- *In general, the results for test-retest reliability and convergent and divergent validity is within acceptable and within reasonable range.*
- *Since the PSD does not aggregate a total score, evaluating internal consistency was not warranted.*
- *This reviewer does not agree that the defined known groups from the PGIS, IGA, DLQI and PASI are appropriate for the assessment of known groups validity as there is limited data to support the numerical cutoffs. Further, this reviewer does not agree with the use of a tertile approach to assess known groups validity for the PASI and DLQI. The tertile approach does not clearly define groups with known meaningful difference. There is caution in the interpretation of results from this approach, as you are more likely to find significant score differences among the groups, which is misleading.*
- *This reviewer does not agree with the approach used to evaluate responsiveness. Generally, responsiveness should be assessed by evaluating the distribution of change on the target instrument by change on each anchor by providing descriptive statistics for improvement in the target instrument for each level of categorical improvement in the anchors.*

<u>Studies PS0009 and PS0013</u>
A total of 1,002 subjects in Study PS0009 (n=567) and PS0013 (n=435) were included in the analysis population.

The results are summarized as follows:

- The treatment arm (bimekizumab 320mg) experienced more change[11] (from Baseline to Week 16) in the PSD itching, pain, and scaling items (-5.18, -4.85, and -5.78, respectively [note items are on a 0-10 scale]) compared to the placebo arm (less than 1-point mean improvement for each item) in Study PS0009. Similar changes were seen in Study PS0013.

- No floor effects (using a cutoff of >25%) were demonstrated for each of three items at baseline.

[7] Grouped as PGIS= 1 and 2 (mild), 3 (moderate), 4 and 5 (severe)
[8] Grouped as IGA= 0, 1, and 2 (mild), 3 (moderate), 4 (severe)
[9] Grouped as PASI tertile split
[10] Grouped as DLQI tertile split
[11] Multiple imputation (using Markov Chain Monte Carlo/monotone regression) was used to calculate the change for each item.

- For item-item correlations, the correlation at baseline between itching and pain was 0.83, itching and scaling was 0.84, and pain and scaling was 0.76.

- For assessment of test-retest reliability, the intra-class coefficients (ICCs) for participants who had the same IGA score at baseline and Week 2 (n=279) were 0.94 for itching, 0.95 for pain, and 0.91 for scaling.

- For assessment of convergent validity, moderate correlations (0.50-0.67) were observed at baseline between each of the three PSD items and the PRO instruments (PGAP[12], DLQI item 1[13], DLQI total). Low correlations (0.12-0.15) were observed between the three PSD items and the ClinRO instruments (IGA and PASI). At Week 16, the correlations for the three PSD items with the PGAP, PASI, IGA, and DLQI scores all increased to moderate to strong correlations (0.59-0.90).

- For assessment of known-groups validity, for the itching, pain, and scaling items, the mean PSD item scores increased in line with increasing severity groups (PGAP[14], PASI[15], IGA[16], and DLQI[17] score groups) according to the PGAP, PASI (percent and total score), IGA, and DLQI (total and item 1 score).

- For the assessment for responsiveness, the correlation coefficients indicate a moderate to strong relationship (0.53-0.75) between changes in the three PSD items and changes in the selected measures (i.e., PASI, DLQI total score, DLQI Item 1 score, and IGA) over the same time interval (i.e., Baseline to Week 16).

Reviewer's comment(s):

- *In general, the results for test-retest reliability and convergent and divergent validity are within acceptable and within reasonable range. The patterns among the correlations between the three PSD items and the ClinRO instruments (PASI and IGA) were lower than 0.40. However, this is not unexpected from a clinical standpoint as there is no evidence to support the relationship between plaque psoriasis severity and individual symptom severity.*

- *Since the PSD does not aggregate a total score, evaluating internal consistency was not warranted.*

- *The applicant utilized tertile groups for the PASI, which is not recommended for evaluating known-groups validity. It was unclear how the Applicated determined the cutoffs for the DLQI total score. The IGA only had subjects in the "moderate" and*

[12] PGAP asks "How severe are your psoriasis-related symptoms right now?" A copy of the scale is in Appendix D.
[13] DLQI item 1 asks "Over the last week, how itchy, sore painful, or stinging has your skin been?" A copy of the DLQI can be found in Appendix E.
[14] Grouped as PGAP score = no or mild symptoms; moderate symptoms; severe symptoms; very severe symptoms
[15] Grouped as PASI score (<33.3%; ≥33.3 - <66.7%; ≥66.7% and ≤1; >1-≤3; >3 -≤5; >5-<12; ≥12)
[16] Grouped as IGA score = clear; almost clear; mild; moderate; severe
[17] Grouped as DLQI score (total score=0-1; 2-5; 6-10; 11-20; 21-30 and item 1 score=not at all; a little; a lot; very much)

"severe" categories at Baseline. An information request was sent to the applicant to obtain rationale for the known-groups validity's group cutoffs, as well as, graphical displays. The applicant stated the following:

- *The applicant indicated that they are not providing evidence for the DLQI cutoffs since clinical anchors indicative of plaque psoriasis severity are more relevant.*
- *For IGA, criteria used to define subgroups of patients with clinically different psoriasis severity levels are the response options of the 5-point IGA scale (clear, almost clear, mild, moderate, severe), which has been shown to be a valid and reliable measure of psoriasis severity.*
- *Absolute PASI cut-off values considered to define subgroups (1, 3, and 5) were in line with the thresholds that were used for responder analyses to assess treatment effect in the Phase 3 PS0009 and PS0013 trials. These cut-offs have been shown to provide more reliable estimates of disease activity that could be used to define treatment goals for psoriasis treatment and facilitate clinical decisions (Gordon et al, 2020). The robustness of these cutoffs has been evaluated recently in a network method analysis (Mrowietz et al, 2021). The absolute PASI cut-off value of 12 was in line with specification for moderate to severe psoriasis from the protocol inclusion criteria.*

Using the applicant's proposed groups for each reference measure, for each of the PSD items, the mean item scores increased with the severity groups for each reference measure.

In general, this reviewer concludes that the evidence generated from the psychometric evaluation of the PSD Item 1, Item3, and Item 5 across all three studies supports the reliability and validity of the instrument.

5.5.6 Interpretation of Meaningful Within-Patient Score Changes

The applicant specified the following meaningful within-patient change thresholds for the three PSD items:

- Item 1 (skin itching): 2.38
- Item 3 (skin pain): 1.98
- Item 5 (skin scaling): 2.86

The applicant performed the following analyses in an effort to support the proposed thresholds for meaningful within-patient change:

- Anchor-based analyses
  - Distribution of change on the Skin Pain NRS by change on PGI-S-AD
  - Anchor-based empirical cumulative distribution function and probability density function curves
- Distribution-based analyses

Reviewer's comment(s): *The applicant averaged results from the anchor-based and distribution-based analyses using phase 2b data from Study PS0010 to generate the specified thresholds (Table 2).*

Table 2. Summary of PSD Responder Definition Estimates for Study PS0010

	Anchor-based			Distribution-based		
PSD Item	Change from Week 0 to 12 (PGIC)[a]	Change from Week 0 to 12 (IGA)[b]	Change from Week 0 to 12 (PGIS)[c]	Change from Week 0 to 12 (0.5 SD)	Change from Week 0 to 12 (1 SEM)	PSD Responder Definition Estimate[d]
Itching	-2.58	-2.71	-2.89	1.41	2.38	2.39
Pain	-1.68	2.35	-2.21	1.41	2.24	1.98
Scaling	-3.09	-3.66	-3.84	1.32	2.38	2.86

[a] Estimate for "Much Improved" subgroup (n=25); [b] Average estimate for IGA change -1 and -2 subgroups (n=64); [c] Average estimate for PGIS change -1 and -2 subgroups (n=80); [d] Average estimate for all change values

To confirm the thresholds, the applicant included the PGAP in the phase 3 trials as an external anchor to assist in the interpretation of the target PSD items. The PGAP is a single-item question asking the patient how they would rate their psoriasis-related symptoms right now on 5-point verbal rating scale ranging from "no symptoms" to "very severe symptoms." However, the PGAP had a large amount of missing data at Week 16 and could not be used to confirm the thresholds for change from baseline to Week 16. As such, the applicant utilized data from Week 12, as well as, utilized the DLQI item 1[13] as an alternative external anchor.

A summary of results is provided below:

- The mean changes in PSD itching item by a 1-point and 2-point improvement level for DLQI item 1 were 3.66 and 6.70, respectively, and for the PGAP were 2.96 and 5.87, respectively.
- The mean changes in PSD pain item by a 1-point improvement level and 2-point improvement level for DLQI item 1 were 3.34 and 6.29, respectively, and for the PGAP were 2.87 and 5.51, respectively.
- The mean changes (95% confidence interval) in PSD scaling item and 2-point improvement level for DLQI item 1 were 4.39 and 6.90, respectively, and for the PGAP were 3.56 and 6.41, respectively.

For more details regarding the results from the anchor-based analyses, refer to the PRO evidence Dossier (Appendix E2).

Also, in Study PS0009, 33% (75/225) of subjects randomized to bimekizumab had PSD score of 0 in all three symptoms (pain, itch and scaling) compared to 0% of subjects in the placebo arm (nominal value<0.001). Similarly, in Study PS0013, 33% (95/286) of subjects randomized to bimekizumab had PSD score of 0 in all three symptoms compared to 0% of subjects in the placebo arm.

Reviewer's comment(s): *In Study PS0010, the applicant utilized patient global anchors (overall psoriasis symptom PGIS and PGIC) to conduct anchor-based analyses; however, these external anchors did not specify the psoriasis symptoms specific to the target PSD items.*

For Studies PS0009 and PS0013, the applicant only had one patient global anchor administered in both studies, the PGAP; however, there was substantial missing data for the item at Week 16, therefore the applicant used Week 12 PGAP and PSD scores for anchor-based analyses. This reviewer notes that the use of Week 12 data for evaluating clinically meaningful-within patient threshold can underreport treatment benefit and therefore it is not appropriate to use change from baseline to Week 12 to conduct anchor-based analyses.

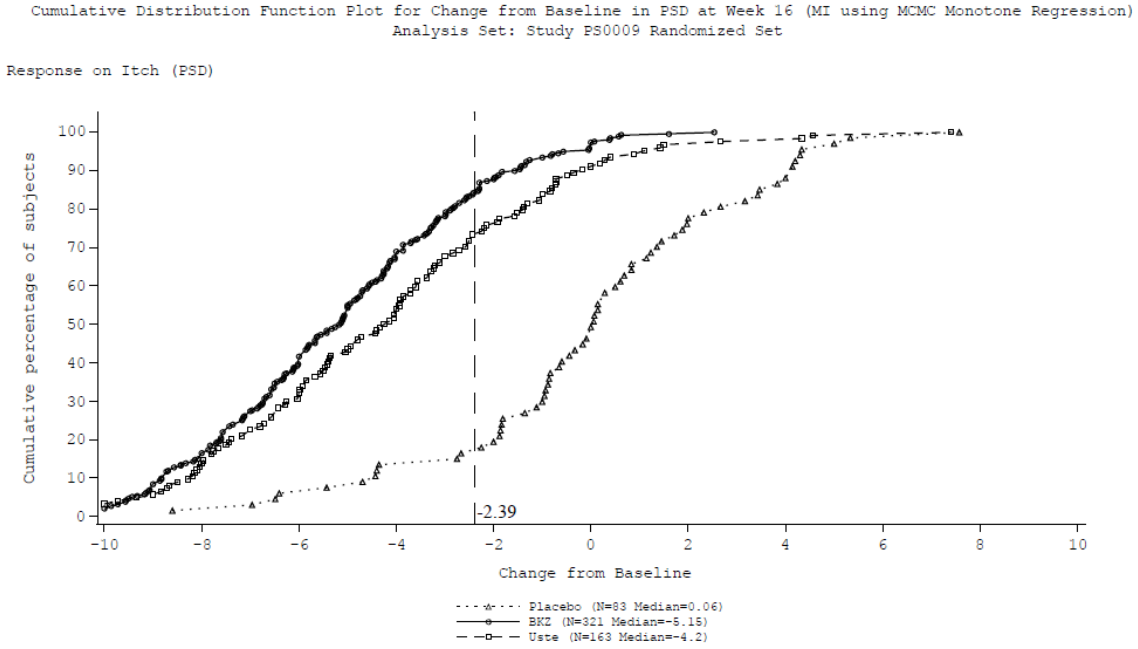
Alternatively, the applicant suggested the DLQI item 1 as an anchor; however, this reviewer notes that the scale is not considered to be an adequate global anchor to derive a clinically meaningful-within patient score change as it measures multiple symptoms in one item (i.e., itch, pain, and stinging).

The applicant concluded that, overall, the thresholds of -3.66, -3.34, and -4.39 points for the itching, pain, and scaling items, respectively, obtained with the DLQI item 1 anchor and the range of thresholds obtained from other relevant anchors were consistent with the four-point FDA-recommended threshold and with US label text of other compounds approved in the same indication. However, the endpoint evaluation of the three items in the two phase 3 studies used thresholds 1.98, 2.39, 2.86 for pain, itching, and scaling, respectively.

This reviewer concludes that thresholds of clinically meaningful within-patient change in the PSD itching, pain and scaling items could not be determined with the applicant's anchor-based analyses.

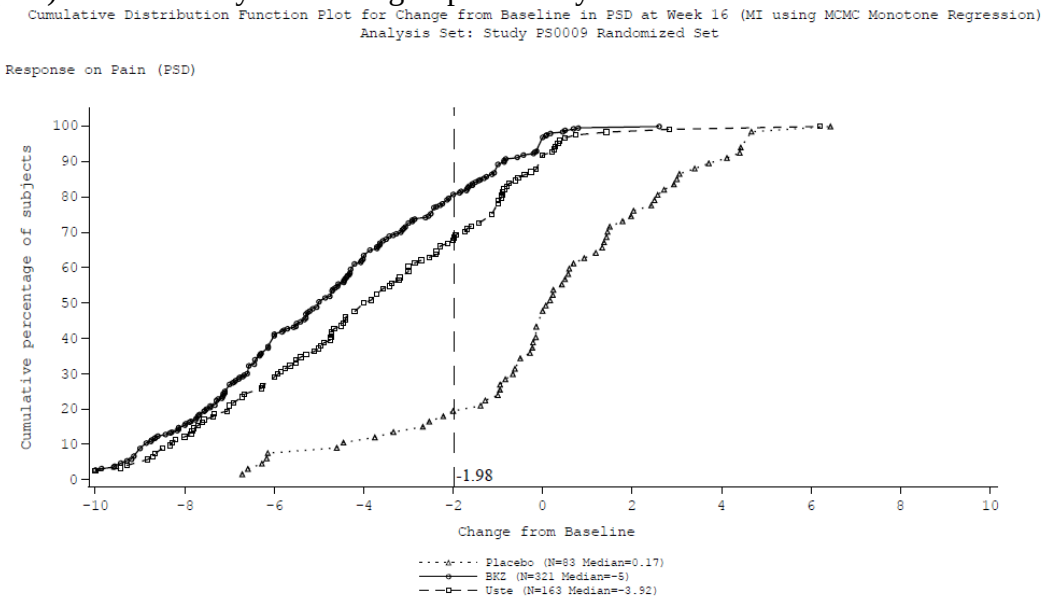
Figures 2 to 7 presents the PSD Item 1, Item 3, and Item 5 change scores from baseline to Week 16 by treatment arms for Studies PS0009 and PS0013.

Figure 2. Cumulative distribution function plot of change from baseline in PSD Item 1 (skin itching) at Week 16 by treatment group for Study PS0009



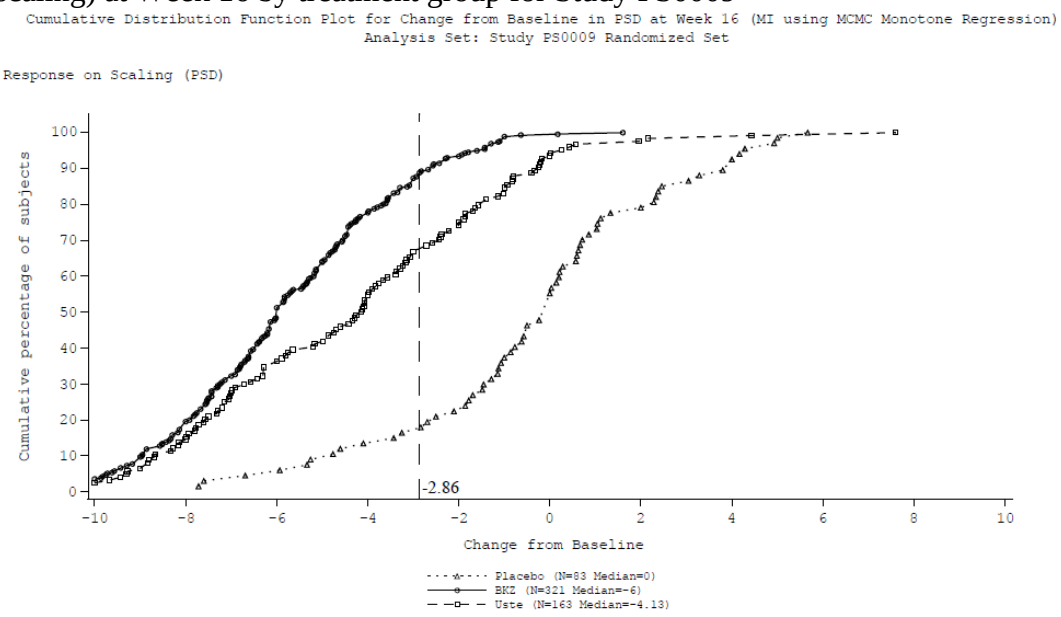
BKZ=bimekizumab, MCMC=Markov Chain Monte Carlo, MI=multiple imputation, PSD=patient symptom diary, Uste=ustekinumab.

Figure 3. Cumulative distribution function plot of change from baseline in PSD Item 3 (skin pain) at Week 16 by treatment group for Study PS0009



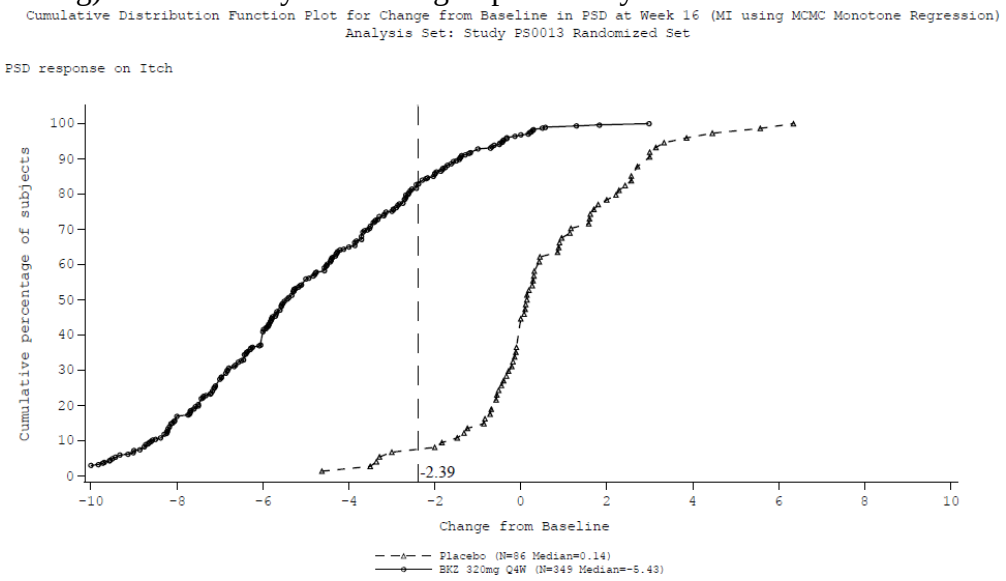
BKZ=bimekizumab, MCMC=Markov Chain Monte Carlo, MI=multiple imputation, PSD=patient symptom diary, Uste=ustekinumab.

Figure 4. Cumulative distribution function plot of change from baseline in PSD Item 5 (skin scaling) at Week 16 by treatment group for Study PS0009



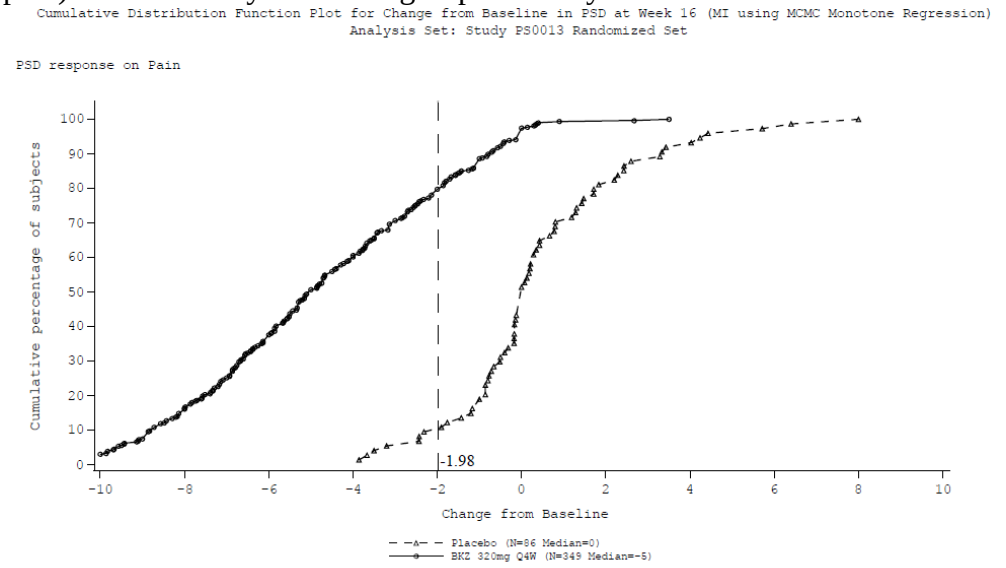
BKZ=bimekizumab, MCMC=Markov Chain Monte Carlo, MI=multiple imputation, PSD=patient symptom diary, Uste=ustekinumab.

Figure 5. Cumulative distribution function plot of change from baseline in PSD Item 1 (skin itching) at Week 16 by treatment group for Study PS0013



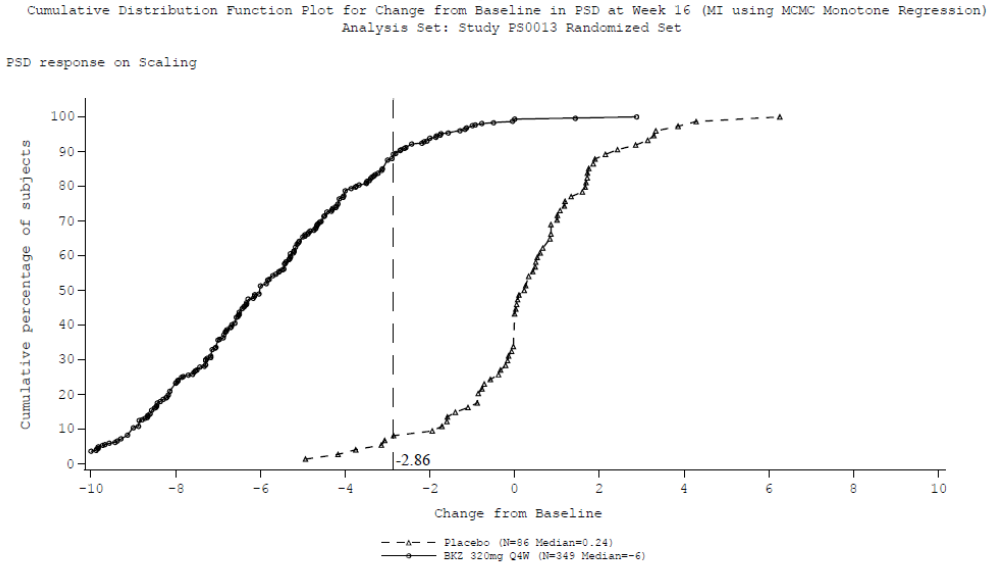
BKZ=bimekizumab, MCMC=Markov Chain Monte Carlo, MI=multiple imputation, PSD=patient symptom diary, Q4W=every four weeks.

Figure 6. Cumulative distribution function plot of change from baseline in PSD Item 3 (skin pain) at Week 16 by treatment group for Study PS0013



BKZ=bimekizumab, MCMC=Markov Chain Monte Carlo, MI=multiple imputation, PSD=patient symptom diary, Q4W=every four weeks.

Figure 7. Cumulative distribution function plot of change from baseline in PSD Item 5 (skin scaling) at Week 16 by treatment group for Study PS0013



BKZ=bimekizumab, MCMC=Markov Chain Monte Carlo, MI=multiple imputation, PSD=patient symptom diary, Q4W=every four weeks.

Reviewer's comment(s): *The change from baseline in the target PSD item scores showed a pronounced separation between the treatment and placebo arm across a range that likely includes a clinically meaningful change threshold, although there is inadequate evidence to define a specific threshold.*

6. APPENDICES

Appendix A: Patient Symptom Diary (PSD), including screenshots for PSD itching, pain, and scaling items

Appendix B: Patient Global Impression of Severity Items (Study PS0010 only)

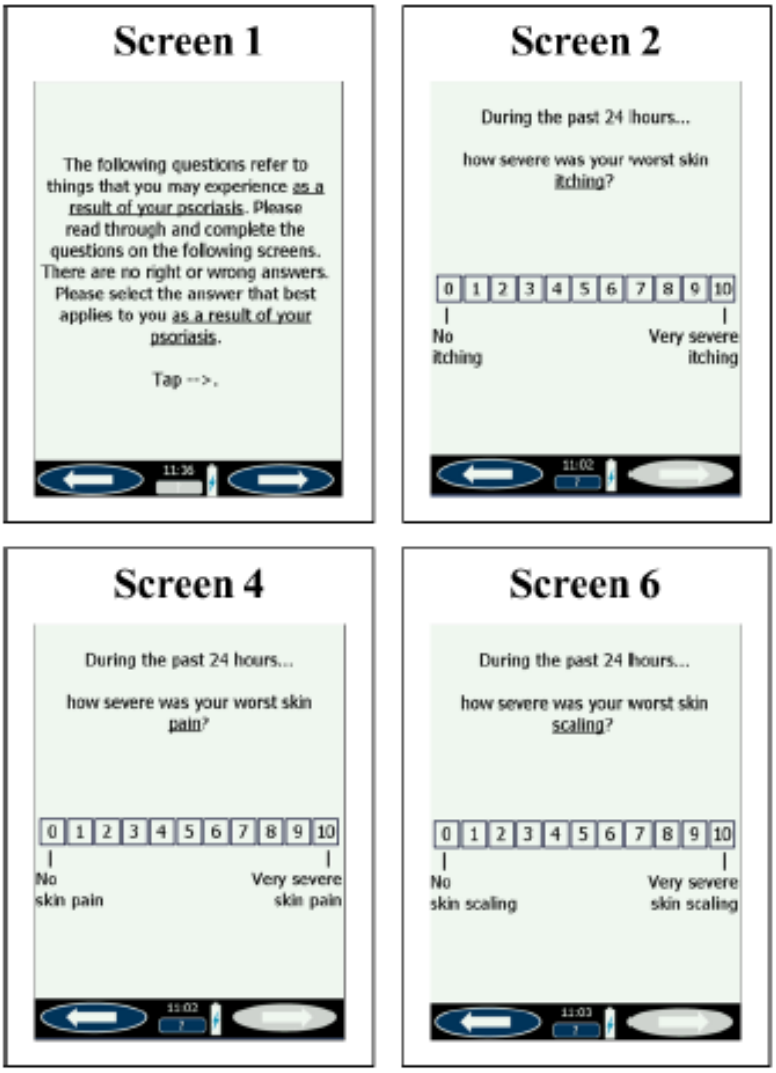
Appendix C: Patient Global Impression of Change Items (Study PS0010 only)

Appendix D: Patient Global Assessment of Psoriasis (PGAP; Studies PS0009 and PS0013)

Appendix E: Dermatology Life Quality Index (DLQI)

Appendix A: Patient Symptom Diary (PSD), including screenshots for PSD itching, pain, and scaling items

Item	Response Scale
1. During the past 24 hours, how severe was your worst skin itching?	0 (No itching) – 10 (Very severe itching)
2. During the past 24 hours, how severe was your worst skin redness?	0 (No skin redness) – 10 (Very severe skin redness)
3. During the past 24 hours, how severe was your worst skin pain?	0 (No skin pain) – 10 (Very skin pain)
4. During the past 24 hours, how severe was your worst skin burning?	0 (No skin burning) – 10 (Very severe skin burning)
5. During the past 24 hours, how severe was your worst skin scaling?	0 (No skin scaling) – 10 (Very severe skin scaling)
6. During the past 24 hours, how severe was your worst skin cracking?	0 (No skin cracking) – 10 (Very severe skin cracking)
7. During the past 24 hours, how severe was your worst skin dryness?	0 (No skin dryness) – 10 (Very severe skin dryness)
8. During the past 24 hours, how severe was your worst skin irritation?	0 (No skin irritation) – 10 (Very severe skin irritation)
9. During the past 24 hours, how severe was your worst skin sensitivity?	0 (No skin sensitivity) – 10 (Very severe skin sensitivity)
10. During the past 24 hours, how severe was your worst skin lesions (red marks, spots, or inflammation)?	0 (No skin lesions) – 10 (Very severe skin lesions)
11. During the past 24 hours, how severe was your worst skin thickening (hardening or roughening)?	0 (No skin thickening) – 10 (Very severe skin thickening)
12. During the past 24 hours, at its worst, how severe was your psoriasis-related fatigue (weariness, tiredness)?	0 (No fatigue) – 10 (Worst possible fatigue)
13. During the past 24 hours, at its worst, how much embarrassment did you feel as a result of your psoriasis?	0 (No feelings of embarrassment) – 10 (Worst possible feelings of embarrassment)
14. During the past 24 hours, at its worst, how much did your psoriasis impact your choice of clothing?	0 (No impact on my choice of clothing) – 10 (Completely impacted my choice of clothing)


Screen 1
The following questions refer to things that you may experience as a result of your psoriasis. Please read through and complete the questions on the following screens. There are no right or wrong answers. Please select the answer that best applies to you as a result of your psoriasis.
Tap -->.
Screen 2
During the past 24 hours...
how severe was your worst skin itching?
0 1 2 3 4 5 6 7 8 9 10
No itching
Very severe itching
Screen 4
During the past 24 hours...
how severe was your worst skin pain?
0 1 2 3 4 5 6 7 8 9 10
No skin pain
Very severe skin pain
Screen 6
During the past 24 hours...
how severe was your worst skin scaling?
0 1 2 3 4 5 6 7 8 9 10
No skin scaling
Very severe skin scaling

Appendix B: Patient Global Impression of Severity Items (Study PS0010 only)

Global Impression Concept (in the past week)	**PGIS Question**	**Response**
Severity of psoriasis-related symptoms- past week	1. In the PAST WEEK, how severe were your psoriasis-related symptoms?	1 = No symptoms 2 = Mild symptoms 3 = Moderate symptoms 4 = Severe symptoms 5 = Very severe symptoms
Severity of itching- past week	2. In the PAST WEEK, how severe was your worst skin itching?	1 = No itching 2 = Mild itching 3 = Moderate itching 4 = Severe itching 5 = Very severe itching
Severity of pain- past week	3. In the PAST WEEK, how severe was your worst skin pain?	1 = No pain 2 = Mild pain 3 = Moderate pain 4 = Severe pain 5 = Very severe pain
Severity of scaling- past week	4. In the PAST WEEK, how severe was your worst skin scaling?	1 = No scaling 2 = Mild scaling 3 = Moderate scaling 4 = Severe scaling 5 = Very severe scaling
Severity of itch-related sleep loss- past week	5. In the PAST WEEK, how severe was your itch-related sleep loss?	1 = No itch-related sleep loss 2 = Mild itch-related sleep loss 3 = Moderate itch-related sleep loss 4 = Severe itch-related sleep loss 5 = Very severe itch-related sleep loss

Global Impression Concept (Current experience)	**PGIS Question**	**Response**
Severity of psoriasis-related symptoms- now	1. How severe are your psoriasis-related symptoms RIGHT NOW?	1 = No symptoms 2 = Mild symptoms 3 = Moderate symptoms 4 = Severe symptoms 5 = Very severe symptoms
Severity of itching- now	2. How severe is your skin itching RIGHT NOW?	1 = No itching 2 = Mild itching 3 = Moderate itching 4 = Severe itching 5 = Very severe itching
Severity of pain- now	3. How severe is your skin pain RIGHT NOW?	1 = No pain 2 = Mild pain 3 = Moderate pain 4 = Severe pain 5 = Very severe pain
Severity of scaling- now	4. How severe is your skin scaling RIGHT NOW?	1 = No scaling 2 = Mild scaling 3 = Moderate scaling 4 = Severe scaling 5 = Very severe scaling

Appendix C: Patient Global Impression of Change Items (Study PS0010 only)

Item	Response Scale
PGIC	
Please think about your psoriasis-related symptoms SINCE YOU STARTED THIS STUDY.	
How would you rate the change in your psoriasis-related symptoms since the start of this study?	Very much improved Much improved Minimally improved No change Minimally worse Much worse Very much worse
How would you rate the change in your skin itching since the start of this study?	Very much improved Much improved Minimally improved No change Minimally worse Much worse Very much worse
How would you rate the change in your skin pain since the start of this study?	Very much improved Much improved Minimally improved No change Minimally worse Much worse Very much worse
How would you rate the change in your skin scaling since the start of this study?	Very much improved Much improved Minimally improved No change Minimally worse Much worse Very much worse
How would you rate the change in your itch-related sleep loss since the start of this study?	Very much improved Much improved Minimally improved No change Minimally worse Much worse Very much worse

Appendix D: Patient Global Assessment of Psoriasis (PGAP; Studies PS0009 and PS0013)

The Patient Global Assessment of Psoriasis (PGAP) consists of a multiple-choice question: "How severe are your psoriasis-related symptoms right now?" The subject may respond "no symptoms" (1), "mild symptoms" (2), "moderate symptoms" (3), "severe symptoms" (4), or "very severe symptoms" (5).

Appendix E: Dermatology Life Quality Index (DLQI)

The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick □ one box for each question.

1	Over the last week, how itchy, sore painful or stinging has your skin been?	Very much A lot A little Not at all	□ □ □ □
2	Over the last week, how embarrassed or self-conscious have you been because of your skin?	Very much A lot A little Not at all	□ □ □ □
3	Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
4	Over the last week, how much has your skin influenced the clothes you wear?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
5	Over the last week, how much has your skin affected any social or leisure activities?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
6	Over the last week, how much has your skin made it difficult for you to do any sport?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
7	Over the last week, has your skin prevented you from working or studying?	Yes No Not relevant	□ □ □
	If "No", over the last week how much has your skin been a problem at work or studying?	A lot A little Not at all	□ □ □
8	Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
9	Over the last week, how much has your skin caused any sexual difficulties?	Very much A lot A little Not at all Not relevant	□ □ □ □ □
10	How much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much A lot A little Not at all Not relevant	□ □ □ □ □

Please check you have answered EVERY question. Thank you.

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/

MIRA J PATEL
04/05/2021 01:45:13 PM

SELENA R DANIELS
04/05/2021 03:16:36 PM

ELEKTRA J PAPADOPOULOS
04/18/2021 01:22:00 PM

Medical Officer Consult Review
Division of Gastroenterology
Center for Drug Evaluation and Research

Date: March 22, 2021

To: Gordana Diglisic, MD, Clinical Team Leader, and
Kevin Clark, MD, Clinical Reviewer,
Division of Dental and Dermatology (DDD)

From: Anil Nayyar, M.B.B.S., M.D., D.M.,
Clinical Reviewer, Division of Gastroenterology (DG)

Through: Tara Altepeter, M.D., Associate Director and Clinical Team Leader, DG
Jessica Lee, M.D., Director, DG

Subject: To review and comment on the Applicant's evaluation of adverse events of inflammatory bowel disease (IBD) and inclusion of IBD in Section 5 of the product labeling, and comment on SAE of hepatic enzyme increased (liver injury) in one patient (Subject# PS0008 (b) (6)).

Application: BLA 761151

Applicant: UCB Inc.

Drug Product: Bimekizumab injection

Proposed Indication: Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

Table of Contents

1. Executive Summary

The Division of Dermatology and Dentistry (DDD) requested consultation for evaluation of the potential risk of bimekizumab (BKZ) in causing new onset of inflammatory bowel disease (IBD) and/or worsening of underlying IBD, in patients with psoriasis. Risks of new onset and worsening of IBD are known to be associated with other IL-17 inhibitors.

Review of the clinical trial data from the psoriasis program (focused on the three submitted phase 3 trials), including our independently conducted analysis of adverse event reports, failed to identify any definite signal of new onset IBD within the clinical trial data submitted. However, evaluation of patients who exhibited signs/symptoms consistent with potential IBD was incomplete to fully exclude the possibility. Enrollment of patients with pre-existing IBD was very limited (3 subjects total), further limiting the ability to comment on the risk of exacerbation/flare of pre-existing IBD. We have provided recommendations (Section 6 of this consultation) on the proposed language to include in the prescribing information, under Warnings and Precautions (Section 5.4), and Adverse Reactions (Section 6.1).

Additionally, the DDD requested evaluation of a single case of potential drug induced liver injury (DILI). The information available on this patient is incomplete to fully exclude other possible etiologies; based upon the available data, this appears to represent a case of liver injury that met Hy's Law criteria, and thus there may be a significant risk of liver injury associated with BKZ. Further review of this case, as well as additional evaluation of the datasets to further assess this signal, are deferred to the Division of Hepatology and Nutrition's (DHN) DILI team.

2. Introduction

The Applicant, UCB, Inc., submitted BLA 761151 for the subcutaneous (SC) injection of bimekizumab (BKZ) for the treatment of moderate to severe plaque psoriasis (PSO) in adult patients who are candidates for systemic therapy or phototherapy. Bimekizumab is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) that binds to interleukin (IL)-17A and IL- 17F. BKZ is not approved in the US.

The Division of Gastroenterology (DG) received the consult request from the Division of Dermatology and Dentistry (DDD) on September 01, 2020 and December 22, 2020.

2.1. Consult request dated September 01, 2020

Review and comment on the Applicant's evaluation of adverse events of Inflammatory Bowel Disease (IBD) and inclusion of IBD in Section 5 of product labeling.

The relevant sections of the draft labeling as proposed by the Applicant appear below:

5.4 Inflammatory Bowel Disease

(b) (4)

6.1 Clinical Trials Experience
Specific Adverse Drug Reactions

(b) (4) [redacted]

2.2. Consult request dated December 22, 2020

Comment on GI SAE of hepatic enzyme increased (liver injury) in one patient (Subject# PS0008-(b) (6) [redacted]).

3. Background

Occurrences of new onset and exacerbation of IBD including Crohn's disease (CD) and ulcerative colitis (UC) have been reported in association with the use of IL-17 inhibitors in patients with inflammatory diseases including psoriasis. However, higher prevalence rates of CD and UC are also reported in patients with psoriasis compared to the general population because of shared genetic and inflammatory pathogenesis pathways in psoriasis and IBD. The association between psoriasis and CD is stronger than for UC.[1, 2] Therefore, evaluation of cases of new onset IBD in patients with psoriasis treated with anti-IL-17 agents may be confounded. Regarding the risk of disease flare/exacerbation in patients with pre-existing IBD who initiate therapy with anti-IL-17 treatment, we note that early phase 2 trials evaluating several IL-17 inhibitors in patients with IBD were discontinued/terminated due to exacerbation of IBD.

A brief overview of the published data relevant to risks of IBD associated with IL-17 inhibitors is provided below.

3.1. Safety in patients with inflammatory bowel disease treated with IL-17 inhibitors

Several studies evaluating anti-IL-17 agents as treatment for IBD patients failed to show benefit, and the use of these agents appeared to be associated with disease worsening in multiple studies (for details see Appendix-A).

3.2. Safety in patients with psoriasis treated with IL-17 inhibitors

Some of the published studies including meta-analyses reported a low incidence of new onset of IBD, as well as exacerbation of pre-existing IBD, in patients with psoriasis treated with IL-17 inhibitors (for details see Appendix-B).

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[1] Cohen AD, Dreiher J, Birkenfeld S. Psoriasis associated with ulcerative colitis and Crohn's disease. J Eur Acad Dermatol Venereol. 2009; 23:561–5.
[2] Christophers E. Comorbidities in psoriasis. Clin Dermatol. 2007; 25:529–34.

The Warning and precaution sections of the labeling for approved IL-17 inhibitors include statements regarding the risk of developing IBD and recommend monitoring patients for onset or exacerbation of IBD (for details see Appendix-C).

4. Targeted review of safety data related to potential signal for inflammatory bowel disease in BLA 761151

Strategy for review:
All treatment emergent adverse events (TEAEs) as per Preferred Term (PT) that could potentially be linked to the signs and symptoms of IBD were identified for evaluation. These included diarrhea, IBD, inflammatory bowel disease, colitis, UC, ulcerative colitis, CD, Crohn's disease, rectal bleeding, bloody diarrhea/hematochezia, acute enterocolitis, acute enteritis, intestinal ulcers, black stools/melena, stomach pain or cramping, loss of appetite/anorexia, constipation, weight loss, fever, or tiredness/fatigue. While many of these signs/symptoms are non-specific, the intended review strategy aimed to cast a wide net to capture any events that could potentially indicate that new onset IBD was developing. The Applicant was also asked to provide information on the number and proportion of patients in each treatment arm experiencing any of the TEAEs listed above if persisting for at least 2 weeks' duration in patients with psoriasis in studies submitted in the BLA (Studies PS0008, PS0009, and PS0013). This cut-off was utilized because IBD is a chronic disease, and excluding the above listed signs/symptoms if very acute in nature would help to focus the evaluation to patients who developed symptoms of longer duration, which could be indicative of a chronic condition. Additional information was also requested from the completed and ongoing clinical trials in other diseases, where cases of new onset and exacerbation of IBD were reported.

Review was performed based on the safety datasets included in the BLA submission as well as additional information provided by the Applicant during the review cycle. The proportion of patients who experienced TEAEs, potentially related to the signs and symptoms of IBD (UC and CD) and persisting for ≥2 weeks, were compared between BKZ treatment and placebo or active comparator (adalimumab).

Summary of the study design and proportion of patients that reported targeted TEAEs (potentially related to IBD) in Studies PS0008, PS0009, and PS0013 is provided.

4.1. Study PS0008 (BE SURE)

Study design:
Study PS0008 was a phase 3, multicenter (MC), randomized (R), double-blind (DB), parallel group (PG), active comparator-controlled (ACC) study that evaluated efficacy and safety of BKZ administered SC versus adalimumab for 16 weeks in the treatment of patients with moderate to severe chronic PSO.

During the 16-week initial treatment period, 478 patients were randomized 1:1:1 to receive the following blinded IMP regimens:

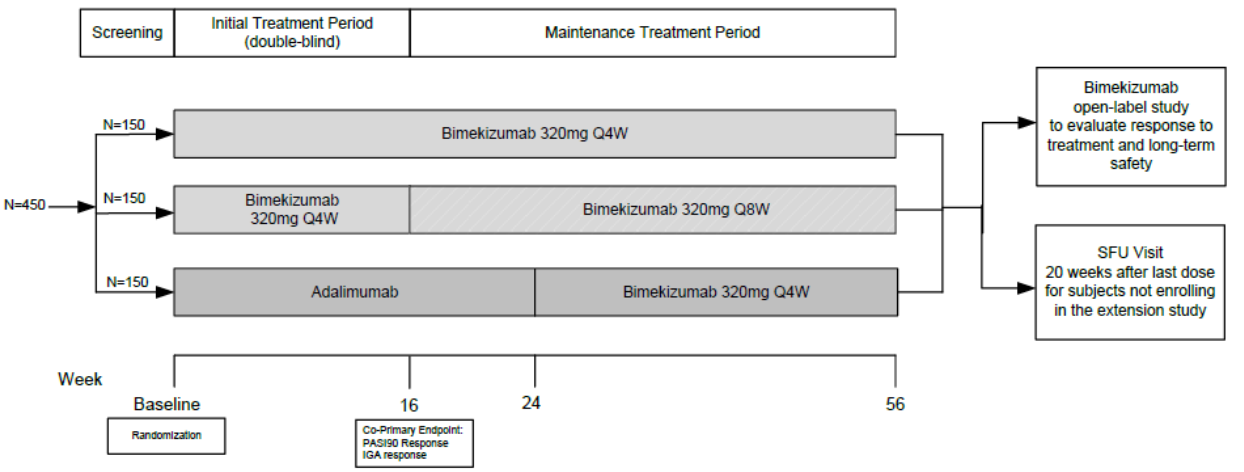
- BKZ 320 mg administered SC every 4 weeks (treatment arm Q4W) for 16 weeks and continued throughout the study (N= approximately 158 patients);

- BKZ 320 mg administered SC every 4 weeks (treatment arm Q4W/Q8W) until Week 16 (N=161); or
- Adalimumab 80 mg administered as an initial dose, followed by 40 mg Q2W starting 1 week after the initial dose (i.e., adalimumab was administered according to the labeling recommendations) until Week 24 (N= approximately 159 patients).

After the 16-week initial treatment period, patients in the BKZ 320 mg Q4W treatment arm continued on the same treatment regimen whereas patients in the BKZ 320 mg treatment arm Q4W/Q8W received BKZ Q8W from Week 16 through Week 52 and patients in the adalimumab treatment arm received BKZ 320 mg Q4W from Week 24 through Week 52 (Figure 1). For additional details please see Medical Officer's review by Dr. Kevin Clark (DDD).

The study protocol specified that patients with inactive IBD (past medical history of IBD) could be included the study; however, it is noted that only three patients with possible past medical history of IBD were enrolled.

Figure 1: Schematic of the study design for clinical Study 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: Refer to Section 3.2.2 for treatments during the Initial Treatment Period and to Section 3.2.3 for treatments during the Maintenance Treatment Period.
Note: At Week 36 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 were defined as nonresponders and should have discontinued IMP.
Source: Figure 3.1 of the interim clinical study report for PS0008.

Results:
Results of the targeted evaluation of specific new onset TEAEs of interest described above (which could potentially be associated with new onset IBD) are summarized below for the initial 24 weeks of treatment period and the combined initial and maintenance treatment periods:

Weeks 24
Table 1 shows the number and proportion of patients who reported any of the TEAEs of interest persisting for at least 2 weeks during the initial 24 weeks of treatment with BKZ 320 mg Q4W compared with adalimumab.

No patient reported TEAEs of IBD (including CD or UC) in the two treatment arms. In general, the rates of persistent (≥14 days) TEAEs of interest were low, and occurred with similar frequency across the BKZ arms vs comparator.

Table 1: TEAEs persisting for ≥ 2 weeks through Week 24 (Study PS0008)

Parameters	Treatment Arms			
	BKZ 320 mg Q4W/Q8W N=161	**BKZ 320 mg Q4W N=158**	**BKZ Total N=319**	**ADA N=159**
Duration of treatment (100 subjects-years)	0.73	0.72	1.45	0.72
Overall Any GI TEAE of interest+ n (%)	2 (1.2)	5 (3.2)	7 (2.2)	3 (1.9)
Diarrhea				
No of subjects (%)	1 (0.6)	2 (1.3)	3 (0.9)	0
Incidence* (95% CI)	1.37 (0.03, 7.66)	2.78 (0.34, 10.04)	2.07 (0.43, 6.06)	0
Event rate**	1.37	2.77	2.06	0
Abdominal pain upper				
No of subjects (%)	0	1 (0.6)	1 (0.3)	1 (0.6)
Incidence* (95% CI)	0	1.39 (0.04, 7.77)	0.69 (0.02, 3.84)	1.38 (0.03, 7.70)
Event rate**	0	1.39	0.69	1.38
Constipation				
No of subjects (%)	0	1 (0.6)	1 (0.3)	0
Incidence* (95% CI)	0	1.39 (0.04, 7.77)	0.69 (0.02, 3.84)	0
Event rate**	0	1.39	0.69	0
Fatigue				
No of subjects (%)	1 (0.6)	1 (0.6)	2 (0.6)	2 (1.3)
Incidence* (95% CI)	1.37 (0.03, 7.61)	1.39 (0.04, 7.74)	1.38 (0.17, 4.98)	2.79 (0.34, 10.10)
Event rate**	1.37	1.39	1.38	2.76

* Incidence of new cases per 100 subject-years. ** event rate per 100 subject-years.
+Patients reporting one or more of the following (Diarrhea, upper abdominal pain, constipation or fatigue) lasting for 14 days or more.
Source: Adapted from Tables 1.1.1 and 1.1.2 of the Applicant Responses dated Nov 06, 2020 to the FDA IR dated Oct 30, 2020.

Diarrhea

One percent (3/319) of patients reported TEAEs of persistent diarrhea during the initial treatment period while receiving BKZ 320 mg Q4W treatment in the two BKZ treatment arms compared to no patient in the ADA treatment arm. The onset of diarrhea in three patients occurred on Days 10, 17 and 111 days from the start of the treatment. In 2 patients, the duration of diarrhea was 15 days and 44 days; the diarrhea was reported to have resolved in these patients and study drug was not changed. It is noted that no additional investigations were performed to confirm the underlying etiology of the persistent diarrhea. The third patient (Pt ID PS0008-(b) (6)) had a history of UC and was withdrawn from the treatment after 17 days of treatment due to TEAE of diarrhea; the duration of diarrhea or investigations performed to confirm the etiology of the diarrhea and rule out exacerbation of UC in this patient were not available.

Fatigue
Less than one percent (0.6%, 2/319) of patients reported TEAE of fatigue during the initial 24 weeks treatment period while receiving BKZ 320 mg Q4W treatment compared to 1.3% (2/159) patients in the adalimumab treatment arm. The duration of the TEAE was 19 days in one patient and not specified for the second patient and was reported as resolved in one of the two cases. The dose was not changed or interrupted in any patient.

Others (abdominal pain and constipation)
TEAEs of abdominal pain and constipation were only 1 each in BKZ and adalimumab group.

Combined initial and maintenance period (52 weeks)
The results in Table 2 show the overall number and proportion of patients with TEAEs persisting for ≥ 2 weeks during the initial and maintenance treatment periods in the two BKZ treatment groups. It is noted that patients in the adalimumab treatment arm were switched to BKZ 320 mg Q4W treatment during the maintenance treatment period.

Table 2: Proportion of patients with TEAEs persisting for ≥ 2 weeks in BKZ set (Combined initial and maintenance period-Study PS0008)

Parameters	Treatment Arms		
	BKZ 320 mg Q8W N=154	**BKZ 320 mg Q4W N=468**	**BKZ Total N=468**
Duration of treatment (100 subjects-years)	1.16	3.06	4.22
Overall Any GI TEAE of interest+ n (%)	4 (2.6)	12 (2.6)	16 (3.4)
Diarrhea			
No of subjects (%)	0	5 (1.1)	5 (1.1)
Incidence* (95% CI)	0	1.64 (0.53, 3.84)	1.19 (0.39, 2.79)
Event rate**	0	1.63	1.19
Fatigue			
No of subjects (%)	2 (1.3)	3 (0.6)	5 (1.1)
Incidence* (95% CI)	1.74 (0.21, 6.28)	0.99 (0.20, 2.88)	1.19 (0.39, 2.79)
Event rate**	1.72	0.98	1.19
Abdominal pain upper			
No of subjects (%)	0	2 (0.4)	2 (0.4)
Incidence* (95% CI)	0	0.66 (0.08, 2.37)	0.48 (0.06, 1.72)
Event rate**	0	0.65	0.47
Constipation			
No of subjects (%)	0	1 (0.2)	1 (0.2)
Incidence* (95% CI)	0	0.33 (0.01, 1.83)	0.24 (0.01, 1.33)
Event rate**	0	0.33	0.24
Erosive duodenitis			
No of subjects (%)	1 (0.6)	0	1 (0.2)
Incidence* (95% CI)	0.86 (0.02, 4.82)	0	0.24 (0.01, 1.32)
Event rate**	0.86	0	0.24
Weight decreased			
No of subjects (%)	0	1 (0.2)	1 (0.2)
Incidence* (95% CI)	0	0.33 (0.01, 1.82)	0.24 (0.01, 1.32)
Event rate**	0	0.33	0.24
Decreased appetite			
No of subjects (%)	1 (0.6)	0	1 (0.2)
Incidence* (95% CI)	0.87 (0.02, 4.82)	0	0.24 (0.01, 1.32)
Event rate**	0.86	0	0.24

* Incidence of new cases per 100 subject-years. ** event rate per 100 subject-years.
+Patients reporting one or more of the following (Diarrhea, fatigue, upper abdominal pain, constipation, erosive duodenitis, weight decreased or decreased appetite) lasting for 14 days or more.
Source: Adapted from Tables 1.1.4 and 1.1.5 of the Applicant Responses dated Nov 06, 2020 to the FDA IR dated Oct 30, 2020.

No patient reported TEAEs of IBD during the study duration.

Overall, the proportion of patients experiencing one or more of the select GI AEs of interest and that persisted for 14 days or more during the combined initial and maintenance treatment period

were similar in the BKZ 320 mg Q4W/Q8W [2.6 % (4/154)] and BKZ 320 mg Q4W/Q4W [2.6% (12/468)] treatment sequence groups. Diarrhea and fatigue were most common.

Diarrhea
Overall, 1.1% (5/468) of patients reported TEAEs of diarrhea while receiving BKZ 320 mg Q4W treatment, as compared to none in the BKZ 320mg Q8W arm. These include 3 patients who reported TEAEs of diarrhea during the initial treatment period.

During the maintenance and post treatment period, approximately 1% (2/159) patients from the adalimumab/BKZ 320 mg Q4W treatment arm reported diarrhea after switching to BKZ 320 mg Q4W for 126 and 53 days with duration of symptoms of 36 days and 91 days, respectively. One patient who reported diarrhea for 36 days was investigated and diagnosis of non-systemic *Candida* enteritis was made. Most of the patients are reported to have recovered spontaneously and no change on drug treatment was needed.

Fatigue
Overall, 1.1% (5/468) of patients reported TEAEs of fatigue while receiving BKZ treatment including two patients during the initial period, compared to 1.3% (2/159) patients who reported fatigue while receiving adalimumab (adalimumab/BKZ 320 mg Q4W treatment group) during the initial treatment period.

No dose changes were made in these patients and all patients are reported to have completed the study.

Other TEAEs (abdominal pain, erosive duodenitis, constipation, decreased weight)
TEAEs of abdominal pain, erosive duodenitis, constipation, and decreased weight were reported in only 1-2 patients for each TEAE listed.

Reviewer comments
The majority of TEAEs were reported at the BKZ 320 mg Q4W dose and during the initial treatment period compared to the maintenance period. TEAEs of diarrhea and fatigue were observed in a higher proportion of patients receiving BKZ compared to adalimumab. Note that the TEAEs of diarrhea, which could be a signal for an early/mild presentation of IBD, were not investigated to rule out the possibility of IBD.

The number of patients with TEAEs of constipation, abdominal pain, erosive esophagitis, decreased weight, and decreased appetite were only 1-2 for each TEAE. Since these TEAEs were not associated with concomitant diarrhea they are considered unlikely to be potential signal for IBD.

4.2. Study PS0009 (BE VIVID)

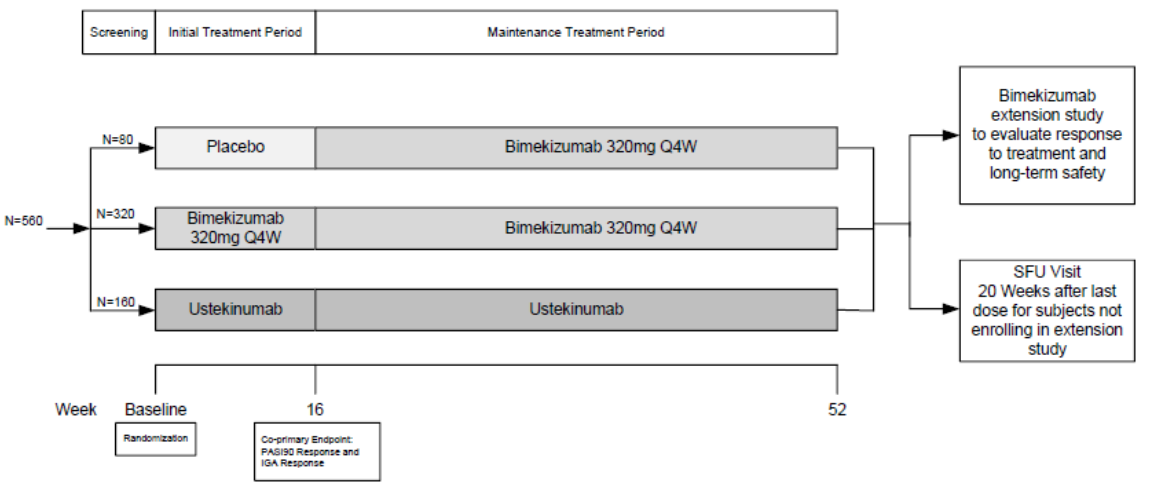
Study design:
Study PS0009 was a Phase 3, MC, R, DB, placebo- and -active controlled study that evaluated efficacy and safety of BKZ versus placebo or ustekinumab in adult patients with moderate to severe chronic PSO at Week 16.

During the 16-week initial treatment period, 567 patients were randomized 4:2:1 to receive the following blinded regimens:

- BKZ 320 mg administered SC every 4 weeks (Q4W);
- Ustekinumab 45 mg SC in patients weighing ≤100kg and 90 mg SC in patients weighing >100kg initially and 4 weeks later, then every 12 weeks; or
- Placebo administered SC Q4W.

During the follow-up maintenance treatment period of 36 weeks, patients in the BKZ and ustekinumab treatment arms continued to receive the same dosing regimen as during the initial treatment phase; however, the patients in the placebo arm were switched to BKZ 320 mg Q4W starting at Week 16 (Figure 2). For additional details please see Medical Officer's review by Dr. Kevin Clark (DDD).

Figure 2: Schematic of the study design for Clinical Study 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, 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 were defined as nonresponders and should have discontinued IMP.

Source: Figure 3.1 of the interim clinical study report for PS0009.

Results:

The select GI TEAEs of interest considered potentially related to IBD, and persisting for at least 14 days, are summarized over the initial 16 weeks, and during the combined initial and maintenance treatment periods:

Initial treatment (16 weeks):

The results in Table 4 show the number and proportion of patients with TEAEs persisting for ≥ 2 weeks and possibly/potentially related to occurrence of IBD in the three treatment groups.

Table 3: TEAEs persisting for ≥ 2 weeks Initial treatment period-overall (Study PS0009)

Parameter	Placebo N=83	BKZ 320 mg Q4W N=321	Ustekinumab N=163
Duration of treatment (100 subjects-years)	0.25	0.99	0.55
Overall Any GI TEAE of interest+ n (%)	2 (2.4)	9 (2.8)	0
Ulcerative colitis			
No of subjects (%)	0	1 (0.3)	0
Incidence* (95% CI)	0	1.01 (0.03, 5.62)	0
Event rate**	0	1.01	0
Diarrhea			
No of subjects (%)	2 (2.4)	5 (1.6)	0
Incidence* (95% CI)	7.97 (0.97, 28.79)	5.10 (1.66, 11.90)	0
Event rate**	11.80	5.04	0
Fatigue/asthenia			
No of subjects (%)	0	3 (0.9)	0
Incidence* (95% CI)	0	3.04 (0.63, 8.88)	0
Event rate**	0	3.02	0
Abdominal pain upper			
No of subjects (%)	0	1 (0.3)	0
Incidence* (95% CI)	0	1.01 (0.03, 5.62)	0
Event rate**	0	2.01	0
Pyrexia			
No of subjects (%)	0	1 (0.3)	0
Incidence* (95% CI)	0	1.01 (0.03, 5.62)	0
Event rate**	0	1.01	0

* Incidence of new cases per 100 subject-years. ** event rate per 100 subject-years.
+Patients reporting one or more of the following (Ulcerative colitis, diarrhea, fatigue, upper abdominal pain, or pyrexia) lasting for 14 days or more.
Source: Adapted from Tables 1.2.1 and 1.2.2 of the Applicant Responses dated Nov 06, 2020 to the FDA IR dated Oct 30, 2020.

Potentially IBD related TEAEs were reported in 3% (9/321) of patients in the BKZ 320 mg Q4W arm, 2.5% (2/83) in the placebo arm, and none in the ustekinumab arm. TEAEs persisting for ≥2 weeks included ulcerative colitis, diarrhea, fatigue, abdominal pain upper, asthenia, and pyrexia. UC, diarrhea, and fatigue were most common, and are described further below:

Ulcerative colitis
One patient (0.3%; 1/321) reported TEAE of IBD in the BKZ 320 mg Q4W treatment group compared to no patient in the placebo or ustekinumab treatment groups. This was a case of new onset UC and resulted in treatment discontinuation.

Diarrhea
Overall, 1.6% (5/321) of patients reported TEAE of persistent diarrhea while receiving BKZ 320 mg Q4W compared to 2.4% (2/83) patients in the placebo arm and no patient in the ustekinumab treatment arm. The onset of diarrhea after start of BKZ 320 mg Q4W treatment ranged between 3 to 49 days and duration of persisting diarrhea ranged between 27 to 219 days. One patient, with new onset of UC (stated above) discontinued treatment. Another patient discontinued due to

abnormal Columbia suicide severity rating scale. The diarrhea was resolved in three patients after 41, 104, and 219 days. It is noted that no additional investigations were performed to confirm the diagnosis of persistent diarrhea and to rule out the diagnosis of IBD. Spontaneous resolution (particularly in the patients with symptoms lasting several months) does not necessarily exclude underlying IBD, as the disease is characterized by a relapsing and remitting course and can at times include periods of spontaneous resolution.

Fatigue
Overall, 1% (3/321) of patients reported TEAE of fatigue in the BKZ 320 mg Q4W treatment group compared to none of the patients in the placebo or ustekinumab groups. The onset of fatigue ranged between 3 to 75 days from the start of the treatment. The duration of fatigue was stated as 14 and 27 days in two patients and one patient was lost to follow-up.

Other TEAEs (abdominal pain upper and pyrexia)
One patient reported abdominal pain upper and another reported pyrexia in the BKZ 320 mg Q4W treatment arm compared to none of the patients in the placebo or ustekinumab arms.

All the TEAEs, described above, were reported in the BKZ 320 mg Q4W treatment arm and were new onset (rather than worsening of condition present at randomization) except for one TEAE of constipation in a patient with preexisting constipation.

Combined initial and maintenance treatment (52 weeks):
The results in Table 4 show the overall number and proportion of patients with TEAEs persisting for ≥2 weeks during the initial and maintenance treatment periods in different groups. During the maintenance period, patients received BKZ 320 mg Q4W or ustekinumab; there was no placebo arm during this period.

Overall, 5.3 % (17/321) of patients in the BKZ 320 mg Q4W treatment arm (randomized at baseline) compared to the 1.2% (2/168) of patients in the ustekinumab treatment arm reported TEAEs potentially related to IBD during the combined initial and maintenance treatment period.

The TEAEs included ulcerative colitis, diarrhea, fatigue, abdominal pain upper, constipation, enterocolitis, intestinal ulcer, asthenia, pyrexia, decreased weight, and decreased appetite. As there was a small difference in the TEAEs in the randomized BKZ treatment group (N=321) compared to the group that included patients who switched from placebo to BKZ 320 mg Q4W (N=395) treatment, the assessment was performed based on the randomized group. A summary of patients who reported the key TEAEs during the 52-week period is provided.

Table 4: Proportion of patients with TEAEs persisting for ≥ 2 weeks (Combined initial and maintenance period-overall- Study PS0009)

Parameters	BKZ 320 mg Q4W (Randomized + Open Label)[A] N=395	BKZ 320 mg Q4W (Randomized)[B] N=321	Ustekinumab N=163
Duration of treatment (100 subjects-years)	3.59	3.08	1.58
Overall Any GI TEAE of interest[+] n (%)	18 (4.6)	17 (5.3)	2 (1.2)
Ulcerative colitis			
No of subjects (%)	1 (0.3)	1 (0.3)	0
Incidence* (95% CI)	0.28 (0.01, 1.55)	0.32 (0.01, 1.81)	0
Event rate**	0.28	0.32	0
Diarrhea			
No of subjects (%)	7 (1.8)	7 (2.2)	0
Incidence* (95% CI)	1.97 (0.79, 4.06)	2.30 (0.93, 4.74)	0
Event rate**	1.95	2.27	0
Fatigue/asthenia			
No of subjects (%)	4 (1.0)	3 (0.9)	0
Incidence* (95% CI)	1.12 (0.31, 2.87)	0.98 (0.20, 2.86)	0
Event rate**	1.11	0.97	0
Abdominal pain upper			
No of subjects (%)	4 (1.0)	3 (0.9)	1 (0.6)
Incidence* (95% CI)	1.12 (0.30, 2.86)	0.98 (0.20, 2.85)	0.64 (0.02, 3.55)
Event rate**	1.39	1.30	0.63
Constipation			
No of subjects (%)	2 (0.5)	2 (0.6)	1 (0.6)
Incidence* (95% CI)	0.56 (0.07, 2.02)	0.65 (0.08, 2.35)	0.63 (0.02, 3.54)
Event rate**	0.56	0.65	0.63
Enterocolitis			
No of subjects (%)	1 (0.3)	1 (0.3)	0
Incidence* (95% CI)	0.28 (0.01, 1.55)	0.32 (0.01, 1.81)	0
Event rate**	0.28	0.32	0
Intestinal ulcer			
No of subjects (%)	1 (0.3)	0	0
Incidence* (95% CI)	0.28 (0.01, 1.55)	0	0
Event rate**	0.28	0	0
Pyrexia			
No of subjects (%)	1 (0.3)	1 (0.3)	0
Incidence* (95% CI)	0.28 (0.01, 1.55)	0.33 (0.01, 1.81)	0
Event rate**	0.28	0.32	0
Weight decreased			
No of subjects (%)	1 (0.3)	1 (0.3)	0
Incidence* (95% CI)	0.28 (0.01, 1.55)	0.32 (0.01, 1.81)	0
Event rate**	0.28	0.32	0
Decreased appetite			
No of subjects (%)	1 (0.3)	0	0
Incidence* (95% CI)	0.28 (0.01, 1.55)	0	0
Event rate**	0.28	0	0

* Incidence of new cases per 100 subject-years. ** event rate per 100 subject-years.
+Patients reporting one or more of the following (ulcerative colitis, diarrhea, fatigue/asthenia, upper abdominal pain, constipation, enterocolitis, intestinal ulcer, pyrexia, weight decreased or decreased appetite) lasting for 14 days or more.
A: Represents randomized patients + open label BKZ treated patients (switched to BKZ 320 mg Q4W group after initial 16 weeks in the placebo group, only events after switch).
B: Represent only randomized patients to BKZ 320 mg Q4W (all subjects who were randomized to BKZ at baseline).
Source: Adapted from Tables 1.2.4 and 1.2.5 of the Applicant Responses dated Nov 06, 2020 to the FDA IR dated Oct 30, 2020.

Diarrhea and fatigue were the most common of the GI events of interest and occurred with greater frequency in the BMK group than active control.

Diarrhea/enterocolitis
Overall, 2.2% (7/321) patients reported TEAEs of diarrhea while receiving BKZ 320 mg Q4W treatment compared to no patients in the ustekinumab treatment arm; these patients include 5 patients from the initial treatment period of 16 weeks as described above.

During the maintenance treatment period, two patients reported TEAEs of diarrhea with a duration of 19 and 60 days. One additional patient reported TEAE of enterocolitis, in the BKZ 320 mg Q4W treatment group, with a duration of 19 days. One patient with diarrhea was hospitalized and diagnosed with gastroenterocolitis; this patient completed the study. In the second patient with diarrhea, the TEAE was stated as not resolved. In the third patient, who reported TEAE of enterocolitis, treatment was interrupted; however, the patient completed the study. No additional investigations were reported to establish the etiology of diarrhea or enterocolitis and rule out diagnosis of IBD in two patients.

Fatigue
Overall, 1% (4/395) of patients reported TEAEs of fatigue while receiving BKZ 320 mg Q4W treatment compared to no patients in the ustekinumab treatment arm. Of the 4 patients, 3 were from the initial treatment period described above.

During the maintenance treatment period, one patient, who was switched from initial placebo arm to BKZ 320 mg Q4W treatment arm, reported TEAEs of fatigue, asthenia, and abdominal pain. Patient had received BKZ 320 mg Q4W for 11 days before onset of the TEAE which lasted for 27 days. The outcome of fatigue was stated to be resolved, however, the patient was discontinued from the treatment due to abnormal LFTs; the abnormal LFTs were considered related to the non-alcoholic steatohepatitis (NASH) and bile duct stricture.

Abdominal Pain
One percent (4/321) of patients reported TEAE of abdominal pain upper in the BKZ 320 mg Q4W treatment group including 1 patient from the initial treatment period compared to 0.6% (1/163) patients in the ustekinumab treatment arm. One of the 3 patients who reported TEAE of abdominal pain during the maintenance treatment period, was switched from placebo to BKZ 320 mg Q4W treatment group.

Other TEAEs (constipation, intestinal ulcer, pyrexia, decreased weight, and decreased appetite)
Only 1-2 patients reported each of the TEAEs of constipation, intestinal ulcer, pyrexia, decreased weight, and decreased appetite, majority in the BKZ group.

Reviewer comments
One patient reported new onset of IBD during the induction period of the trial as described above and a slightly higher proportion of patients reported other TEAEs in the BKZ treatment group compared to ustekinumab group. Of all the reported TEAEs, a higher proportion of patients with persistent or chronic diarrhea was reported in the BKZ 320 mg treatment group compared to no patient in the comparator ustekinumab arm. Similar to Study PS0008, patients reporting TEAE of diarrhea were not adequately investigated in this trial.

The reported incidence of persistent diarrhea in BKZ treatment group in Study PS0009 was 2.2% compared to 1.6% in Study PS0008. The reported incidences in these two trials appears to be similar to the incidence rates reported in the labelings for the other approved IL-17 inhibitors i.e., brodalumab (2.2%) and secukinumab (2.6 to 4.1%). However, it is unknown how many patients treated with brodalumab or secukinumab reported persistent TEAEs of diarrhea and whether they were investigated to rule out the development of IBD.

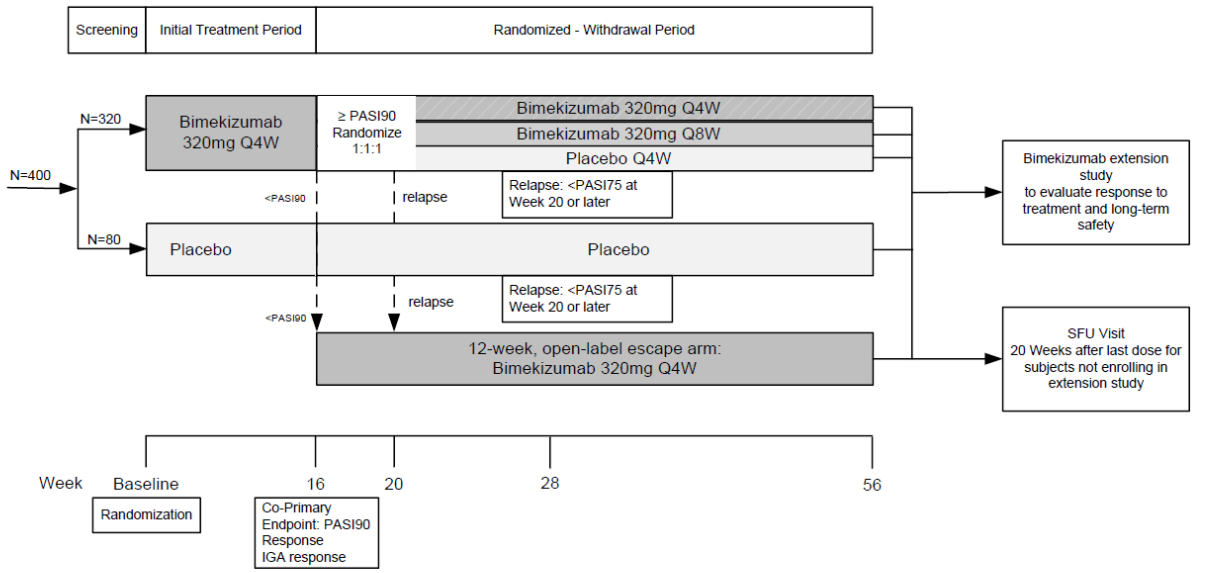
The majority of the other TEAEs were reported in patients receiving BKZ treatment and included fatigue (n=3), abdominal pain (n=3), constipation (n=2), enterocolitis (n=1), pyrexia (n=1), decreased weight (n=1), decreased appetite (n=1), abdominal pain (n=1), and constipation (n=1). Note that these patients did not have other concomitant symptoms such as diarrhea, fever, or rectal bleeding. These TEAEs appear unlikely to be a potential signal for risk of developing IBD in psoriatic patients receiving BKZ. However, the incidence rates including all patients, irrespective of duration, may be higher in the trial; the events described included patients having persistent symptoms for more than 2 weeks.

4.3. Study PS0013 (BE READY)

Study Design:
Study PS0013 was a Phase 3, MC, R, DB, PC study that evaluated the efficacy and safety of a 16-week initial treatment BKZ 320 mg SC Q4W followed by a 40-week randomized-withdrawal period in 435 adult patients with moderate to severe chronic PSO. Patients were randomized 4:1 and received BKZ 320 mg administered SC (N=349) or placebo (N=86) Q4W for 16 weeks. At Week 16 study visit, patients who achieved a PASI90 and IGA response, continued into a 40-week randomized withdrawal period. Patients initially randomized to BKZ 320 mg Q4W were re-randomized 1:1:1 to receive BKZ 320 mg Q4W, BKZ 320mg Q8W, or placebo (i.e., treatment withdrawal) and patients initially randomized to placebo who achieved a PASI90 response at Week 16 were continued to receive placebo Q4W.

Patients who did not achieve a PASI90 response at Week 16 of the Initial Treatment Period and patients who relapsed at Week 20 or later during the randomized-withdrawal period (up to Week 56) received open-label BKZ 320 mg Q4W for 12 weeks (Figure 3). For additional details please see Medical Officer's review by Dr. Kevin Clark (DDD).

Figure 3: Schematic of the study design for Clinical Study PS0013



IGA=Investigator's Global Assessment; PASI=Psoriasis Area and Severity Index; Q4W=every 4 weeks; Q8W=every 8 weeks; SFU=Safety Follow-Up
Note: Study participants who did not achieve a PASI90 response at Week 16 were allocated to an escape arm and receive open-label bimekizumab 320mg Q4W for 12 weeks.
Note: Relapse was defined as not achieving a PASI75 response. All study participants who relapsed at Week 20 or later were allocated to an escape arm and received open-label bimekizumab 320mg Q4Wfor 12 weeks.
Note: Study participants in the placebo treatment arm in the Initial Treatment Period continued to receive placebo Q4W at Week 16 and later visits provided a PASI90 response was achieved at Week 16.

Source: Figure 3.1 of the interim clinical study report for PS0013.

Results:

The TEAEs potentially related to IBD reported during the initial treatment period as well as randomized withdrawal period are summarized:

Initial Treatment period

Table 5 shows the overall number and proportion of patients with TEAEs persisting for ≥2 weeks during the initial treatment period in the 320 mg Q4W treatment and placebo arms.

Table 5: TEAEs persisting for ≥ 2 weeks during initial treatment period (Study PS0013)

Parameter	Placebo N=86	BKZ 320 mg Q4W N=349
Duration of treatment (100 subjects-years)	0.26	1.08
Overall Any GI TEAE of interest+ n (%)	1 (1.2)	6 (1.7)
Diarrhea		
No of subjects (%)	0	1 (0.3)
Incidence* (95% CI)	0	0.92 (0.02, 5.15)
Event rate**	0	0.92
Fatigue		
No of subjects (%)	0	2 (0.6)
Incidence* (95% CI)	0	1.85 (0.22, 6.70)
Event rate**	0	1.84
Constipation		
No of subjects (%)	0	1 (0.3)
Incidence* (95% CI)	0	0.92 (0.02, 5.14)
Event rate**	0	0.92
Diverticular perforation		
No of subjects (%)	0	1 (0.3)
Incidence* (95% CI)	0	0.92 (0.02, 5.14)
Event rate**	0	0.92
Weight decreased		
No of subjects (%)	0	1 (0.3)
Incidence* (95% CI)	0	0.92 (0.02, 5.14)
Event rate**	0	0.92
Decreased appetite		
No of subjects (%)	1 (1.2)	1 (0.3)
Incidence* (95% CI)	3.82 (0.10, 21.31)	0.92 (0.02, 5.14)
Event rate**	3.82	0.92

* Incidence of new cases per 100 subject-years. ** event rate per 100 subject-years.
+Patients reporting one or more of the following (Diarrhea, fatigue, constipation, diverticular perforation, weight decreased, or decreased appetite) lasting for 14 days or more.
Note: n=number of subjects reporting at least one TEAE within System Organ Class/High Level Term/Preferred Term.
Note: Incidence=Incidence of new cases per 100 subject-years and associated 95% CI.
Note: Event Rate=event rate per 100 subject-years.
Source: Adapted from Tables 1.3.1 and 1.3.2 of the Applicant Responses dated Nov 06, 2020 to the FDA IR dated Oct 30, 2020.

Overall, 1.7% (6/349) patients in the BKZ 320 mg Q4W treatment arm reported 7 TEAEs (persisting for ≥2 weeks) compared to 1.2% (1/83) in the placebo arm.

The majority of the TEAEs were reported in the BKZ 320 mg Q4W treatment group: 2 patients reported fatigue, and 1 patient each reported TEAE of diarrhea, constipation, diverticular perforation, decreased weight, and decreased appetite compared to one patient with decreased appetite in the placebo treatment group. Onset of the diarrhea reported in one patient was after 37 days of treatment and lasted for 25 days. Onset of fatigue in two patients was 10 and 22 days after start of treatment and lasted for 289 days in one patient; the duration was not reported for the second patient. Onset of the other TEAEs ranged between 4 days and 97 days after start of the BKZ treatment and symptoms lasted from 21 days to 84 days. All the TEAEs were new onset

(none were reported as exacerbation of symptoms that were present at time of enrollment). No changes in the dose were made and all patients completed the study.

Randomized withdrawal period
No additional TEAEs were reported except one patient in the placebo group with TEAE of constipation.

Reviewer comments
All the TEAEs described above were new onset. However, the number of patients reporting the TEAEs are only 1-2 for each TEAE.

4.4. Reports of inflammatory bowel disease in clinical trials for other indications
The Applicant was asked to provide information regarding patients who reported new onset and or exacerbation of IBD in the other ongoing clinical programs.

The Applicant provided a summary of patients who reported IBD during completed and ongoing clinical trials for the indications of axial spondylitis [(AS) Studies AS0008, AS0009, AS0011, and AS0013) and psoriatic arthritis (PsA) (Studies PA0008, PA0009, and PA0010). Studies PA0009, PA0010, AS0009 and AS00011 are blinded and currently ongoing. The majority of IBD reports with BKZ are from the completed Study AS0008 and its open label ongoing extension Study AS0009. For details see Appendix-D.

The risk of new onset of IBD (CD/UC) reported in these indications, although small, appears slightly higher compared to the risk reported in patients with psoriasis (Studies PS0008, PS0009, and PS0013).

It is noted that the indications of UC and rheumatoid arthritis are no longer under development by the Applicant.

Reviewer comments
A small number of patients reported new onset of CD and UC as well exacerbation of pre-existing 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.

4.5. Summary and Conclusions
This review evaluated signs and symptoms that could potentially be related to inflammatory bowel disease across the three submitted phase 3 trials.

The evaluation focused on specific GI symptoms of interest (diarrhea, fatigue, abdominal pain, erosive duodenitis, pyrexia, enterocolitis, diverticular perforation, decreased weight, and decreased appetite) and specifically evaluated the number and proportion of patients

experiencing any of these AEs for 14 days duration or longer, in each of the submitted phase 3 trials (PS0008, PS0009, and PS0013).

Of the targeted GI symptoms with duration ≥14 days evaluated, diarrhea was the most common TEAE. The reported incidence of persistent diarrhea, defined by ≥14 days duration, in BKZ treatment groups was 1.6% and 2.2% in Studies PS0008 and PS0009, respectively. None of the patients reported TEAEs of persistent diarrhea in the active comparator groups in the two studies; note that adalimumab was administered for initial 16 weeks in Study PS0008 and ustekinumab for 52 weeks in Study PS0009. However, the incidence rate of diarrhea was 2.4% in patients who received placebo for initial 16 weeks in Study PS0008. These incidence rates appear to be similar to the incidence rates of diarrhea reported in the labeling for the other approved IL-17 inhibitors i.e., brodalumab (2.2%) and secukinumab (2.6 to 4.1%)[3]. Persistent or chronic diarrhea was reported in a higher proportion of patients treated every 4 weeks with BKZ (BKZ 320 mg Q4W dose group) compared to those treated every 8 weeks (BKZ 320 mg Q8W dose group). Most of the patients recovered spontaneously (some recovered after a prolonged period) and no change in drug treatment was needed; these results are not strongly suggestive of new onset IBD, which when present, typically requires treatment in order to rapidly resolve symptoms.

Overall, limitations to assess the causality between BKZ treatment and possible IBD (represented by persistent diarrhea) include the relatively small number of patients in the trials, small number of patients experiencing persistent diarrhea, limited duration of drug exposure compared to duration of use in clinical practice, and inadequate investigations performed in patients with persistent diarrhea.

Additional information that was considered included preliminary information provided by the Applicant from studies conducted with bimekizumab in other indications including AS and PsA. These trials showed a slightly greater proportion of new onset as well as exacerbation of CD and UC in bimekizumab treated patients, compared to patients with psoriasis in Studies PS0008, PS0009, and PS0013. We also reviewed the labeling and published literature for other biologics in this class. Risk of IBD associated with IL-17 inhibitors appears to be a class effect.

In summary, the rate of persistent diarrhea was relatively low (1-2%) in bimekizumab treated patients with psoriasis. Informed by the known risk of causing or exacerbating IBD within this drug class, as well as the limitations of the evaluation conducted for patients who experienced persistent diarrhea in the psoriasis development program, we cannot definitively exclude the possibility that cases of IBD occurred in association with bimekizumab treatment in a small number of psoriasis patients. Therefore, we agree with including information on the potential risk of IBD associated with bimekizumab use within the prescribing information and have made labeling recommendations to the primary review team, as outlined in Section 6 of this review below.

[3] Of note, those labels report the incidence of any diarrhea (rather than persistent diarrhea) so a direct comparison of rates may be misleading.

5. Review of liver injury in one patient (Subject# PS0008-[redacted])

A 21-year-old white female who weighed 103 kg (BMI 35 kg/m^2) with a medical history of autoimmune thyroiditis and psoriasis was taking Euthyrox (levothyroxine) and Nolpaza (pantoprazole, not available in US) Patient was considered screening failure on [redacted] due to elevated aspartate aminotransferase (AST) of 134U/L (normal range: 5 to 34U/L), alanine aminotransaminase (ALT) of 68 U/L (normal range: 0 to 55U/L), and blood lactate dehydrogenase (LDH) of 359U/L (normal range: 125 to 220U/L). She reported no alcohol and tobacco use within the past 6 months. The Principal Investigator attributed these laboratory abnormalities to a high-protein and fat diet. The laboratory values returned to normal limits in [redacted] (date not specified).

The patient was enrolled in the study on [redacted] and received bimekizumab 320 mg Q4W from [redacted] until [redacted] (16 weeks) and switched to BKZ 320 mg Q8W. The final dose of the study drug was taken on [redacted] and the final visit (Withdrawal Visit) was on [redacted].

The AEs reported during the trial, are summarized in chronological order.

- [redacted]: The patients reported a nonserious adverse event (AE) of dyspepsia and abdominal pain. An ultrasound performed showed gall bladder wall thickness of 5 mm and no cholelithiasis. The patient was treated with ciprofloxacin and pantoprazole. In addition to Euthyrox and Nolpaza, the patient was started on Tribux Forte (trimebutine, not approved in US) and Scopolan (antispasmodic, not approved in US) on [redacted] and continued Tribux Forte and Scopolan (hyoscine/metamizole, not approved in US) until [redacted] and [redacted], respectively. The details of concomitant medications patients took prior to developing elevated liver enzymes are as follows:
  - Euthyrox (75 mg tablet): Patient was taking one tablet a day for the indication of Hashimoto's disease.
  - Nolpaza (20 mg): Patient was taking Nolpaza, a PPI, twice daily for dyspepsia from [redacted] to unknown date in [redacted].
  - Tribux Forte (200 mg capsule): It contains trimebutine maleate as an ingredient in Poland; the drug is not approved in the United States. It is a parasympatholytic drug indicted for use in patients with IBS (spastic colon). Patient took the medication from [redacted] to [redacted]. A case report showed development of erythema multiforme and hepatitis during treatment with trimebutine.[4]
  - Scopolan (10 mg capsule): It contains hyoscine butylbromide and metamizole sodium monohydrate. Hyoscine butylbromide relieves contraction of smooth muscles and metamizole sodium monohydrate has strong analgesic and antipyretic effects. The drug is indicated for painful contractions of the gastrointestinal tract, biliary ducts and the urogenital system. Patient took Scopolan as needed from [redacted] to [redacted]

The symptoms resolved on [redacted]. The following tests were performed:

[4] Bacq Y *et al*. Erythème polymorphe grave et hépatite au cours d'un traitement par la trimébutine [Severe erythema multiforme and hepatitis during treatment with trimebutine]. Gastroenterol Clin Biol. 1989 May;13(5):522-3. French. PMID: 2753294.

- [redacted]: Liver functions tests (AST, ALT, GGT, and bilirubin) were reported normal.
- [redacted] CT scan abdomen reported normal.
- [redacted]: Abdominal ultrasounds reported

- [redacted]: Patient reported a nonserious AE of vomiting and received treatment with itopride and pantoprazole. The symptom resolved on [redacted]. The relationship of the study drug to the event was reported as related.

- [redacted]: Patients reported a SAE of increased hepatic enzymes approximately 190 days after study drug initiation. Patient also had abdominal pain, jaundice, pruritus, fevers of 39°C, and vomiting (which started 7 days before admission) and required admission to the hospital. The patient had received last dose of BKZ 21 days prior to onset of these symptoms.

  At admission ultrasound of the abdomen showed normal liver with no focal lesions, enlarged gall bladder (100 mm X 30 mm), no gall stones, and normal intra-hepatic biliary tracts and common bile duct. Pancreas and spleen were reported normal. The ultrasound findings were confirmed by CT cholangiography and any obstructive lesions in the biliary/pancreatic tracts were ruled out. Gastroscopy showed congested duodenal bulb with minor erosions, and erosive bulbitis and ampulla of Vater's was without any evidence of pathology (suggestive of no recent passage of stone through the papilla). Additional investigations conducted included CMV IgM (negative), CMV IgG (positive), stratified epithelium-specific-antinuclear antibodies (negative), and autoimmune hepatitis markers (negative; markers include ANA-HEP2:1/80 titer, staining pattern granular and microgranular cytoplasmic fluorescence), negative anti-mitochondrial antibodies, and positive antibodies to Ro52. During hospitalization, the patient received treatment with levothyroxine, sodium chloride, metronidazole, ciprofloxacin, ursodeoxycholic acid, tramadol, ondansetron, drotaverine, and metamizole.

  The Applicant was asked to provide additional information on testing performed to rule out the other potential causes of acute hepatitis. The Applicant stated that the hepatitis A, hepatitis B, and hepatitis C tests were negative; however, testing for hepatitis E, EBV and HSV infections were not performed (for details see Appendix-E).

- Patient was discharged from the hospital on [redacted] and withdrawn from the study. The liver enzymes peaked in next 6-7 days after admission and started trending down thereafter. The subsequent report dated [redacted] showed all liver enzymes within normal limits. However, the details of LFTs between [redacted] and [redacted] are not provided. As per the Investigator, the elevated liver enzymes were not a consequence of Cytomegalovirus infection/re-activation. Obesity with dietary mistakes were proposed as possible causes for the elevated liver enzymes.

The Applicant consulted a hepatologist who stated that the elevated liver enzymes were not related to the study drug and that the therapy with the study drug could be continued.

Summary of events and TEAEs including trending of liver enzymes are summarized in Table 6.

Table 6: Chronology of events and TEAEs (Patient PS0008 (b) (6))

Dates	Events	TEAEs Elevated LFTs					Applicant's comments
		ALT (0 to 55U/L)	AST (5 to 34U/L)	LDH (125 to 220U/L)	ALP (40-150 U/L)	S. bilirubin (0-20.5 µmol/L)	
(b) (6)	Screen failure	68	134	359	NA	NA	Laboratory abnormalities attributed to a high-protein and fat diet.
	Normalized	WNL	WNL	WNL	WNL		
	Started BKZ 320 mg Q4W	WNL	WNL	WNL	WNL	Completed 16 weeks of BKZ 320 mg Q4W treatment	
	Switched to BKZ 320 mg Q8W	WNL	WNL	WNL	WNL	WNL	
	Dyspepsia, abdominal pain. Resolved March 11, 2019)	WNL	WNL	WNL	WNL	WNL	Gallbladder was 5mm thick, no gall stones
	No symptoms	WNL	WNL	WNL	WNL	WNL	
	No symptoms	WNL	WNL	WNL	WNL	WNL	
	Vomiting, Resolved March 09, 2019.	NA	NA	NA	WNL	WNL	The relationship of the study drug to the event was reported as related.
	Abdominal pain, jaundice, pruritus, fevers of 39°C, and vomiting.	624	361	291	166	79	~ 190 days after study drug initiation. The relationship of the study drug to the event was reported as not related.
	-	792	474	223	134	76	
	-	824	425	207	131	63	
	-	597	267	164	133	33.5	
	-	270	106	NA	111	21	
	-	22	23	NA	NA	0.63	

AST: aspartate aminotransferase, ALT: alanine aminotransaminase, LDH: lactate dehydrogenase, ALP: alkaline phosphatase, NA: Not available.
WNL: Within normal limits.

Reviewer comments

The patient's clinical presentation while receiving BKZ included acute onset of symptoms of abdominal pain, fevers, jaundice, pruritis, disproportionately marked elevation of ALT, AST (x15 ULN) and bilirubin (x3.5 ULN) with mild increase in ALP; the biochemical parameters (R value ~11 and possible Hy's criteria of severe liver injury) are currently accepted liver damage markers (hepatocellular injury) in clinical trials and in post marketing studies. In addition, patient's clinical and laboratory tests are graded as moderately severe liver injury as per U.S. Drug-Induced Liver Injury Network (DILIN)[5] and FDA regulatory scientists[6] criteria for drug induced liver injury. It is noted that the ratio (R value) of ALT activity to ALP activity is expressed as multiples of ULN, based on the first set of laboratory tests and used to categorize the injury pattern of DILI as hepatocellular, cholestatic or mixed:

$$R = \frac{ALT/ULN}{ALP/ULN}$$

The following criteria are generally used to categorize liver injury:

- *If the R value ≤2, injury is categorized as Cholestatic Injury.*
- *If the R values >2, to ≤5 injury is categorized as Mixed Injury.*
- *If the R value ≥5, the injury is categorized as Hepatocellular injury.*

The possibility of underlying liver disease in this patient was considered in view of her morbid obesity (NASH) and possibility of alcoholic liver disease due to transient elevation of AST (134 IU) and ALT (68 IU) during earlier screening period (screen failure). It is important to note that AST/ALT ratio was ~2 which is suggestive of alcohol injury; however, prior history of alcohol use before enrollment was not specified and ultrasound and CT scan abdomen did not report steatosis. As the patient was stated to abstain from alcohol during the trial, markedly elevated ALT and AST compared to ALP reported on (b) (6) *are suggestive of non-alcoholic injury. The hepatocellular injury appears to be reversible as the acute rise of liver enzymes decreased gradually and returned to normal within 2 months after withdrawal of the BKZ and Tribux Forte.*

The etiology of acute hepatitis-like presentation is broad and includes medical conditions such as acute viral hepatitis, autoimmune hepatitis, cholangitis, cholecystitis, alcoholic hepatitis, Wilson disease and nonalcoholic steatohepatitis (NASH). These medical conditions may mimic DILI. Rare causes of hepatocellular liver injuries caused by Epstein-Barr virus (more commonly in young patients), cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus infections are often more common typically in immuno-suppressed individuals. Additionally, acute onset of symptoms and elevated liver enzymes, as observed in this patient, are also key presentation of patients with acute cholangitis and acute cholecystitis, however the reports of ultrasound and MRCP did not show evidence of biliary stones/obstruction or intra-hepatic biliary dilatation. Most of the tests for causes of acute liver cell injury such as hepatitis A, hepatitis B, hepatitis C, CMV, and autoimmune hepatitis were negative including anti-

[5] Fontana R J et al. Standardization of nomenclature and causality assessment in drug-induced liver injury: summary of a clinical research workshop. Hepatology. 2010 August; 52(2): 730–742.
[6] Avigan M et al. perspectives on the regulatory and clinical science of drug-induced liver injury (DILI). Drig induced liver toxicity pp 367-393.

mitochondrial antibodies. However, the Applicant did not perform tests for hepatitis E, HSV, and EBV infections. (for details see Appendix-E).

Occurrence of Hy's law in one patient is concerning however interpretation based on an isolated case has limitations. In view of the negative testing for the most common causes of acute hepatitis and ongoing concomitant medication (Tribux Forte) at the time of acute liver injury the role of BKZ alone or in combination with Tribux Forte cannot be ruled out as a potential cause for liver injury and the likelihood of BKZ causing DILI appears probable. This reviewer does not agree with the Applicant's justification that the liver injury in this patient was caused by obesity and "dietary mistakes."

Additional analyses on the incidence of elevation of liver enzymes (hepatic injury) in other patients enrolled in the clinical program are being performed by the DHN's DILI team.

6. Recommendations

The labeling changes and post-marketing studies recommended are as follows:

A: Labeling changes

The following changes were discussed with the primary review the final labeling changes are described (the additions are double-underlined and deleted text is striked out):

5.4 Inflammatory Bowel Disease

Cases of inflammatory bowel disease (IBD) have been reported in patients treated with IL-17 inhibitors, including BIMZELX. (b) (6) *see Adverse Reactions (6.1)]*. BIMZELX is not recommended in patients with active IBD. (b) (6) During BIMZELX treatment, monitor patients for signs and symptoms of IBD and discontinue treatment if worsening of signs and symptoms occurs. (b) (6)

6.1 Clinical Trials Experience

Specific Adverse Drug 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 1789 subjects exposed to BIMZELX accounting for 1830 patient-years, new onset of ulcerative colitis (UC) was reported in one subject (0.05 per 100 patient-years) and resulted in discontinuation of therapy. (b) (6) In clinical development programs for other indications, new cases of Crohn's disease (CD) and UC, some serious, and

exacerbations of pre-existing CD and UC, were reported with BIMZELX use. (b) (6)

Reviewer's comments: *The following considerations were discussed with the DDD clinical team.*

In section 5.4, avoid the term (b) (6) *and instead provide more specific guidance to physicians.*

In section 6, the applicant's proposal to (b) (6)

Therefore, we recommended DDD consider whether it would be possible to accurately compare the event rate for IBD in bimekizumab treated patients against that for the active control(s) and placebo, presenting each group's exposure adjusted incidence rate separately. We acknowledge DDD's concerns with including information on the active control arms within the prescribing information including avoidance of comparative safety claims, and lack of bridging between US and EU sourced comparator products. In that case, we recommend reporting the event rate in bimekizumab treated patients only (b) (4) . (b) (6) .

B: Post-marketing requirement/commitment

1. To gain more information on the extent of risk of developing IBD while on BKZ treatment we recommend DDD consider evaluation of persistent diarrhea and of any reported new cases of CD or UC within the planned post-marketing longer term safety study(ies). In order to improve the interpretability of the results, the protocol should specify a plan for evaluation of patients who experience persistent diarrhea associated with bimekizumab treatment (which should include a full evaluation including colonoscopy, in situations where diarrhea persists and an alternate etiology is not identified).

Appendix-A: Summary of safety studies in patients with inflammatory bowel disease treated with IL-17 inhibitors

- ***Bimekizumab (IL-17A and IL-17F antagonist)***

In a phase 2a proof-of-concept study (Study No. UC0011[7]) the Applicant evaluated BKZ (560 mg IV loading dose followed by 420 mg SC administration every 3 weeks) in patients with moderately to severely active UC. The study was terminated early based on an imbalance in treatment emergent adverse events (TEAEs) and serious adverse events (SAEs) between BKZ and placebo treatment groups. Additionally, there was an increase in clinical symptoms of UC, and C reactive protein (CRP) elevations in the BKZ arm. The Applicant states that "the observed increase in clinical symptoms suggestive of UC was not reflected in similar changes in the objective measures of disease activity (i.e., total Mayo scores), including endoscopy assessments." However, the number of patients who had endoscopy (N=18), was too small to enable definitive conclusions.

- ***Secukinumab* (IL-17A antagonist)**

The study by Hueber *et al.*[8] evaluated safety and efficacy of secukinumab in 59 patients with moderate to severe CD; patients were randomized in a ratio of 2:1 to receive either secukinumab given at a dose of 10 mg/kg or placebo administered as 2 h intravenous infusions on Days 1 and 22. The primary efficacy endpoint was the effect of secukinumab on mean CD activity index (CDAI) scores at Week 6. Safety assessments were up to 18 weeks. The results showed a higher proportion of patients in the secukinumab group, compared to the placebo group, who discontinued treatment prematurely due to insufficient therapeutic effect (21% and 10 % respectively). Higher rates of SAEs (17% and 3%, respectively) as well as infections (44% and 0%, respectively) were also reported to occur in those treated with secukinumab as compared to placebo. However, there were some limitations that precluded drawing definitive conclusions from this study, including imbalance in baseline characteristics and small sample size. A higher proportion of patients randomized to secukinumab group, compared to the placebo group, had severe disease at baseline, longer duration of active disease (12.2 years vs 10.3 years, respectively), previous bowel surgery (48.7% vs 15.0%, respectively), previous TNF antagonist therapy exposure (17.9% vs 0.0%, respectively), and prior antibiotic use (17.9% vs 5.0%, respectively). Note that patients received a higher dose of secukinumab (10 mg/kg) than that approved (300 mg) for psoriasis and psoriatic arthritis (PsA).

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[7] Source: BLA 761151, Section 5.3.5.4.
[8] Hueber W, Sands BE, Lewitzky S, *et al*. Secukinumab, a human anti-IL-17A monoclonal antibody, for moderate to severe Crohn's disease: unexpected results of a randomized, double-blind placebo-controlled trial. Gut. 2012;61: 1693–700.

- ***Brodalumab* (IL-17A receptor antagonist)**

Based on a failed study (Hueber *et al.*[8]) of secukinumab that inhibits only IL-17A, Targan *et al.*[9] investigated whether targeting IL-17RA receptor, that blocks the biologic activity of multiple IL-17 cytokines including IL-17A, IL-17F, and IL-17A/F heterodimer, would be effective in CD. The authors conducted a randomized, double-blind, placebo-controlled phase 2 study to evaluate the safety and efficacy of IL-17RA monoclonal antibody brodalumab in patients with moderate-to-severe active CD. Patients were randomized to receive brodalumab (210, 350, or 700 mg at baseline and week 4) or placebo. The primary endpoint was proportion of patients achieving CDAI remission (≤150) at Week 6. The study was terminated early after130 of the initially planned 216 patients were enrolled. The reasons for early termination included an imbalance between arms in patients experiencing worsening of CD (patients treated with brodalumab experienced more CD related AEs and had higher CRP concentrations as compared to the placebo treated patients). It is noted that clinical response to brodalumab in patients with PsA and psoriasis could be achieved with doses as low as 140 mg Q2W; this suggests that inability to effectively block IL-17RA was not the explanation for lack of efficacy in patients with CD who received much higher doses in this trial.

[9] Targan SR, Feagan B, Vermeire S, et al. A randomized, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. Am J Gastroenterol. 2016; 111:1599–607.

Appendix-B: Summary of studies supporting safety in patients with psoriasis treated with IL-17 inhibitors

- ***Secukinumab***

Long term safety of secukinumab was first reported by Van de Kerkhof *et al*.[10]. The authors analyzed pooled data (N=3993) from four phase 2 and six phase 3 randomized, double blind studies investigating use of secukinumab for moderate-to-severe PSO for 52 weeks. The exposure-adjusted incidence rate (EAIR) per 100 subject years (SYs) of IBD in the secukinumab arm (n = 3430) was low (0.33) and comparable to that of the etanercept arm (0.34); EAIR of CD and UC in patients receiving secukinumab (n = 3430) was low at 0.11 and 0.15, respectively, per 100 SYs. Two of the 3 reported cases of CD were exacerbations of previously diagnosed CD and third case had a history suggestive of undiagnosed CD. Two of the 4 UC reported cases had a history of diagnosed disease. No clinically meaningful difference in the incidence of CD and UC was observed across treatment groups during the 52-week period. No IBD case was reported in the placebo group (N=793) over a period of 12 weeks. The authors concluded that secukinumab therapy is unlikely to be related to the exacerbation and occurrence of IBD; however, the incidence rate observed requires further investigation based on the extended time of treatment exposure.

Schreiber *et al*.[11] reported incidence rates of IBD in patients with psoriasis, PsA and ankylosing spondylitis treated with secukinumab in a retrospective analysis of pooled data from 21 clinical trials. Patients with psoriasis (n=5181) followed for up to 5 years showed 14 cases of UC, 5 cases of CD and 1 case of IBD unclassified (IBDU), with EAIRs of 0.13, 0.05 and 0.01, respectively. Of these 20 cases, 14 were new-onset IBD cases.

- ***Ixekizumab***

Gordon *et al*.[12] reported 60-week efficacy and safety data based on approximately 3800 patients who were enrolled in three phase3 clinical trials (UNCOVER-1, UNCOVER-2, and UNCOVER-3) for the use of ixekizumab in patients with moderate-to-severe PSO. UC was reported in seven patients and CD in four patients. Three patients who received placebo during the randomized withdrawal period, after they had received ixekizumab during the induction period, reported CD at Days 23, 70, and 134. The authors concluded that further evaluation is needed to understand the relationship between IL-17 inhibitors and IBD.

- ***Brodalumab***

Section 5.5 of the SILIQ (brodalumab) labeling states that CD occurred in one patient during treatment with SILIQ and led to discontinuation of therapy in patients with psoriasis[13]. It is also stated that SILIQ is contraindicated in patients with CD and the drug should be discontinued if

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[10] Van de Kerkhof *et al*. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol. 2016; 75:83–98.e4.
[11] Schreiber S, Colombel JF, Feagan BG, *et al*. Incidence rates of inflammatory bowel disease in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis treated with secukinumab: a retrospective analysis of pooled data from 21 clinical trials. Annals of the rheumatic diseases. 2019; 78(4):473-9.
[12] Gordon KB, Blauvelt A, Papp KA, *et al*. Phase 3 trials of ixekizumab in moderate-to-severe plaque psoriasis. N Engl J Med. 2016; 375:345–56.
[13] https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761032lbl.pdf.

the patient develops CD while taking SILIQ. The psoriasis trials excluded patients with active CD.

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Appendix-C: Key labeling information for IBD included in the approved IL-17 inhibitors

- **Secukinumab (COSENTYX)**

Secukinumab is approved in adult patients for the treatment of moderate to severe PSO who are candidates for systemic therapy or phototherapy, active psoriatic arthritis (PsA), active ankylosing spondylitis (AS), and active non-radiographic axial spondyloarthritis (nr-axSpA) with objective signs of inflammation.

The following is stated in Section 5.3 (Inflammatory Bowel Disease), under Heading 5 (Warnings and Precautions):

> Caution should be used when prescribing COSENTYX to patients with inflammatory bowel disease. Exacerbations, in some cases serious, occurred in COSENTYX treated patients during clinical trials in PSO, psoriatic arthritis and ankylosing spondylitis. In addition, new onset inflammatory bowel disease cases occurred in clinical trials with COSENTYX. In an exploratory study in 59 patients with active CD, there were trends toward greater disease activity and increased adverse events in the secukinumab group as compared to the placebo group. Patients who are treated with COSENTYX should be monitored for signs and symptoms of inflammatory bowel disease *[see Adverse Reactions (6.1)]*.

- **Ixekizumab (TALTZ)**

Ixekizumab is approved in adult patients for the treatment of moderate to severe PSO patients who are candidates for systemic therapy or phototherapy, active psoriatic arthritis (PsA) and active ankylosing spondylitis (AS) and for the treatment of moderate to PSO in patients aged 6 years or older who are candidates for systemic therapy or phototherapy.

The following is stated in Section 5.4 (Inflammatory Bowel Disease), under Heading 5 (Warnings and Precautions) of the approved labeling:

> Patients treated with TALTZ may be at increased risk of inflammatory bowel disease. In clinical trials, Crohn's disease and ulcerative colitis, including exacerbations, occurred at a greater frequency in the TALTZ group than the placebo control group [see Adverse Reactions (6.1)]. During TALTZ treatment, monitor for onset or exacerbation of inflammatory bowel disease and if IBD occurs, discontinue TALTZ and initiate appropriate medical management.

- **Brodalumab (SILIQ)**

Brodalumab (SILIQ) is approved in adult patients with moderate to severe PSO who are candidates for systemic therapy or phototherapy and have failed to respond or have lost response to other systemic therapies.

The following is stated in Section 5.5 (Crohn's Disease), under Heading 5 (Warnings and Precautions) of the approved labeling:

> In psoriasis trials which excluded subjects with active CD, CD occurred in one subject during treatment with SILIQ and led to discontinuation of therapy. In other trials, exacerbation of CD was observed with SILIQ use.
> SILIQ is contraindicated in patients with CD.
> Discontinue SILIQ if patient develops CD while taking SILIQ.

Appendix-D: Reports of IBD for other indications

Summary of cases of new onset and exacerbation of IBD (CD and UC) reported in the completed and ongoing clinical trials for other indications is provided.

Following is the list of completed and ongoing studies:

- *Completed studies:*
  - Phase 1 study for psoriatic arthritis (PsA): PA0007
  - Phase 2 study for hidradenitis suppurativa (HS): Study HS0001
  - Phase 2a studies for rheumatoid arthritis (RA): RA0123
  - Phase 2 a study in ulcerative colitis: UC0011
  - Phase 2b studies for PA and axial spondylitis (AS): PA0008 and AS0008
  - Phase 2a study: AS0013

- *Ongoing studies:*
  - Phase 2b studies: PA0009 and AS0009
  - Phase 3 studies: PA0010, PA0011, PA0012, AS0010, AS0011, AS0014, HS0003, and HS0004

As per the Applicant the reports of new onset and exacerbation of IBD (CD, UC, or IBDU were reported for AS (Studies AS0008, AS0009, and AS0011), PsA (Study PA0010) and UC (Study UC0011) clinical programs. The TEAEs in these programs are summarized based on the indication. [redacted] (b) (4).

Axial spondylitis:
Overall, approximately 13 patients reported new onset/flare of IBD (CD/UC) during the Phase 2 and Phase 3 AS studies (Table I and Table II). Summary of these patients is provided:

- *Study AS0008 (completed):* Three patients reported new onset of moderate to severe IBD (CD=2, and UC=1) and one patient reported UC flare while on the 160 mg/320 mg BKZ dose. The onset of symptoms from the 1st dose of IMP ranged from 39 days to 396 days. Study drug was discontinued in 1 of the CD patients. Dose was not changed in 2 patients (one each with CD and UC), treatment with mesalazine and/or budesonide was added, and patients were rolled over to Study AS0009. One of these 2 patients reported UC flare and drug was discontinued.

- *Study AS0009 (ongoing):* Four patients reported new onset of moderate to severe IBD (CD=2, UC=1, and IBDU=1) and one patient reported UC flare while on the 160 mg Q4W BKZ dose. The onset of symptoms ranged from 351 days to 1111 days (after the 1st dose in the feeder study (Study AS0008). Study drug was discontinued in 3 patients; one patient each with new onset of CD and UC and one patient with UC flare. One patient's symptoms resolved with sulphasalazine treatment while continuing with BKZ dosing; patient reported CD flare one year later when the BKZ was discontinued. In patient with IBDU, the symptoms resolved with mesalazine treatment, while continuing treatment with BKZ.

- *Study AS0013 (completed):* None of the 51 patients that received 48-week BKZ treatment, reported new IBD cases; 1 patient with history of IBD completed the study uneventfully.

- *Study AS0011 (ongoing):* In this ongoing Phase 3 placebo-controlled study, 3 patients reported moderately severe IBD; 2 patients reported new onset of IBD (CD=1, and UC=1) and one patient flare of CD. The onset of the IBD symptoms were 8 days to 221 days from the 1st dose of IMP. The IMP was withdrawn in all 3 patients. Patients symptoms resolved with sulfasalazine, methylprednisone treatment in 2 patients and not resolved in 1 patient. It is noted that the treatment allocation is currently blinded.

Psoriatic Arthritis:
One patient reported flare of UC during PsA studies (Table II).

- *Studies PA0008 (completed) and PA 0009 (ongoing):* None of the patients reported IBD event.

- *Study PA0010 (ongoing):* One patient in the study reported moderately severe flare of UC 221 days after the 1st dose of IMP. Patients was treated with Salofalk suppository and BKZ dose was not changed. The symptoms were reported as not resolved.

Ulcerative colitis (UC):
Study UC0011: Four patients reported worsening of UC (Table III). This was a Phase 2a study that evaluated efficacy and safety of BKZ (intravenous loading dose 560 mg followed by subcutaneous 420 mg dose every 3 weeks) in patients with moderately to severely active UC. The study was discontinued based on unblinded data review by the Data Monitoring Committee (DMC) that showed an imbalance in TEAEs and SAEs in the active treatment group, and absence of evidence of benefit of BKZ in this population. It is noted that the dose for the other inflammatory medical conditions such psoriasis, AS, PsA is much less compared to UC. For additional details see Section 2.1 above. (b) (4)

Table-I: Reports of IBD in study participants receiving BKZ in Studies AS0008 and AS0009

Study participant ID/Dose of BKZ	Age/ Gender	Relevant GI medical history	Relevant Concomitant medication	Event	Severity/ Reported causality/ Seriousness/	Onset in days (from 1st dose of IMP)	Action taken/Course of disease/Mitigation strategy
AS0008-(b) (6) (b) (6) 64mg/320mg	31/M	None	Diclofenac	New diagnosis CD	Moderate, not related. SAE	266 days	Dose not changed, treated with mesalazine, budesonide with good response. Rolled over to AS0009. No further flare.
AS0008-(b) (6) (b) (6) 16mg/320mg	25/M	Hemorrhoids; blood in stools 31 day prior to 1st dose	Diclofenac	New diagnosis UC	Moderate, not related, NS	39 days	Dose not changed, treated with mesalazine with good response. Rolled over to AS0009.
				UC flare (during AS0009).	Severe; not related, SAE	396 days	UC flare during AS0009 and IMP was withdrawn. Gastroenterologist follow up. Mesalazine dose increased and UC flare resolving.
AS0008-(b) (6) (b) (6) 16mg/160mg	33/M	None	Unknown	New diagnosis CD	Moderate, not related, NS	345 days (65 days after last dose)	IMP temp discontinued after 194 days due to abdominal pain, hematochezia and anal fissure. IBD excluded at that time by gastroenterologist and IMP resumed. Study participant subsequently withdrew consent (to father a child) and new onset UC was later diagnosed in post follow up period.
AS0008-(b) (6) (b) (6) 16mg/320mg	53/M/	UC	Ultracet, methylprednisolone, mesalazine	UC flare	Mild, not related NS	163 days	Dose not changed, treated with mesalazine. Event reported as resolved with treatment. Rolled over to AS0009
AS0009-(b) (6) (b) (6) 160mg Q4W	37/F	None	Diclofenac, desogestrel & ethinyl estradiol	New diagnosis of CD following SAE of perianal abscess.	Moderate, not related. SAE	351 days (after 1st dose in feeder study)	IMP withdrawn. Gastroenterologist started patient on Adalimumab 40 mg for CD. Surgical treatment was provided (Abscess revision, excision, abscess evaluation and tamponade).
AS0009-(b) (6) (b) (6) 160mg Q4W	33/F	None	Diclofenac sodium	IBDU (described as chronic colitis)	Moderate, not related/NS	527 days (after 1st dose in feeder study)	Dose unchanged. Resolved under mesalazine treatment.
AS0009-(b) (6) (b) (6) 160mg Q4W	35/M	None	Meloxicam	New diagnosis CD during AS0009	Moderate, not related/NS	757 days (after 1st dose in feeder study)	Dose unchanged. Treated with sulphasalazine. Resolved
				CD flare (1 year later)	Severe, not related SAE	1022 days (after 1st dose in feeder study)	IMP temp discontinued. Not resolved. Poor compliance with prior IBD medication reviewed and need for compliance reiterated.
AS0009-(b) (6) (b) (6) 160mg Q4W	57/F	UC	Ultracet, methylprednisolone, sulfasalazine,meloxicam	UC flare	Moderate, not related/NS	941 days (after 1st dose in feeder study)	IMP temp discontinued. Had proctocolectomy /ileostomy. Resolved with sequelae. Study participant had arbitrarily withdrawn IBD medication prior to event.
AS0009-(b) (6) (b) (6) 160mg Q4W	38/M	Gastritis/reflux/gastroenteritis/haemorrhoids	Meloxicam	New diagnosis UC	Mild, not related /NS	1111 days (after 1st dose in feeder study)	IMP temp discontinued. Treated with mesalazine. Resolving.

BKZ=bimekizumab; CD= Crohn's disease; IBDU =inflammatory bowel disease unclassified; M=male F=female; NS=nonserious; SAE=serious TEAE; IMP=investigational medicinal product; UC=ulcerative colitis

Dosing: Study participants in AS0008 in Table 5-1 received either BKZ 16mg, 64mg, 160mg, or 320mg Q4W/sc injection up to week 12. At Week 12, 16 or 64 mg study participants were re-randomized to either BKZ 160 mg or 320mg Q4W/sc injection. All study participants in Table 5-1 enrolled in AS0009 received BKZ 160mg Q4W/sc injection

Source: Table 5.1 of the Applicant responses to FDA information Request dated October 30, 2020.

Table II: Reports of IBD in blinded-treatment study participants in ongoing Studies PA0010 and AS0011

Study participant ID	Age/ Gender	Relevant GI medical history	Relevant Concomitant medication	Event	Severity/ Reported causality/ Seriousness/	Onset in days (from 1st dose of IMP)	Action taken/Course of disease/Mitigation strategy
PA0010 – (b) (6)	37/M	UC	Mesalazine	UC flare	Moderate/related/ NS	221 days	Dose not changed. Not resolved. Treated with Salofalk suppository.
AS0011- (b) (6)	58/F	CD, gastric bypass	Naproxen	CD flare	Moderate/related NS	221 days	IMP withdrawn. Treated with ciprofloxacin and Spamomem. Not resolved.
AS0011- (b) (6)	35/M	None	Diclofenac	New onset UC	Severe/related/SAE	49 days	IMP withdrawn. Treatment with loperamide, sulfasalasyn, methylprednisolone, mesalazine, Resolved with sequelae (dilute stool)
AS0011- (b) (6) (b) (6)	45/M	None	Etoricoxib	New Onset CD	Moderate/related/ SAE	8 days	IMP withdrawn. Treated with prednisone. Resolved with sequelae

BKZ=bimekizumab; CD= Crohn's disease; M=male; F=female; NS=nonserious; SAE=serious TEAE; IMP=investigational medicinal product; UC=ulcerative colitis
Dosing: Study participants in PA0010 receive bimekizumab/160mg Q4W sc injection or placebo or Adalimumab 40mg Q2W/sc injection. Study participants in AS0011 receive bimekizumab or PBO/160mg Q4W/ sc injection.

Source: Table 5.2 of the Applicant responses to FDA information Request dated October 30, 2020.

Table III: Reports of IBD in study participants with moderate to severe active UC in Study UC0011

Study participant ID	Age/Gender	Event	Maximum Severity/ Reported causality/ Seriousness	Onset in days (from 1st dose of IMP)	Action taken/Course of disease/Mitigation strategy
UC0011– (b) (6) (b) (6)	18/F	Worsening UC (3 events)	Moderate/not related/SAE/NS/SAE	23 days/73 days/109 days	Dose not changed/Resolved/Study stopped prematurely
UC0011- (b) (6)	33/M	Worsening UC	Severe/not related/SAE	43 days	Dose not changed/Resolved/ Study stopped prematurely
UC0011 - (b) (6)	48/M	Worsening UC (3 events)	Severe/related/NS	8 days/20 days/48 days	IMP withdrawn/Resolved/ Study stopped prematurely
UC0011 - (b) (6)	22/M	Worsening UC	Moderate/not related/NS	62 days	Dose not changed/Resolved/ Study stopped prematurely

BKZ=bimekizumab; M=male F=female; NS=nonserious; SAE=serious TEAE; IMP=investigational medicinal product; UC=ulcerative colitis
Dosing: All study participants in Table 5-3 received 560mg loading dose iv infusion (Day 1) then 420mg bimekizumab sc at Day 22 and Day 43.

Source: Table 5.3 of the Applicant responses to FDA information Request dated October 30, 2020.

Appendix-E: The status of tests evaluated in Patient PS0008/ (b) (6)

1. Hepatitis A: Ruled out
2. Hepatitis B: Ruled out
3. Hepatitis C: Ruled out
4. Hepatitis E: Not performed
5. EBV acute infection: Not performed
6. HSV acute infection: Not performed
7. CMV acute infection: Ruled out
8. Biliary obstruction: Ruled out
9. Autoimmune hepatitis: Ruled out
10. Alcoholic hepatitis: Unlikely based on clinical presentation.
11. Sepsis: Unlikely based on clinical presentation
12. Ischemic hepatitis: Unlikely based on clinical presentation
13. Sinusoidal obstruction syndrome: There is no mentioning of sinusoidal obstruction syndrome in the report of the liver US or MRI.
14. Wilson disease: The Applicant stated that the study participant did not have a history of Wilson Disease.
15. Hemochromatosis: No information was provided related to presence of hemochromatosis; however normal iron levels were reported
16. Alpha-1 antitrypsin deficiency: The Applicant stated that the study participant did not have a history of Alpha-1 antitrypsin deficiency
17. Primary biliary cholangitis: Ruled out by MRCP
18. Hepatic steatosis: There is no mention of hepatic steatosis on ultrasound and MRI reports.

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/

ANIL K NAYYAR
03/22/2021 03:19:28 PM

TARA A ALTEPETER
03/22/2021 03:30:20 PM

JESSICA J LEE
03/22/2021 03:33:23 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	3/17/2021		
To:	Anh-Thy Ly (CDER/OPQ/OPRO/DRBPMI/RBPMB1)		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	CDER/OII/DDD
From	Matthew Ondeck OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, MS, Acting Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Rumi Young, MS, Acting Assistant Director OPEQ/OHT3/DHT3C		
Subject	BLA 761151, bimekizumab ICC2000619 Case #00023177 (Premarket) & #00023181 (Facilities/QS)		
Recommendation	**Filing Recommendation Date: 8/6/2020** Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter.		
	Mid-Cycle Recommendation Date: 10/20/2020 CDRH has no deficiencies to be communicated to the Sponsor at this time. CDRH recommends that a Pre-Approval Inspection (PAI) be completed at UCB Pharma SA, FEI# 3003909356. This recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection is not mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. This was communicated at the November 30, 2020, Mid-cycle meeting. See Section 5.2 for full discussion.		
	Final Recommendation Date: 3/17/2021 CDRH recommends 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. See Section for the Executive Summary.		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Matthew Ondeck -S Digitally signed by Matthew Ondeck -S Date: 2021.03.17 13:04:13 -04'00'		Rumi Young -S Digitally signed by Rumi Young -S Date: 2021.03.18 15:00:33 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	BLA 761151
Sponsor	UCB, Inc.
Drug/Biologic	bimekizumab
Indications for Use	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Device Constituent	Prefilled Syringe and Auto-Injector
Related Files	IND 128707 – Meeting Request Reviews

Review Team		
Lead Device Reviewer	Matthew Ondeck	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**
N/A*	N/A*	N/A*

* No additional CDRH consults necessary for this review

Important Dates	Due Date
Receipt Date	7/15/2020
Filing Date	9/11/2020
CMC Alignment Meeting	11/2/2020
Midcycle Date	12/11/2020
Final Lead Device Review Memo Due	5/10/2021
Action Date	7/15/2021

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends 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.

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. Of note the drug facilities team also requested a Pre-Approval Inspection.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

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3. PURPOSE/BACKGROUND

3.1.Scope

UCB, Inc. has submitted BLA 761151 for review of bimekizumab injection. The device constituents of the combination product is a prefilled syringe (PFS) and autoinjector (AI).

CDER/OPQ has requested the following consults for review of the device constituent of the combination product:

- Case #00023177 (Premarket – Review of PFS and AI devices)
- Case #00023181 (Facilities/QS – Review of Facilities and Quality Systems Information)

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product; however, The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2.Prior Interactions

The Sponsor had submitted previous meeting requests under IND 128707, where CDRH issued comments regarding device information that should be included to support a BLA submission.

3.3.Indications for Use

Combination Product	Indications for Use
bimekizumab injection	Treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy
Pre-Filled Syringe and Autoinjector	Delivery of the Drug Product

3.4.Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**
device-reviewers-guide	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\12-cover-letters
cover-initial-bla	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\12-cover-letters
drug-product-container-closure-system-maa	\\CDSESUB1\evsprod\BLA761151\0001\m2\23-qos
356h	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\11-forms
description-and-composition-dp-maa-ss-1ml	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p1-desc-comp
description-and-composition-dp-maa-ai-1ml	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p1-desc-comp
description-and-composition-pfs-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p1-desc-comp
pharmaceutical-development-container-closure-ss-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p2-pharm-dev
pharmaceutical-development-container-closure-ai-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p2-pharm-dev
pharmaceutical-development-container-closure-pfs-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p2-pharm-dev
md-q-101725	\\CDSESUB1\evsprod\BLA761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5354-other-stud-rep\md-q-101725
md-q-101724	\\CDSESUB1\evsprod\BLA761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5354-other-stud-rep\md-q-101724
ifu_pfs_202008-sub	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\114-labeling\draft\labeling
ifu_ai_202008-sub	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\114-labeling\draft\labeling
medguide-202008-sub	\\CDSESUB1\evsprod\BLA761151\0001\m1\us\114-labeling\draft\labeling
ir5-response-1-25sep20	\\CDSESUB1\evsprod\BLA761151\0012\m1\us\111-information-amendment
ir5-response-2-25sep20	\\CDSESUB1\evsprod\BLA761151\0012\m1\us\111-information-amendment
ir5-response-3-25sep20	\\CDSESUB1\evsprod\BLA761151\0012\m1\us\111-information-amendment
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specifications-pfs-1ml-bla-us	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p5-contr-drug-prod\32p51-spec
specifications-ai-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p5-contr-drug-prod\32p51-spec
control-critical-steps-ai-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
control-critical-steps-pfs-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
control-critical-steps-ss-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
manuf-process-and-controls-ai-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
manuf-process-and-controls-ss-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
process-validation-ai-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
process-validation-ss-1ml-maa	\\CDSESUB1\evsprod\BLA761151\0001\m3\32-body-data\32p-drug-prod\bimekizumab-sol-inj-common\32p3-manuf
Dv0002-body-text-1ml	\\CDSESUB1\evsprod\BLA761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5352-stud-rep-uncontr\dv0002
Dv0006-body-text-1ml	\\CDSESUB1\evsprod\BLA761151\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\pso\5352-stud-rep-uncontr\dv0006
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us21030140us-fda-response-1-11mar21	\\CDSESUB1\evsprod\BLA761151\0044\m1\us\111-information-amendment

4. DEVICE DESCRIPTION

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

- Safety Syringe (SS - PFS); i.e. accessorized PFS
- Autoinjector (AI)

The original "container closure" for the device is a prefilled and prestaked prefilled syringe, intended to deliver 1 mL of bimekizuab 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 (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) needle cover and a (b) (4) rigid shield. Figure 1–1 provides a simplified overview of the primary packaging components.

Figure 1–1: Overview of glass syringe barrel with staked needle and plunger stopper

Table 1–1: Materials of construction of the primary packaging

Component	Description	Supplier
1mL long syringe	Glass barrel: (b) (6) glass with staked stainless steel, 27G ½" special thin wall needle	(b) (4)
Plunger stopper	(b) (6) rubber	
Rigid needle shield (RNS)	Needle shield: (b) (6) (b) (6) Rigid shield: (b) (6)	

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.*

Reviewer Note:
The sponsor clarifies that primary container/PFS components are the only which have fluid contact or are fluid path contacting; therefore, this means that CDER CMC reviewers will address the potential for leachables/extractables of these materials into the drug product, which adequately addresses biocompatibility from CDRH assuming that this data is found to be adequate. Given this information, CDRH will only address biocompatibility of the SS and AI surface/skin contacting components.

The "container closure/PFS" described above is assembled with additional components into a safety syringe (SS-PFS) or autoinjector (AI), which are the final device presentations. See the device description for each device constituent below.

4.1. SS-PFS Description

The following regarding the device "container closure" is taken from docs:

- drug-product-container-closure-system-maa
- description-and-composition-dp-maa-ss-1ml
- pharmaceutical-development-container-closure-ss-1ml-maa

The bimekizumab-SS-1mL consists of the drug product in the PFS and the following device components which are shown in Figure 1–2.

- *Plunger rod*
- *Syringe unit*
- *Small round flange (SRF)* (b) (4)
- *Extended finger flange*
- *Overcap* (b) (4)

Reviewer Note:
It is noted that while the Sponsor speaks to a Prefilled syringe (PFS) and a Safety Syringe (SS), document: pharmaceutical-development-container-closure-pfs-1ml-maa, refers to the PFS as a standard PFS; i.e. a barrel, with plunger, and 27 G, 0.5 inch thin walled needle. The PFS is loaded into the safety syringe and is marketed and supplied to the user in this way.

The bimekizumab-SS-1mL is a customized version of the (b) (4) *safety syringe. The function of the safety syringe components is to protect the user from the needle following injection of the contents of the syringe. The safety syringe components do not have any fluid path and do not have any contact with the drug product contained within the pre-filled syringe. The bimekizumab-SS-1mL has a limited contact duration with intact skin.*

(b) (4)

Figure 1–1: Bimekizumab-SS-1mL before use

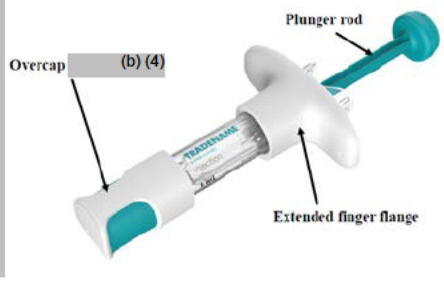
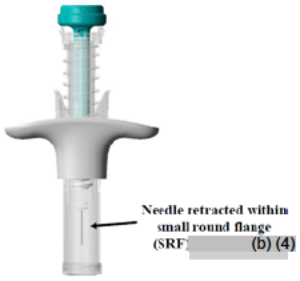


Figure 1–2: Bimekizumab-SS-1mL after use



The (b) (4) *are customized components designed to improve the handling of the safety syringe by the users. Table 1–2 provides an overview of the materials of construction for the bimekizumab-SS-1mL.*

Table 1–2: Materials of construction of the bimekizumab-SS-1mL

Device component	Materials of construction
Plunger rod	(b) (4)
SRF (b) (4)	
Extended finger flange	
Overcap (b) (4)	

The design and development activities for the bimekizumab-SS-1mL are a collaboration between [redacted] *and UCB.* [redacted] *is responsible for the manufacture and supply of the device components for the bimekizumab-SS-1mL. The pre-filled syringe is supplied by* [redacted] *drug product manufacturing site. The design verification testing was performed at* [redacted] *UCB is responsible for the assembly, release, and supply of the bimekizumab-SS-1mL. The qualification and validation of the assembly process was performed at UCB. Both* [redacted] *and UCB have quality systems in place in accordance with ISO 13485.*

The principles of operation and user steps are below:

The principles of operation of the bimekizumab-SS-1mL safety feature are as follows:

- *At the end of the injection, when the plunger rod is pushed to the end of the syringe, the passive safety feature is activated.*
- *When the plunger rod is released the needle is automatically retracted and locked within the small round flange* [redacted] *to prevent needle stick injury.*

The user follows the instructions for use to perform the injection, and the main steps are summarized below.

1. Setting up for your injection
   a) Ensure the bimekizumab-SS-1mL is at room temperature
   b) Inspect the bimekizumab-SS-1mL
2. Choose and prepare the injection site
3. Inject bimekizumab
   a) Remove the overcap [redacted]
   b) Gently pinch and hold a fold of skin with one hand, with the other hand insert the needle into your skin at about a 45° angle. Push the needle all the way in then gently let go of your skin.
   c) Firmly push the plunger rod all the way down until all the medicine is injected and you cannot push the plunger rod any more.
   d) Lift your thumb off the plunger rod, the needle will automatically move back and lock in place.
4. Dispose of the used bimekizumab-SS-1mL
5. To perform the second injection required for a 320mg dose repeat steps 1 to 4

Reviewer Note:
Based on the principle of operation, this functions identically to a typical PFS with a needle safety device (NSD).

Of note based on current best review practices performance of the PFS devices, only the NSD will require review for device performance (needle safety activation, lockout, preactivation/drop testing, etc.), within FDA Guidance: Medical Devices with Sharps Injury Prevention Features (https://www.fda.gov/media/71142/download) and ISO 23908.

4.2. AI Description

The following regarding the device "container closure" is taken from doc: drug-product-container-closure-system-maa AND description-and-composition-dp-maa-ai-1ml.

The bimekizumab-AI-1mL consists of the drug product in the PFS and the following bimekizumab-AI-1mL components which are shown in Figure 1–3.

- (b) (4)

The bimekizumab-AI-1mL is a customized version of the (b) (4) *1mL auto-injector. The function of the auto-injector components is to automate the injection and to protect the user from the needle following injection of the contents of the syringe. The auto-injector components do not have any fluid path and do not have any contact with the drug product contained within the pre-filled syringe. The bimekizumab-AI-1mL has a limited contact duration with intact skin.*

Figure 1–3: Overview of the bimekizumab-AI-1mL

(b) (4)

Figure 1–1: Bimekizumab-AI-1mL before use

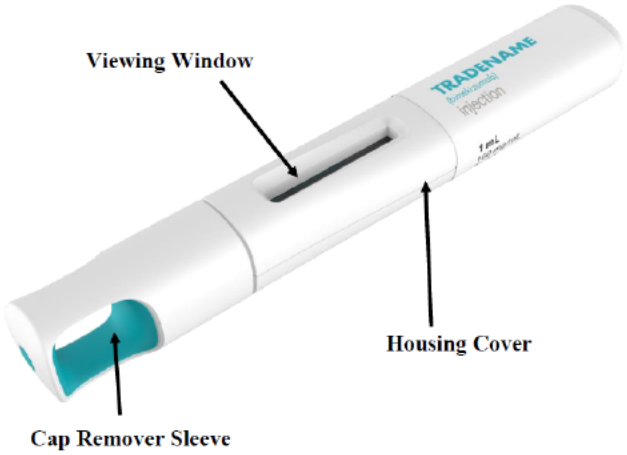
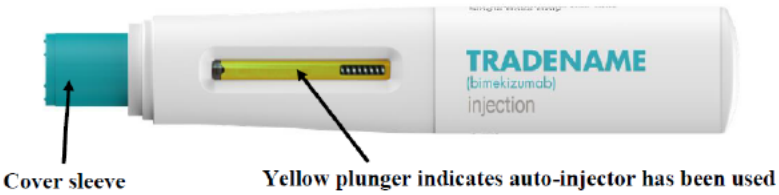


Figure 1–2: Bimekizumab-AI-1mL after use



There is a window to allow the user to inspect the drug appearance prior to injection and confirm the injection has been completed by checking the window is filled with the plunger rod. There is clear audible feedback at the start and end of the injection. The auto-injector conforms to ISO 23908 for the needle protection safety feature. The feature activates and locks to cover the needle

after the injection, once the bimekizumab-AI-1mL is released from the injection site.

The (b) (4) *are customized components designed to improve* (b) (4) *the auto-injector by the users. The syringe* (b) (4) *shipped to the bimekizumab-AI-1mL assembly site. Table 1–3 provides an overview of the materials of construction for the bimekizumab-AI-1mL.*

Table 1–3: Materials of construction of the bimekizumab-AI-1mL

Device component	Materials of construction
(b) (4)	

The principles of operation and user steps are below:

The principles of operation of the bimekizumab-AI-1mL are as follows:

- *Remove the cap remover sleeve which also removes the rigid needle shield from the prefilled syringe*
- *The pressure applied by the user when pressing the bimekizumab-AI-1mL against the skin retracts the cover sleeve into the device and moves the needle through the skin.*
- *The movement of the cover sleeve stops when the needle reaches the injection depth and the injection starts.*
- *The injection spring is released, a first audible click confirms the start of the injection, and the drug is expelled into the subcutaneous tissue.*
- *The travel of the plunger rod is visible through the viewing window.*
- *At the end of the injection, a second audible click confirms the plunger rod is fully depressed.*
- *When the bimekizumab-AI-1mL is removed from the skin the needle cover deploys automatically and locks into position to prevent needle stick injury.*

The user follows the instructions for use to perform the injection, and the main steps are summarized below.

1. Setting up for your injection
   a) Ensure the bimekizumab-AI-1mL is at room temperature
   b) Inspect the bimekizumab-AI-1mL
2. Choose and prepare the injection site
3. Inject bimekizumab
   a) Remove the cap remover sleeve
   b) Hold the bimekizumab-AI-1mL at a 90° angle to the injection site
   c) Place the bimekizumab-AI-1mL against the skin and firmly press down. You will hear a click sound.
   d) Keep holding the bimekizumab-AI-1mL pressed firmly against the skin. You will hear a second click within approximately 15 seconds after you hear the first click. The second click tells you the injection has finished. You should see the yellow color indicator filling the viewing window.
   e) Remove the bimekizumab-AI-1mL by carefully pulling the auto-injector straight up from your skin. The needle guard will automatically cover the needle.
4. Dispose of the used bimekizumab-AI-1mL
5. To perform the second injection required for a 320mg dose repeat steps 1 to 4

DEVICE DESCRIPTION REVIEW CONCLUSION
The device description is **ADEQUATE**

5. FILING REVIEW

CDRH performed a filing review and the content and results of the filing review can be found below.

5.1.Filing Review Checklist

Filing Review Checklist				
Description	**Present**			
	Yes	**No**	**N/A**	**Location/Notes**
Description of Device Constituent	X			• Seq0001.3.2.P.2 • Seq0001.3.2.P.7 • Seq0001.2.3
Device Constituent Labeling	X			Seq0001.14
Essential Performance Requirements (EPRs) defined by the application Sponsor	X			Seq0001.3.2.P.2 (EPRs referred to as Critical Quality Attributes)
Design Requirements Specifications included in the NDA / BLA by the application Sponsor	X			Seq0001.3.2.P.2 – container closure
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file.	X			Seq0001.3.2.P.2 – container closure
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X*		Seq0001.3.2.P.2 – container closure Risk management files are referenced but not provided. Will be necessary for the autoinjector device.

					*See Section 13.1 – IR to Sponsor – Resolved.
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X			Seq0001.3.2.P.2 – container closure
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X			• Seq0001.3.2.P.2 – container closure • Seq0001.3.2.P.5 Summary testing is provided.
	Engineering Performance	X			Seq0001.3.2.P.2 – container closure
	Biocompatibility/Chemistry	X			Seq0001.3.2.P.2 – container closure Biocompatibility is only referenced in this document. Full test reports need to be provided to determine if methods used are appropriate. See Section 13.1 – IR to Sponsor – Resolved.
	Sterility			X	Device components are not required to be sterile – Only container closure which the review of sterility is deferred to CDER.
	Shelf Life	X			Seq0001.3.2.P.2 – container closure
	Use Life			X	N/A – Single Use
	Transportation	X			Seq0001.3.2.P.3 – process validation ss & AI
	Clinical Validation	X			• Seq0001.3.2.P.2 – microbiology • Seq0001.3.2.R – HF clin summary
	Human Factors Validation	X			• Seq0001.3.2.P.2 – container closure • Seq0001.5.35.4 – pso Note - The review of this information is deferred to CDER/OSE/DMEPA
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X			• Seq0001.3.2.P.2 – container closure • Seq0001.3.2.P.3 – critical steps

	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	X			Seq0001.3.2R – quality systems
	CAPA Procedure	X			Seq0001.3.2R – quality systems
	Control Strategy provided for EPRs	X			Seq0001.3.2.P.2 – Manuf Process

Reviewer Comment
As of 8/6/2020, there is some information missing from the submission that will be necessary to conduct a full review; however, it is information that should be able to be provided from the Sponsor during the course of the review clock.

See Section 13.1 – IR to Sponsor. Note that these information requests were
Resolved during the course of the review.

5.2.Facilities Information

This review includes only the final finished device manufacturers. This excludes component manufacturers, device testing facilities, etc.

Upon review of the 356h form, the final finished device manufacturers (PFS and AI) is: **UCB Pharma SA**

Firm Name:	UCB Pharma SA
Address:	Chemin du Foriest Braine-l'Alleud, Belgium 1420
FEI:	3003909356
Responsibilities:	Storage of master and working cell banks; manufacture and storage of drug product; final assembly of finished product; secondary packaging and labeling; quality control testing of drug substance (back-up), drug product, and finished product; stability testing of drug substance (back-up testing of samples only), drug product, and finished product; batch release of drug substance, drug product, and finished product.

Inspectional History
There has been no past device inspections of this manufacturer. Past drug inspections appear to be VAI or NAI inspections

Inspection Recommendation:
A Pre-Approval Inspection is recommended for the following reasons:

- The firm is responsible for major activities related to the manufacturing of the final combination product device constituent, specifically final product assembly, finished product secondary packaging and labeling, and finished product quality control, batch release, and stability testing.
- There has been no previous device inspection of the firm.

Reviewer Note:
On 8/14/2020, Lindsey Fleischman, having received the PAI request, asked the following to the CDRH regarding a PAI recommendation:

Do you know if this is mission critical? In order to travel for a device PAI it must be deemed mission critical given the current situation.

Based on information discussed with CDRH compliance officer reviewer Marc Neubauer and previous ORA investigator LCDR Michael Simpson, it was determined that based on the fact that the devices are intended to deliver low criticality products, where it is not an emergency and there is not a public safety concern, that a PAI inspection is not mission critical. I stated in response to Ms. Fleischman:

The product is not a necessarily a high risk medication, in that it is not an emergency use treatment where there is a public safety concern; therefore, I would say that it is NOT mission critical. However, the device manufacturer had not previously been inspected, so that is why we recommended PAI.

Given this information a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. This was communicated at the November 30, 2020, Mid-cycle meeting. Of note the drug facilities team also requested a Pre-Approval Inspection.

In addition, the CDER facilities team (Wayne Seifert – primary and Zhong Li – secondary) alerted the CDRH lead reviewer at the November 30, 2020, Mid-cycle meeting that there are potential data integrity accusations with the drug substance and drug quality systems, which will lead to a For Cause Inspection recommendation as the subject of an inspection, in addition to recommendations for device and drug quality systems inspections.

Wayne Seifert emailed Lindsey Fleischman (ORA) on November 30, 2020 requesting a status update on the inspections. Ms. Fleischman stated:

This facility was pushed for PAI. The goal date is 7/15/21. We will evaluate this facility to see if it will qualify for 704a4 review when we evaluate the PAI's pushed with July goal dates.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

5.3.Quality System Documentation Triage Checklist

Device Type Table

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☐ No ☑ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☑ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☑ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☑ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	

☐ High Risk of cGMP issues:
If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.

Reviewer Comment
Both devices have low to moderate risk of cGMP issues given that the devices are relatively simple manufacturing/assembly processes. A summary QS review will be conducted in Section 12.

FILING REVIEW CONCLUSION

It is recommended that that BLA 761151 be **FILED**

A **Pre-Approval Inspection is recommended** for the following firm:

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

Reviewer Note:
A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place. See Section 5.2 for full discussion.

6. LABELING

6.1.General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?			
	Yes	No	N/A	Comments
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X			N/A
Drug name is visible on device constituent and packaging	X			Packaging provided in Seq001.1.14
Device/Combination Product Name and labeling is consistent with the type of device constituent	X			N/A
Prescriptive Statement/Symbol on device constituent	X			N/A
Warnings	X			N/A

Contraindications	X			N/A
Instructions for Use	X			See Section 6.2 for IFU review
Final Instructions for Use Validated through Human Factors	X – See note			Human Factors validation testing is provided. Note – The review of this information is deferred to CDER/OSE/DMEPA

6.2.Instructions for Use Review

The Sponsor provided the AI and PFS cartons for each product. Below is an image of the AI carton labeling:

	Carton Labeling
AI	(b) (4)
	This appears to contain all required content from a device perspective.

2 Pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer Comments
The instructions for use contain necessary components. CDER/OSE/DMEPA will review human factors validation to support that the instructions for use and device design is adequately validated.

LABELING REVIEW CONCLUSION

The Labeling and Instructions for Use is Adequate.

7. DESIGN CONTROL SUMMARY

7.1.Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	Comments
Risk analysis conducted on the combination product	X		In response to a a CDRH IR the sponsor provided aSeq0012.1.11 IR Response #1. Resolved.
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		N/A
Mitigations are adequate to reduce risk to health	X		N/A
Version history demonstrates risk management throughout design / development activities	X		N/A
Design Inputs/Outputs	**Yes**	**No**	**Comments**
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	**Yes**	**No**	**Comments**
Validation of essential requirements covered by clinical and human factors testing	X		Seq001- pharmaceutical-development-container-closure-ai-1ml-maa Seq001- pharmaceutical-development-container-closure-ss-1ml-maa
To-be-marketed device was used in the pivotal clinical trial		X*	In response to CDRH IR the sponsor provided Seq0012.1.11 IR Response #2.

			It is stated that there were minor changes that have occurred to the device design: - PFS-SS – Changes to the finger flanges - AI – Changes to AI housing cover (b) (4) These changes would not appear to change how the device would have been clinically validation; however, this will be reviewed within Section 10 – Clinical Validation.
Bioequivalence Study utilized to-be-marketed device		N/A	See Section 10 – Clinical Study; no BE study completed.
Verification methods relevant to specific use conditions as described in design documents and labeling	X		Yes
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	X		Sponsor relies on ISO 11608 and other recognized standards for testing. There are no additional testing reliability requirements or recommendation from the Agency based on risk.
Traceability demonstrated for specifications to performance data	X		Seq001- pharmaceutical-development-container-closure-ai-1ml-maa Seq001- pharmaceutical-development-container-closure-ss-1ml-maa

Reviewer Comments
It should be noted that it is DHT3C's internal policy is to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and breakloose and glide force will not be addressed within this review. This approach was discussed with Rumi Young (Injection TL) on 8/6/2020 by email and Skype.

7.2.Design Inputs and Outputs

The Sponsor provides a summary of the inputs and outputs of the devices within documents:

- Seq001- pharmaceutical-development-container-closure-ai-1ml-maa

- Seq001- pharmaceutical-development-container-closure-ss-1ml-maa

Essential Performance Requirements
The following are what the Sponsor deems to be the essential performance requirements (EPRs) for the SS and AI

PFS – SS	
Design Inputs (Essential Performance Requirement)	**Design Outputs (Specification)**
Dose Accuracy (extractable volume)	≥ (b) (4) mL
Cap Removal Force	≤
Safety feature activation force	≤ (b) (4) N

Safety feature overriding force	≥ (b) (4) N

AI	
Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Dose Accuracy (extractable volume)	≥ (b) (4) mL
Injection Time	≤ (b) (4) seconds
Actuation Force	(b) (4) ≤ F ≤ (b) (4) N
Needle Extension	(b) (4) mm
Cap Removal Force	≤ (b) (4) N
Audible Click	Click heard at end of injection
Visual indicators	Yellow color fills viewing window at end of injection

Reviewer Comments
These EPRs or Critical Quality Attributes (CQA) as identified by the Sponsor appear appropriate. As noted in previous sections only the NSD functions of the PFS-SS will be reviewed for safety and efficacy.

As stated previously in the review memo, it is current DHT3C's internal policy to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and break-loose and glide force will not be addressed within this review. This approach was address with Rumi Young (Injection TL) on 8/6/2020 by email and Skype.

DESIGN CONTROL REVIEW CONCLUSION

The Design Control information is adequate.

8. RISK ANALYSIS

8.1.Risk Management Plan

In the original submission (Seq0001), the Sponsor provided a summary of the risk management plan of the SS-PFS and AI. They state:

Risk management activities are conducted in accordance with medical devices risk management standard ISO 14971 and ICH Q9. Potential risks that may arise from the design, use or misuse of the bimekizumab-AI-1mL, and from the assembly process were identified, assessed and mitigated. Risk management covers the lifecycle of the product from design and development planning through lifecycle management and until discontinuation from market.

Risk management activities were conducted throughout the product design and development to identify hazards, estimate and evaluate risks, control these risks and monitor the effectiveness of the controls to ensure patient safety and product functionality. A risk-benefit analysis was conducted and showed the benefits that the bimekizumab-AI-1mL provides to the user outweigh the residual risks. Acceptability of individual residual risks and the overall residual risks associated with the device are documented in the risk-benefit analysis

The sponsor uses an ISO 14971 approach and examines all design, use, and process related risks. The Sponsor uses a semi-quantitative approach to demonstrated adequacy of risk via severity and probability. These documents were provided in response to an IR in Seq0012, #1. The general methodology grading of risk is aligned with ISO 14971:

Table 1: Severity levels of harm and definitions

Severity level	Rating	Definition
Catastrophic	5	Results in patient death
Critical	4	Results in permanent impairment or life-threatening injury
Serious	3	Results in injury or impairment requiring professional medical intervention
Minor	2	Results in temporary injury or impairment not requiring professional medical intervention
Negligible	1	Inconvenience or temporary discomfort
No Harm	0	No Harm

Table 2: Definition and rating of the probability of harm

Probability level	Rating	Probability Range
Frequent	5	$\geq 10^{-3}$
Probable	4	$< 10^{-3}$ and $\geq 10^{-4}$
Occasional	3	$< 10^{-4}$ and $\geq 10^{-5}$
Remote	2	$< 10^{-5}$ and $\geq 10^{-6}$
Improbable	1	$< 10^{-6}$

Table 3: Risk Acceptability Matrix for bimekizumab-AI-1mL

			Qualitative Severity levels					
			No Harm	Negligible	Minor	Serious	Critical	Catastrophic
			0	1	2	3	4	5
Semi-quantitative probability levels	Frequent	5	A	I	U	U	U	U
	Probable	4	A	I	U	U	U	U
	Occasional	3	A	A	I	I	I	U
	Remote	2	A	A	I	I	I	I
	Improbable	1	A	A	A	I	I	I

Table 4: Risk Acceptability Coding Definitions

Coding	Definition
U	Unacceptable risk
I	Investigate further risk reduction (IFRR)
A	Acceptable risk

The approach that the Sponsor provides is acceptable. Note that the SS-PFS risk analysis is not being analyzed for adequacy, only the AI design related risk analysis will be analyzed for adequacy.

8.2.Hazard Analysis and Risk Summary Report

The Sponsor in addition to the design manufacturer conducted a dFMEA for the AI device in Seq0012, doc: pharmaceutical-development-container-closure-ai-1ml-maa. The support of low risk uses probability of harm based on design mitigations and design verification testing. The sponsor utilizes this data to show post mitigation reduction of risk. The risk analysis addresses design related failures and supports adequate mitigation of risk associated with failure with no unacceptable related risks.

RISK ANALYSIS REVIEW CONCLUSION

The risk analysis is adequate.

9. DESIGN VERIFICATION REVIEW

9.1.Performance/Engineering Verification

9.1.1. *Essential Performance Requirement Evaluation*

The verification testing of the AI and SS-PFS devices' EPRs will be reviewed below.

As stated previously in the review memo, it is current DHT3C's internal policy to not review Prefilled Syringe functionalities outside of the needle safety device (NSD) performance; i.e. NSD activation, lockout, etc. The PFS-SS performance such as dose accuracy and break-loose and glide force will not be addressed within this review. This approach was addressed with Rumi Young (Injection TL) on 8/6/2020 by email and Skype.

9.1.1.1.Safety Syringe – Prefilled Syringe Verification:

Summary testing is provided in doc: pharmaceutical-development-container-closure-ss-1ml-maa. Shipping testing was provided in doc: process-validation-ss-1ml-maa

Essential Performance Requirement (Design Input)	Specification (Design Output)	Method Acceptable (Y/N)	Verification (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Validation (Y/N)
Safety feature activation force	(b)(4)N	Yes – Uses force testing (force cell) to measure force.	All Passed – Safety feature activation force is measured at all preconditions in ISO 11608-1. Between 20-60 samples were tested depending on the conditioning.	All Passed – 60 samples were tested. Safety feature activation force all met specification	All Passed – 48 samples were tested. Safety feature activation force all met specification	Yes – See Section 11. Validated with human factors. The Sponsor also did a "*sharps handling testing*" validation testing, aligned with ISO 23908 (FDA recognized). Results showed "*that no lock-out failures or critical use errors were observed in 560 simulated injections*."

Safety feature overriding force	(b) (4) N	Yes – Uses force testing (force cell) to measure force.	All Passed – Safety feature overriding force is measured at all preconditions in ISO 11608-1. Between 20-60 samples were tested depending on the conditioning.	All Passed – 60 samples were tested. Safety feature activation force all met specification	All Passed – 48 samples were tested. Safety feature activation force all met specification	Yes – See Section 11. Validated with human factors. The Sponsor also did a "*sharps handling testing*" validation testing, aligned with ISO 23908 (FDA recognized). Results showed "*that no lock-out failures or critical use errors were observed in 560 simulated injections*."

Reviewer Comments

- While, dose accuracy and break-loose and glide force of the SS-PFS was not part of the CDRH review, the Sponsor provided this information and it appeared that all passed its specification.
- An accelerated aging study at 55 deg C (154 days) was completed to support the EPR meeting its specification up to the expiry.
- Shipping study was conducted per FDA recognized standard ASTM D4169.

9.1.1.2.Autoinjector EPR Verification:

Summary testing is provided in doc: pharmaceutical-development-container-closure-ai-1ml-maa. Shipping testing was provided in doc: process-validation-ai-1ml-maa

Essential Performance Requirement (Design Input)	Specification (Design Output)	Method Acceptable (Y/N)	Verification (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Validation (Y/N)

Dose Accuracy (extractable volume)	(b) (4) mL	Yes – Uses FDA recognized standard ISO 11608-1:2014, with all necessary conditions based on a single dose and fixed dose autoinjector device – cool, standard warm atmosphere, free fall, dry heat/cold storage, vibration, etc.	All Passed – Accuracy after preconditioning as designated in the standard for verification testing. Between 30-60 samples were tested depending on the conditioning. Requirement met.	All Passed – 60 samples were tested. Dose accuracy testing was completed, and all met specification	All Passed –50 samples were tested. Dose accuracy testing was completed, and all met specification.	Yes – See Section 10. Clinically validated.
Injection Time	≤ (b) (4) econds Note: The sponsor should support the adequacy of a (b) (4) second injection with design validation testing; e.g. human factors testing. Of note the labeling states to wait 15 seconds to remove injector from site.	Yes – measures time for full dose to be delivered. Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	All Passed – Injection time is measured at all preconditions in ISO 11608-1. Between 30-60 samples were tested depending on the conditioning. Note that the max injection time (~11.8 s) is seen after cool atmosphere exposure and cool storage. Requirement met	All Passed – 60 samples were tested. Injection time was completed, and all met specification	All Passed –50 samples were tested. Injection time testing was completed, and all met specification.	Yes – See Section 10 & 11. Clinically validated and with human factors.
Actuation Force	(b) (4) ≤ F ≤ (b) (4) N	Yes – Uses force testing (force cell) to measure force.	All Passed – Activation Force is measured at all preconditions in ISO	All Passed – 60 samples were tested. Actuation force was	All Passed –50 samples were tested. Actuation force testing was	Yes – See Section 11. Validated with human factors.

		Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	11608-1. Between 20-60 samples were tested depending on the conditioning. Note that the max actuation force (~8 N) is seen after cool storage. Requirement met	completed, and all met specification	completed, and all met specification.	
Needle Extension	(b) (4) mm	Yes – Cap sleeve is removed and needle length is measured for verification testing.	All Passed – Needle Extension is measured at all preconditions in ISO 11608-1. Between 20-60 samples were tested depending on the conditioning. Note that the min and max needle extension (5.60 and 5.98 mm) is seen at cool atmosphere and cool storage respectively. Requirement met	All Passed – 60 samples were tested. Needle extension was completed, and all met specification	All Passed –50 samples were tested. Needle extension testing was completed, and all met specification.	Yes – See Section 10. Clinically validated.
Cap Removal Force	(b) (4) N Note: The sponsor should support the adequacy of a	Yes – Uses force testing (force cell) to measure force. Uses preconditions as designated in ISO	All Passed – Safety Cap Removal Force is measured at all preconditions in ISO 11608-1. Between 20-60 samples were	All Passed – 60 samples were tested. Cap Removal Force was completed, and all met specification.	All Passed –50 samples were tested. Cap removal force testing was completed, and all met specification.	Yes – See Section 11. Validated with human factors.

	(b) (4) second injection with design validation testing; e.g. human factors testing. Of note the labeling states to wait 15	11608-1: 2014 for verification testing.	tested depending on the conditioning. Note that the max safe cap removal force (~17.19 N) is seen after cool atmosphere exposure. Requirement met			
Audible Click /Visual indicators	Click heard at end of injection Yellow color fills viewing window	Yes- Audible click/visual indicator were observed on dose accuracy testing samples. Uses preconditions as designated in ISO 11608-1: 2014 for verification testing.	All Passed – Audible click/visual indicator were observed on dose accuracy samples Requirement met	All Passed – Audible click/visual indicator were observed on dose accuracy samples	All Passed –50 samples were tested. Audible click/visual indicator were observed on dose accuracy samples after dose delivered.	Yes – See Section 11. Validated with human factors.

Reviewer Comments

- Dose accuracy testing was completed per FDA recognized standard ISO 11608-1 for a single dose, fixed dose device. This is acceptable.
- An accelerated aging study at 55 deg C (154 days) was completed to support the EPR meeting its specification up to the expiry.
- Shipping study was conducted per FDA recognized standard ASTM D4169. This is acceptable.

9.1.2. *Verification of Design Inputs Evaluation*

The Sponsor provides summary verification of the design outputs to demonstrate how they support the design inputs in documents: pharmaceutical-development-container-closure-ai-1ml-maa AND pharmaceutical-development-container-closure-ss-1ml-maa, for the AI and SS-PFS respectively.

DESIGN VERIFICATION REVIEW CONCLUSION
The Design Verification Documentation is adequate

9.2.Discipline Specific Sub-Consulted Review Summary

Based on the device designs the following discipline specific reviews are completed to support the adequacy of the device design verification documentation:

Discipline	Review Location	Comments
Biocompatibility	See below	N/A
Sterility	N/A	The device components are not sterile. The container closure of the prefilled syringe is, and this is deferred to CDER
Human Factors	Section 11	A cursory review will be conducted to address validation of the usability related specifications. The adequacy of the human factors study is deferred to CDER/OSE/DMEPA.

Biocompatibility:

The sponsor identifies all components of the SS-PFS and AI devices as skin contacting components with < 24 hours of total intact skin contact. I agree with this assessment of the contact duration and type from the Sponsor. Based on the contact type and duration type, the Sponsor provides cytotoxicity (C), sensitization (S), and irritation (I) testing to support the biocompatibility of the device. Full test reports were requested from the Sponsor in an IR. In Seq0012 will provide a summary of the CSI testing and results for the SS-PFS and AI device below:

Cytotoxicity:

Testing is provided in Seq0012, doc: md-q-101676. Cytotoxicity testing was conducted in accordance FDA recognized standard 10993-5 using L929 mouse fibroblast to support whether the device surface contacting components are cytotoxic. The testing was conducted separately for the SS-PFS and AI. The extraction conditions for each surface contacting component is below:

Sample	Amount	Vehicle	Volume	Ratio	Time/Temperature
Test Article	244.08 cm^2	complete MEM	81.4 mL	3 cm^2/mL	24 ± 2 hours at 37 ± 1 °C
Positive Control	30 cm^2	complete MEM	10.0 mL	3 cm^2/mL	24 ± 2 hours at 37 ± 1 °C
Negative Control	30 cm^2	complete MEM	10.0 mL	3 cm^2/mL	24 ± 2 hours at 37 ± 1 °C
Untreated Control	N/A	complete MEM	10.0 mL	N/A	24 ± 2 hours at 37 ± 1 °C

N/A: Not Applicable

The extracts for each sample above were incubated in fibroblast cell cultures to see the effects. The results were provided – the positive control showed viability issues and the negative and device test samples showed no significant viability issues. This is acceptable.

Sensitization:

Testing is provided in Seq0012, doc: md-q-101678. Sensitization testing was conducted in accordance FDA recognized standard 10993-10 using the Klingman Maximization test. The following extraction conditions were used: *The test article (244.08 cm2 as per Sponsor) was combined with 81.4 mL of vehicle following an 10993—12 ratio of 3 cm2 per 1 mL. The test article was separately extracted in NaCl and 080 at 70 :l: 2 for 24 2 hours*

under dynamic conditions. Intradermal injections were made into Guinea pigs to investigate for Sensitization issues through 7 days. Results were provided that supports that the test samples showed no significant sensitization issues, while the positive control showed significant sensitization issues. This is acceptable.

Irritation:
Testing is provided in Seq0012, doc: md-q-101677. Irritation testing was conducted in accordance FDA recognized standard 10993-10 using the intracutaneous injection testing with new Zealand white rabbits. The following extraction conditions were used: *The test article (244.08 cm2 as per Sponsor) was combined with 81.4 mL of vehicle following an ISO 10993—12 ratio of 3 cm2 per 1 mL. The test article was separately extracted in NaCl and C80 at 70 2 °C for 24 2 hours under dynamic conditions*. Test samples were injected intracutaneously into three rabbits at 5 sites for the test extract, positive, and negative controls. Results in the form of skin reaction scores and animal weights and clinical observations were provided. The results of the test sample extracts support that samples do not result in irritation. This is acceptable.

BIOCOMPATIBILTY REVIEW CONCLUSION
The Biocompatibility Documentation is adequate

10.CLINICAL VALIDATION REVIEW

There is no device specific clinical study information to review; however, this section will serve to discuss how the final device design has been clinically validated. An IR was sent to the Sponsor requesting that they confirm that the final finished device was used in the pivotal clinical study(s) to support validation of the device design. They stated in response in Seq0012

Two minor changes have been made to the device presentations used in clinical studies DV0002 and UP0033 to improve manufacturability. One change was made to the extended finger flange component part of the safety syringe, and the other change was made to the housing cover component part of the auto-injector. The changes do not impact the appearance, materials of construction, functionality, usability or safety of the device presentations. Details of the changes are as follows:

The CDER clinical reviewer stated that the autoinjector presentation was also clinically used in the study DV0006.

Safety Syringe:

(b) (4)

Figure 1: Exploded view of the bimekizumab-SS-1mL

(b) (4)

Reviewer Note:
The only changes are to add [redacted] (b) (4) This appears to be a minor manufacturing change and would be unlikely to affect the EPRs of the device that was seen during clinical testing. In addition, performance testing was conducted with the final finished SS-PFS device and it met its specifications. The design of the SS-PFS device is adequately validated from a clinical perspective.

Auto-injector:

[redacted] (b) (4)

Figure 3: Exploded view of the bimekizumab-AI-1mL

[redacted] (b) (4)

Reviewer Note:
The only changes are being made to aid in [redacted] (b) (4) in the injector body component. This appears to be a minor manufacturing change and would be unlikely to affect the EPRs of the device that was seen during clinical testing. In addition, performance testing was conducted with the final finished SS-PFS device and it met its specifications. The design of the SS-PFS device is adequately validated from a clinical perspective.

This appears to be a minor manufacturing change and would be unlikely to affect the EPRs of the device that was seen during clinical testing. In addition, performance testing was conducted with the final finished SS-PFS device and it met its specifications. The design of the SS-PFS device is adequately validated from a clinical perspective.

Reviewer Note:

The clinical reviewer, Kevin Clark, emailed me on 2/8/2021 regarding potential failures of the autoinjector presentation within the DV0002 clinical study. In his email he stated:

"*In the pivotal Phase 3 trials (PS008, PS0009, and PS0013), only the PFS presentation was used and injections were administered by study staff. The only time the autoinjector presentation was used was in the clinical-use studies DV0002 and DV0006, which were substudies of open-label extension Trial PS0014. We recommended that a minimum of 100 devices per presentation be collected and examined for any evidence of failure*."

In the clinical study document, Dv0002-body-text-1ml, Section 8.3.3, it is stated that of the 254 bimekizumab SS 1 mL device presentations, there no devices that showed structural integrity issues or functionality issues, which is acceptable. However of the 258 bimekizumab AI 1mL devices used in this study they state the following:

- 1 investigational AI device showed signs of "*post-use structural integrity issues*". "*Even with this issue, the site reported (and re-confirmed upon follow up) that the study participant had self-injected the complete dose safely and effectively. An evaluation of the PK trough concentrations associated with self-injection for this study participant (study participant* (b) (6) *) was consistent with incomplete administration of bimekizumab at the Baseline visit.*"
- 2 investigational AI devices showed signs of "*post-use functional compromise*": with 2 study participants:
  - *One of these 2 investigational device presentations (Kit Number 175050) was summarized in Section 8.3.3.1. The source data reports that both investigational device presentations in Kit Number 175050 used at the Baseline self-injections were functionally compromised.*
  - *The second investigational device presentation (1 of 2 in Kit Number 175334) reported with functional compromise, was used by a study participant to self-administer the first injection at Baseline (Listing 6.1b). Even with this reported issue, the site reported that the study participant had self-injected the complete dose safely and effectively using another kit.*

The Sponsor does not provide any additional context to these failures, such as what the failures were, the root causes of these failures, and how they were corrected for the future to be marketed product.

Update 3/10/2021
The Sponsor provided a response regarding the device failures, root causes, and any CAPA related activities in Section 13.3 and 13.4 of the memo. The Sponsor details two different types of failure modes:

- Kit #175343 – The expected root cause is: "*the cap had been removed and then replaced by the treating health care professional, which had activated the auto-injector causing the injection to start.*" The Sponsor states that warning is within the labeling to warn the user against recapping the injector. On 3/10/2021, I requested the sponsor detail their full risk mitigation strategy around this failure mode, as labeling only may not be adequate.

  Update 3/17/2021:
  In response to the information request the Sponsor clarifies that it is not the removal or the act of recapping the device that triggers the premature activation, but it is the accidental pressure or contact that a user may apply the needle cover which could trigger activation. The design of the injector, however, should prevent this potential use error. The sponsor also discusses potential mitigation measures to this, which include activation force testing and labeling. The response is adequate.

- Kit #175050 (PR#185312) – The expected root cause is: "*the absence of a syringe inside the auto-injector*", which caused the yellow plunger to fall out of the device. The Sponsor opened a CAPA related to implemented multiple 100% inspection on assembly related to the prefilled syringe (separate inspections of component presence, proper positioning of the syringe within the AI and prefilled syringe presence) and

retraining of the device manufacturers. These actions are appropriate, and the sponsor describes that this failure mode has not been identified since that time.

CLINICAL VALIDATION REVIEW CONCLUSION

The device has been clinically validated.

11. HUMAN FACTORS VALIDATION REVIEW

The human factors review is deferred to CDER/OSE/DMEPA. This section serves to support how the device EPR specifications have been adequately validated.

PFS-SS Human Factors Validation:

The sponsor provides summary information regarding the performance requirements and how they were validated in document: pharmaceutical-development-container-closure-ss-1ml-maa. The following is a summary of the human factors information (formative and summative):

Table 1–15: Human factors overview for the bimekizumab-SS-1mL

Study	Date	Objective	Conclusion
Formative evaluation 1	Feb 2017	Evaluation of cap removal force and instructions for use	All participants (16) were able to remove the cap at 20N and 30N. Two participants failed to remove the cap at 40N. This was further evaluated in formative evaluation 2 but it should be noted painted prototypes were used and the caps did not have the rubberized finish. **Design changes made as a result:** [redacted] Improvements made to the instructions for use
Formative evaluation 2	April 2017	Evaluation of cap removal force, instructions for use, packaging concepts	All participants (17) were able to remove the cap at 35N and 40N **Design changes made as a result:** Improvements made to the instructions for use
Formative evaluation 3	September 2017	Evaluate design changes	All participants (40) delivered the full dose of bimekizumab. No unacceptable risks were found and the resulting residual use-related risk was acceptable **Design changes made as a result:** Improvements made to the instructions for use
Validation testing	October 2018	Confirm the user needs and intended user requirements are met	75 participants performed injections and were evaluated against the critical tasks identified. The intended users of the bimekizumab-SS-1mL can use the safety syringe safely and effectively. The residual use-related risk that remains after human factors validation is very low and cannot be further mitigated.

The HF validation report is provided in doc: md-q-101725. This document, specifically the critical tasks and results were briefly reviewed; there did not appear to be any specific concern where a large number of users failed to properly administer the product. I defer full review of the human factors review to CDER/OSE/DMEPA.

AI Human Factors Validation:

The sponsor provides summary information regarding the performance requirements and how they were validated in document: pharmaceutical-development-container-closure-ai-1ml-maa. The following is a summary of the human factors information (formative and summative):

Table 1–22: Human factors overview

Study	Date	Objective	Conclusion
Formative evaluation 1	Feb 2017	Evaluation of cap removal force, actuation force, and instruction for use	All participants (16) were able to remove the cap at 20N, 30N, and 40N and all could activate the bimekizumab-AI-1mL with activation force set out at 10N.
Formative evaluation 2	April 2017	Evaluation of use, instructions for use, packaging concepts	15 of 17 participants could perform a simulated injection and delivered a full dose on their first attempt. Two participants lifted the bimekizumab-AI-1mL away from the injection pad early resulting in a full dose not being delivered. These participants could self-correct when directed to refer to the instructions for use **Design changes made as a result:** Plunger color changed to yellow to improve visibility of injection progress Improvements made to the instructions for use
Formative evaluation 3	September 2017	Evaluate design changes	45 simulated injections were performed. All users delivered the full dose of bimekizumab. No unacceptable risks were found, and the resulting residual use-related risk was acceptable
Validation testing	October 2018	Confirm the user needs and intended user requirements are met	75 participants performed injections and were evaluated against the critical tasks identified. The intended users of the bimekizumab-AI-1mL can use the auto-injector safely and effectively. The residual use-related risk that remains after human factors validation is very low and cannot be further mitigated.

The HF validation report is provided in doc: md-q-101724. This document was briefly reviewed to analyze how the usability related essential performance requirements (needle cap removal force, injection time, activation force) were validated. See summary results below:

EPR	Validation Notes:
Safety Cap removal force	It is noticed that there is on user who couldn't' remove the cap and two other'\s that experienced difficulties. After review of the failure and difficulties they were not associated with the removal force. One user recapped the device prior to administering and others did not attempt to remove the cap. They also reference testing in formative evaluation where users were able to remove the safe cap. Given the low risk associated with failure to meet this specification and that the design verification consistently met this requirement, this specification is adequately validated through human factors testing.
Activation Force	There does not appear to be any failure or difficulties directly do the activation force of the device. Given this information, this specification is adequately validated through human factors testing.
Injection Time/Audible Click	It states within the human factors report that *6/75 participants removed the bimekizumab-AI-1mL early. Of the second attempts given, 1participant pulled away too early*. It is noted that the injection time specification is 12 seconds and the instructions for use states to hold the activated device to inject for 15 seconds. This is a known issue with usability associated with autoinjectors, in that users can have difficulty holding it in place for the full injection. It is noted that it is a general thought that an injection over about 10 seconds can create difficulties for the user. Given that the specification for injection for this device is 12 seconds and that all users, except for one held the device in place to inject (inclusive of first and second try), the specification is adequately validated and demonstrates that users are capable of injecting the full dose.

I defer full review of the human factors review to CDER/OSE/DMEPA.

HUMAN FACTORS VALIDATION REVIEW CONCLUSION

The human factors validation review is deferred to CDER/OSE/DMEPA.

12.FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

See Section 5.2 of the subject review memo. A preapproval device QS inspection was recommended for UCB Pharma SA; however, the PAI inspection is not mission critical. Of note the drug facilities team also requested a Pre-Approval Inspection.

The CDER facilities team (Wayne Seifert – primary and Zhong Li – secondary) alerted the CDRH lead reviewer at the November 30, 2020, Mid-cycle meeting that there are potential data integrity accusations with the drug substance and drug quality systems, which will lead to a For Cause Inspection recommendation as the subject of an inspection, in addition to recommendations for device and drug quality systems inspections.

Wayne Seifert emailed Lindsey Fleischman (ORA) on November 30, 2020 requesting a status update on the inspections. Ms. Fleischman stated:

This facility was pushed for PAI. The goal date is 7/15/21. We will evaluate this facility to see if it will qualify for 704a4 review when we evaluate the PAI's pushed with July goal dates.

At a late cycle meeting with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be conducted in this review cycle due to constraints about foreign inspection scheduling. They also stated that the CDER facilities team will continue to work with the ORA inspection team to schedule a Pre-Approval Inspection past the goal date, assuming that there are no approval deficiencies from the review team, so that a review decision on this application can be made. Given this discussion, I asked the CDER/OPQ team if CDRH should recommend Approval (Pending a Pre-approval inspection) and the CDER/OPQ team agreed with this approach.

Facility Regulatory History Review	
Firm Name:	UCB Pharma SA
Address & FEI:	Chemin du Foriest Braine-l'Alleud, Belgium 142 FEI#: 3003909356
Responsibilities:	Storage of master and working cell banks; manufacture and storage of drug product; final assembly of finished product; secondary packaging and labeling; quality control testing of drug substance (back-up), drug product, and finished product; stability testing of drug substance (back-up testing of samples only), drug product, and finished product; batch release of drug substance, drug product, and finished product. **Reviewer Note:** From a device perspective, the firm is the final device manufacturer and is responsible for final assembly of the combination product. The device quality systems will be reviewed to see if it is acceptable for approval.
Site Inspection Recommendation:	N/A – See Inspection Report Review below

Inspectional Report Review:
The inspection could not be conducted during this review cycle.

12.2. Quality Systems Documentation Review

As described in Section 5.3 of the review memo the device has low cGMP risk based on the intended use and device design. Based on the device design and overall complication of the manufacturing, the QS information will be reviewed for AI device and the assembly of the SS-PFS.

In support of the device manufacturer's ability to appropriately manufacture the device constituents, the Sponsor includes process validation of the device constituent's ability to meet the essential performance requirements specifications for three lots of product in documents: process-validation-ai-1ml-maa AND process-validation-ss-1ml-maa for the AI and SS-PFS respectively. All product met specification.

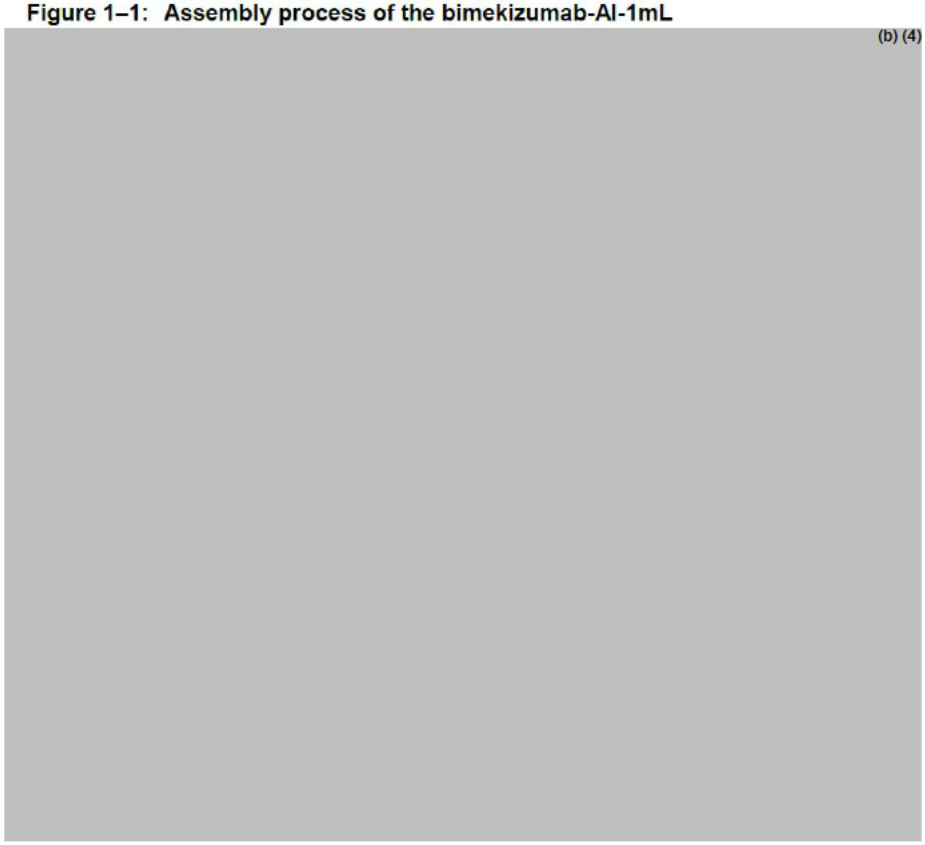
12.2.1. *Description of the Device Manufacturing Process - AI*

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the AI combination product, including the drug product/biologic and device constituent parts for the AI device in document: manuf-process-and-controls-ai-1ml-maal. The following is a summary.

Figure 1–1: Assembly process of the bimekizumab-AI-1mL

(b) (4)



The Sponsor describes the receipt of the device components and assembly of the drug and device component in (doc: manuf-process-and-controls-ai-1ml-maa).

At the final assembly site (UCB, Braine), (b) (4) *The components are listed below and shown in Figure 1–2.*

- *syringe unit* (b) (4)
- *drive unit* (b) (4)
- *housing covers*
- *cap remover sleeve*
- *pre-filled syringe*

Figure 1–2: Bimekizumab-AI-1mL components

(b) (4)

Assembly:

(b) (4)

The device manufacturing information is adequate.

12.2.2. *Description of the Device Manufacturing Process – SS-PFS*

Summary of Manufacturing Process / Production Flow

The Sponsor provided the following summary of the manufacturing process of the SS-PFS combination product, including the drug product/biologic and device constituent parts for the SS-PFS device in document: manuf-process-and-controls-ss-1ml-maa. The following is a summary.

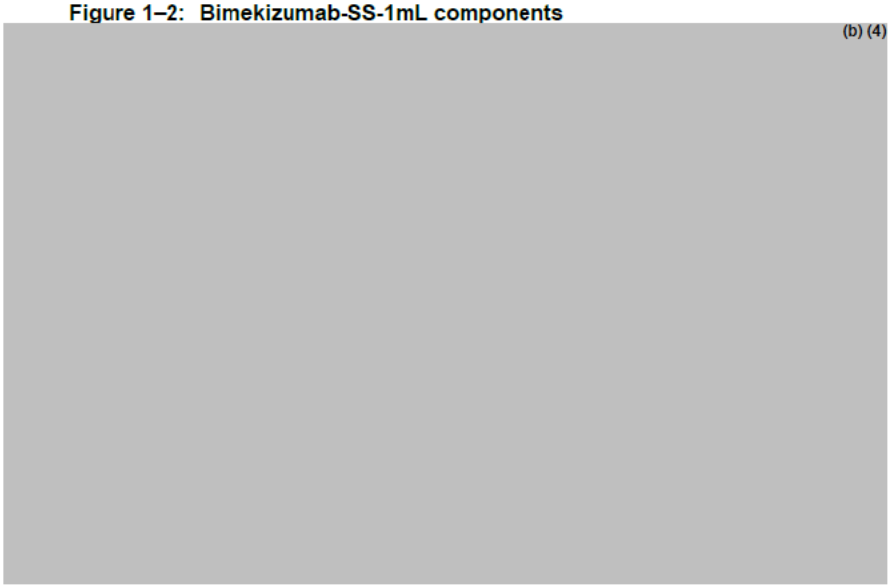
Figure 1–1: Assembly process of the bimekizumab-SS-1mL

The Sponsor describes (b) (4) in (doc: manuf-process-and-controls-ai-1ml-maa).

At the final assembly site (UCB, Braine), (b) (4)

Figure 1–2: Bimekizumab-SS-1mL components

(b) (4)



Assembly:

(b) (4)

Device Manufacturing Process Conclusion
The Sponsor provided adequate information for the summary of the manufacturing process / production flow

12.2.3. *cGMP Review*

As described in Section 5.3 of the review memo the device has low cGMP risk based on the intended use and device design. Based on the device design and overall complication of the manufacturing, the QS information will be reviewed for AI device only, not the SS-PFS. The Sponsor chose a drug based, device cGMP streamlined approach. The information is taken from document: regional-us-quality-system-app-maa

21 CFR 820.20 Summary of Management Responsibility	Firm(s): UCB Pharma SA	**Reviewer Discussion** – The following information is provided within the submission: (b) (4)

		(b) (4) This information adequately fulfills this requirement.
21 CFR 820.30 Summary of Design Controls	Firm(s): UCB Pharma SA	**Reviewer Discussion –** Reviewed in detail in Section 7 . The following information is provided within the submission (b) (4) This information adequately fulfills this requirement.
21 CFR 820.50 Summary of Purchasing Controls	Firm(s): UCB Pharma SA	**Reviewer Discussion –** The following information is provided within the submission: (b) (4) This information adequately fulfills this requirement.

21 CFR 820.100 Summary of Corrective and Preventive Actions	Firm(s): UCB Pharma SA	**Reviewer Discussion** – The following information is provided within the submission *UCB's CAPA system provides the process for initiating corrective and preventive actions related to non-conformities arising from various sources of quality data.* (b) (4) [redacted]
		This information adequately fulfills this requirement.

GMP Compliance Summary Conclusion
The Sponsor provided adequate summary information about the GMP compliance activities

12.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents for the AI (doc: control-critical-steps-ai-1ml-maa) and SS-PFS (doc: control-critical-steps-ss-1ml-maa). The Sponsor also described process validation of the device functionalities – AI (doc: process-validation-ai-1ml-maa) and SS-PFS (process-validation-ss-1ml-maa). This is reviewed within the table below.

Essential Performance Requirements Control Strategy Table

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N)
Autoinjector Control Strategy		

Dose Accuracy (extractable volume)	The sponsor describes the following which are a component of their control strategy for ensuring the dose accuracy of the combination product is met: • (b) (4) • • • • There are adequate controls to ensure dose accuracy for the device will be met.	Yes
Injection Time	The sponsor describes the following which are a component of their control strategy for ensuring the injection time of the combination product is met: • (b) (4) • • • • There are adequate controls to ensure injection time for the device will be met.	Yes
Actuation Force	The sponsor describes the following which are a component of their control strategy for ensuring the actuation force of the combination product is met: • (b) (4) • • • • There are adequate controls to ensure actuation force for the device will be met.	Yes
Needle Extension	The sponsor describes the following which are a component of their control strategy for ensuring the needle extension length of the combination product is met: • (b) (4) • • There are adequate controls to ensure actuation force for the device will be met.	Yes
Cap Removal Force	The sponsor describes the following which are a component of their control strategy for ensuring the cap removal force of the combination product is met: • (b) (4) • • There are adequate controls to ensure cap removal force for the device will be met.	Yes

Audible Click/Visual indicator	The sponsor describes the following which are a component of their control strategy for ensuring the audible click/visual indicator (after delivery) specification of the combination product is met: • (b) (4) • [redacted] • There are adequate controls to ensure audible click/visual indicator for the device will be met.	
Safety Syringe – Prefilled Syringe Control Strategy		
Dose Accuracy	The sponsor describes the following which are a component of their control strategy for ensuring the dose accuracy of the combination product is met: • (b) (4) • [redacted] • There are adequate controls to ensure dose accuracy for the device will be met.	
Breakloose & Glide force	The sponsor describes the following which are a component of their control strategy for ensuring the breakloose/glide force of the combination product is met: • (b) (4) • [redacted] • • There are adequate controls to ensure breakloose/glide force for the device will be met.	
Safety feature activation force	The sponsor describes the following which are a component of their control strategy for ensuring the safety feature activation force of the combination product is met: • (b) (4) • [redacted] • There are adequate controls to ensure safety feature activation force for the device will be met.	Yes
Safety feature overriding force	The sponsor describes the following which are a component of their control strategy for ensuring the safety feature activation force of the combination product is met: • (b) (4) • [redacted] • There are adequate controls to ensure safety feature override force for the device will be met.	Yes

Control Strategy Conclusion

The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION

The facilities and quality systems information is adequate.

As stated in Section 5's recommendation, a Pre-Approval Inspection was recommended for:

UCB Pharma SA
Chemin du Foriest
Braine-l'Alleud, Belgium 1420
FEI#: 3003909356

A Pre-Approval Inspection (PAI) recommendation was communicated to ORA on 8/14/2020 and that the PAI inspection is not mission critical. Because this inspection would not be mission critical, a device quality systems inspection should take place when ORA inspectors are able to complete foreign travel or a 704(a)(4) inspection (paper-based inspection) should take place.

At a late cycle with CDER/OPQ on 3/10/2021, CDER facilities discussed that an inspection will not be able to be conducted in this review cycle. Therefore, assuming that there are no approval deficiencies from the review team the CDER team will continue the review past the goal date, so that a review decision on this application can be made.

<<END OF REVIEW>>

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Memorandum

From: Selena DeConti, PharmD, MPH
Safety Analyst, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Through: Mary Ross Southworth, PharmD
Deputy Director for Safety, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Norman Stockbridge, MD
Director, Division of Cardiology and Nephrology
Office of New Drugs/CDER/FDA

Date: March 3, 2021

Subject: **Cardiovascular safety** of bimekizumab (BLA 761151)

This memo responds to the consult requesting a review of cardiovascular (CV) events that were reported in the bimekizumab psoriasis (PSO) program and recommendations regarding appropriate language for labeling. We received and reviewed the BLA submission package: \\CDSESUB1\evsprod\BLA761151.

DCN Summary and Assessment

The primary safety analysis included a review of the CV events[1] reported in the initial treatment period (ITP; 16-week placebo-controlled) for the primary safety pool, Pool S1, which includes bimekizumab 320 mg Q4W (n=670) or placebo (n=169), from the Phase 3 trials PS0009 and PS0013. Individual trial data were also reviewed for consistency of results.

The results of the analysis include:

- The patient characteristics, baseline cardiac risk factors, and baseline history of CV disease were relatively evenly distributed between the treatment groups.
- The CV events were reported in a higher proportion in the placebo arm than for bimekizumab; placebo (5%) and bimekizumab (4%). The estimated annualized rates of CV events per 100-person years were: placebo (16%) and bimekizumab (14%). An analysis of individual trials did not reveal an imbalance. No trend was observed with respect to the time to onset of any CV event.
- The number of adjudicated MACE for bimekizumab was low, occurring in one subject (0.1%; 0.1 per 100 patient-years) versus none for placebo. The subject experienced a fatal outcome and had multiple CV risk factors.

[1] any adverse event reported in the MedDRA System Organ Class (SOC) Cardiac Disorders or Vascular Disorders

- Adjudicated CV events were low and had a higher incidence in the placebo group (2.4%) compared with bimekizumab (1.6%).

There is no clinical concern from the cardiovascular perspective and no labeling language is necessary.

Background

UCB Biopharma, Inc submitted BLA 761151 for bimekizumab, a humanized IgG1 monoclonal antibody that targets the human interleukin (IL) 17A, 17F, and 17-AF cytokines, and inhibits their interaction with the IL-17RA/IL-17RC receptor complex. IL-17A and IL-17F are involved in the inflammatory process and independently cooperate with other inflammatory mediators to drive chronic inflammation and damage across multiple tissues. The proposed indication for bimekizumab is for treatment of moderate to severe plaque PSO in adults. The proposed dosage is 320 mg 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. The half-life of bimekizumab is approximately 19-26 days. Bimekizumab is not currently approved in any country.

Psoriasis is associated with increased prevalence of CV risk factors including smoking, limited physical activity, obesity, diabetes, hypertension and hyperlipidemia (Parisi et al, 2015). In addition, PSO patients have an increased risk of vascular inflammation and major adverse cardiac events (MACE) beyond that attributable to known CV risk factors (Egeberg et al, 2017; Gelfand et al, 2006). Among patients with moderate to severe PSO, the incidence rate of MACE was 6.5/1000 person-years in The Health Improvement Network database (1994-2010) in the United Kingdom (Ogdie et al, 2015). Of note, there are studies suggesting that low serum levels of IL-17 are associated with a higher risk of MACE (Lockshin et al, 2018; Simon et al, 2012).

Two monoclonal antibodies targeting IL-17A (secukinumab, ixekizumab) and one antibody against the IL-17 receptor (brodalumab) have been approved for the treatment of moderate-to-severe plaque psoriasis. No CV adverse events are included in the labeling for these products.

For bimekizumab, there were no preclinical findings to suggest CV safety concerns. In the Applicant's repeat-dose toxicity studies in Cynomolgus monkeys there were no abnormalities in the ECG waveform or morphology that could be directly attributed to administration of bimekizumab, no changes in CV variables or heart rate, and no significant effects on ECG Lead II parameters noted at any bimekizumab dose.

MACE, defined as CV death, non-fatal myocardial infarction (MI), or stroke, was a pre-specified safety topic of interest due to epidemiological associations between PSO and CV events and the potential association between other anti-cytokine (immunomodulating biologic) therapies and CV events. MACE were reported as adverse events. Extended MACE was defined as all MACE plus adjudicated event types of hospitalization for unstable angina with urgent revascularization, hospitalization for heart failure, transient ischemic attack, coronary revascularization procedures (percutaneous coronary intervention, coronary artery bypass grafting, or urgent cerebrovascular revascularization procedures (i.e. due to symptoms of brain ischemia or pending infarction.) Events were classified and adjudicated by the CV Clinical Event Adjudication Committee (CV-

CAC). The Applicant conducted analyses on adjudicated MACE, extended MACE, and other serious non-MACE CV events as detailed in the integrated statistical analysis plan. The proposed labeling does not include adverse drug reactions for CV events.

Safety Analysis Pools

The Phase 2 and Phase 3 trials constituting the relevant safety pools used in the Integrated Summary of Safety (ISS) are provided in the Appendix. The primary safety pool, Pool S1, includes 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; it is the same as Efficacy Pool 1.

Treatment Duration

Treatment duration for bimekizumab and placebo is provided in Table 1 below. Subjects in the bimekizumab group had approximately 4 times the person-time at risk, with 207.7 patient-years versus 51.6 patient years for placebo. Mean duration of bimekizumab treatment was approximately 110 days.

Table 1: Study Drug Treatment Duration for Pool S1

	BKZ 320mg Q4W (N=670)	**PBO (N=169)**
Duration (days)		
Mean (SD)	110.6 (7.3)	107.4 (16.8)
Median	112.0	112.0
Min, Max	28, 122	28, 120
Total time at risk (participant-years)	207.7	51.6

ADA=adalimumab, BKZ=bimekizumab, PBO=placebo, SD= standard deviation, UST = ustekinumab; Source: ISS Tables 5-4 & 5-3

Pooled Subject Demographics and Baseline Characteristics

Baseline CV risk factors and history of CV events were relatively evenly distributed between the randomized treatment groups. There was a slightly higher proportion of subjects reporting previous or ongoing cardiac disorders in the bimekizumab group (8%) compared with the placebo group (6%).

Cardiovascular Events

Cardiovascular events included any adverse event reported in the Cardiac Disorders or Vascular Disorders MedDRA System Organ Class (SOC) and are presented in Table 2. The incidence of CV events was higher in the placebo group (4.7%; 16 per 100 patient-years) than the bimekizumab (4.3%; 14 per 100 patient-years). CV events reported in 2 or more subjects in the bimekizumab group was hypertension (n=12), presyncope (n=5), palpitations (n=2), and syncope (n=2). There were a variety of single (n=1) events (e.g., bradycardia, bundle branch block right, cardiac arrest, cardiac failure acute, chest discomfort, defect conduction intraventricular, ECG

ST segment depression, left ventricular hypertrophy) and overall, no meaningful differences in specific CV events that warranted further subgroup analyses.

Table 2. CV Adverse Events[1] for the Safety Pool S1

CV Event	BMK 320mg (N=670)	PBO (N=169)	Risk Difference (95% CI)
Any AE	29 (4.3)	8 (4.7)	-0.4 (-2.5, 5.0)
SAE	1 (0.1)	2 (1.2)	-1.1 (0.01, 4.1)
SAE with fatal outcome	1 (0.1)	0	0.1 (-2.1, 0.8)
AE from CV FMQs[2]			
Acute myocardial infarction[3]	1 (0.1)	1 (0.6)	-0.5 (-0.3, 3.2)
Angina pectoris	0	1 (0.6)	-0.6 (-0.2, 3.3)
Atrial fibrillation	0	1 (0.6)	-0.6 (-0.2, 3.3)
Bradycardia	1 (0.1)	0	0.1 (-2.1, 0.8)
Bundle branch block right	1 (0.1)	0	0.1 (-2.1, 0.8)
Cardiac arrest	1 (0.1)	0	0.1 (-2.1, 0.8)
Cardiac failure acute	1 (0.1)	0	0.1 (-2.1, 0.8)
Chest discomfort	1 (0.1)	0	0.1 (-2.1, 0.8)
Defect conduction intraventricular	1 (0.1)	0	0.1 (-2.1, 0.8)
Electrocardiogram ST segment depression	1 (0.1)	0	0.1 (-2.1, 0.8)
Hypertension[4]	12 (1.8)	3 (1.8)	0.0 (-1.8, 3.4)
Left ventricular hypertrophy	1 (0.1)	0	0.1 (-2.1, 0.8)
Mitral valve prolapse	0	1 (0.6)	-0.6 (-0.2, 3.3)
Orthostatic hypotension	0	1 (0.6)	-0.6 (-0.2, 3.3)
Palpitations	2 (0.3)	0	0.3 (-1.9, 1.1)
Presyncope	5 (0.7)	0	0.7 (-1.6, 1.7)
Syncope	2 (0.3)	0	0.3 (-1.9, 1.0)

[1] Includes treatment emergent AE defined as any event that had a start date on or following the first dose of drug up to 140 days following the final dose
[2] MedDRA preferred term from FMQ Acute Coronary Syndrome, FMQ Arrhythmia, FMQ Hypotension, FMQ, Myocardial Infarction, FMQ Myocardial Ischemia, FMQ Palpitations, FMQ Syncope, FMQ Systemic Hypertension
[3] Includes PT myocardial infarction
[4] Includes PT blood pressure increased
Source: Reviewer's Table; MAED, OCS Analysis Studio PS0009 & PS0013, adae.xpt, adsl.xpt,

Table 3 summarizes incidences of adjudicated MACE, extended MACE, and CV events. Adjudicated MACE for bimekizumab was infrequent, occurring in one subject (0.1%; 0.05 per 100 patient-years); the subject had multiple CV risk factors and experienced a fatal outcome 4 days after a non-STEMI which was considered resolved. 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. The Appendix provides additional information for the adjudicated MACE and fatal outcome for Pool S1. Adjudicated CV events were low and had a higher incidence in the placebo group (2.4%) compared with bimekizumab (1.6%).

Overall, there is no clinical concern from the cardiovascular perspective and no labeling language is necessary.

Table 3: Adjudicated MACE, Extended MACE, and CV Adverse Events for Safety Pool S1

Variable [n (%)]	BMK 320mg (N=670)	PBO (N=169)	Risk Difference
Adjudicated MACE	**1 (0.1)**	**0**	**0.1 (-2.1, 0.8)**
PT			
Cardiac arrest	1 (0.1)	0	0.1 (-2.1, 0.8)
Outcome			
Fatal	1 (0.1)	0	0.1 (-2.1, 0.8)
Adjudicated Extended MACE[b]	**1 (0.1)**	**0**	**0.1 (-2.1, 0.8)**
PT			
Cardiac failure acute	1 (0.1)	0	0.1 (-2.1, 0.8)
Adjudicated CV Event	**11 (1.6)**	**4 (2.4)**	**0.8 (-1.1, 4.4)**
Hospitalization for HF	1 (0.1)	0	0.1 (-2.1, 0.8)
Arrhythmia (not associated with ischemia)	0	1 (0.6)	-0.6 (-0.2, 3.3)
Coronary Revascularization Procedure	0	1 (0.6)	-0.6 (-0.2, 3.3)
Other CV event[c]	3 (0.4)	0	0.4 (-1.8, 1.2)
Sudden cardiac death	1 (0.1)	0	0.1 (-2.1, 0.8)
Non-CV death	0	1 (0.6)	-0.6 (-0.2, 3.3)
Non-CV event	5 (0.7)	1 (0.6)	0.1 (-2.6, 1.2)
Not enough information to adjudicate	1 (0.1)	0	0.1 (-2.1, 0.8)

[a] Includes PT myocardial infarction
[b] Includes the MACE events presented above
[c] i.e., heart failure, pulmonary embolism, or CV procedure-related
Source: ISS-PSO-BKZ-Tables 5.1.9.5.3; ISS-PSO-BKZ Table 6-19

References

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Appendices

Table 4. Phase 2 and 3 Trials Constituting Relevant Safety Pools

Study/Design	Treatment Duration	Treatment Groups	Safety Population (S/C)	Safety Pool
Phase 3 Controlled				
PS0008 16-week MC, R, DB, PG, AC ITP, followed by 40-week DoseB, MTP	ITP – 16 weeks	ADA 40mg	159/149	S2
		BKZ 320mg Q4W	158/152	
		BKZ 320mg Q4W/Q8W	161/149	
	MTP – 40 weeks	ADA/BKZ 320mg Q4W	149/133	
		BKZ 320mg Q4W/Q4W	152/143	
		BKZ 320mg Q4W/Q8W	149/143	
PS0009 16-week MC, R, DB, PC and AC ITP, followed by 36-week PG extension period	ITP – 16 weeks	PBO	83/74	S1
		UST 45/90mg	163/157	S2
		BKZ 320mg Q4W	321/306	S1
	EP – 36 weeks	UST 45/90mg	157/141	S2
		BKZ 320mg Q4W	380/352	
PS0013 16-week MC, DB, PC ITP, followed by 40-week PC RWP	ITP – 16 weeks	PBO	86/82	S1
		BKZ 320 mg Q4W	349/340	
	RWP – 40 weeks	PBO/PBO	1/1	S2
		BKZ 320 mg Q4W/PBO	105/33	
		BKZ 320 mg Q4W/Q8W	100/93	
		BKZ 320mg Q4W/Q4W	106/94	
Phase 3 Uncontrolled				
PS0014[a] OLE	144 weeks	BKZ 320mg Q4W	1285/not-reported	S2
		BKZ 320mg Q8W		
Phase 2 Controlled				
PS0010 MC, R, DB, PC, PG	12 weeks	BKZ 64mg Q4W	39/36	S2
		BKZ 160mg Q4W	43/38	
		BKZ 160mg Q4W w/LD	40/34	
		BKZ 320mg Q4W	43/40	
		BKZ 480mg Q4W	43/39	
		PBO	42/37	
PS0011[b] DB, PC, PG	48 weeks	BKZ 64mg Q4W	15/15	S2
		BKZ 160mg Q4W	111/92	
		BKZ 320mg Q4W	91/75	
PS0016	4 weeks	BKZ 320mg + PBO	32/28	S2

MC, R, DB	16 weeks	BKZ 320mg	17/15	
Phase 2 Uncontrolled				
PS0018[c] OLE	48 weeks	BKZ 320mg + PBO	28/24	S2
		BKZ 320mg	15/13	

AC=active control, ADA=adalimumab, BKZ=bimekizumab, DB=double-blind, DoseB=dose blind, EP=extension period, ITP=initial treatment period, MC=multi-center, MTP=maintenance treatment period, OLE=open label extension, PBO=placebo, PC=placebo controlled, PG=parallel group, PSO= psoriasis, R=randomized, RWP=randomized withdrawal period, S/C=number of subjects started/completed, S1=Safety Pool 1 includes only the ITP and placebo-controlled Phase 3; it is the same as Efficacy Pool 1, S2=Safety Pool 2 and combines all treatment periods, UST = ustekinumab; [a] ongoing; feeder studies PS008, PS009, or PS0013; includes sub-studies DV0002 and DV0006 and an additional OL Cohort B in Japan; clinical cut-off 11/1/19; [b] feeder study PS0010; [c] feeder study PS0016; Source: Integrated Summary of Safety, SAP, Tables for individual trials

Table 5. Adjudicated MACE with Fatal Outcome for Bimekizumab, Safety Pool S1 and S2

Subject ID/ Gender/ Age (yrs)	Study when MACE occurred/ Safety Pool	Study Period	Treatment at time of death	Time to Event (days)	Country	Preferred Term	Comment/CV Risk Factors
06139 F/63	PS0009/ S1	ITP	BKZ 320mg Q4W	31	Poland	Cardiac arrest	Sudden death 4 days after a non-STEMI which was treated and considered resolved. CV risk factors included hypertension, hyperlipidemia, BMI>30kg/m^2, smoker, mitral valve incompetence, and aortic valve stenosis.
07461 M/49	PS0014/ S2	OLE	BKZ 320mg Q4W	213	Hungary	Cardio-pulmonary failure	First cardiorespiratory arrest during a left hip joint replacement surgery, successfully resuscitated. Post-operation, embolism of the left femoral artery occurred, and urgent femoral bypass was performed. Second cardiorespiratory failure occurred postoperatively, in ICU. CV risk factors included hypertension, diabetes mellitus, morbidly obese, BMI 52.7 kg/m^2, and tobacco smoker.

ITP = initial treatment period, OLE = open label extension period, STEMI =ST elevation myocardial infarction, BMI = body mass index
Source: CRFs for PS0009, PS0014

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DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatric and Maternal Health
Office of Rare Disease, Pediatrics, Urology, and Reproductive Medicine
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Division of Pediatric and Maternal Health Memorandum

Date: February 3, 2021 **Date Consulted:** August 4, 2020

From: Kristie Baisden, DO, Medical Officer, Maternal Health
Division of Pediatric and Maternal Health (DPMH)

Through: Tamara Johnson, MD, MS, Team Leader, Maternal Health, DPMH

Lynne Yao, MD, Director, DPMH

To: Strother Dixon, Regulatory Project Manager (RPM)
Division of Dermatology and Dentistry (DDD)

BLA: 761151

Drug: Bimzelx (bimekizumab-bkzx)[1] injection, for subcutaneous use

Proposed Indication: For the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.

Applicant: UCB, Inc.

Subject: Pregnancy and Lactation labeling

Materials Reviewed:

- BLA 761151 submitted on July 15, 2020.
- DPMH PLLR Review of Tremfya (guselkumab) BLA 761061 by Leyla Sahin, MD, dated April 12, 2017. DARRTS Reference ID: 4083650.[2]

[1] The nonproprietary name has not yet been conditionally accepted. The suffix "-bkzx" is used here as a placeholder.
[2] DPMH consults for Tremfya (guselkumab) (BLA 761061) and Dupixent (dupilumab) (BLA 761055) were reviewed as background and are not being relied upon for any decisions regarding approval of Bimzelx, including its labeling. DPMH's recommendations for Bimzelx labeling discussed below are based on the Bimzelx development program and information from the published literature that is not specific to a particular product.

- DPMH PLLR Reviews of Dupixent (dupilumab) BLA 761055 by Christos Mastroyannis, MD, dated January 13, 2017 (DARRTS Reference ID: 4041992) and October 12, 2018 (DARRTS Reference ID: 4335984).[2]
- Applicant's response to information request (IR) submitted on December 10, 2020.

Consult Question: DDD requests DPMH assistance with the PLLR labeling review for this original BLA.

INTRODUCTION

On July 15, 2020, the applicant, UCB, Inc., submitted an original BLA for Bimzelx (bimekizumab-bkzx) injection. On August 4, 2020, the Division of Dermatology and Dentistry (DDD) consulted the Division of Pediatric and Maternal Health (DPMH) to assist with the labeling review for the *Pregnancy*, *Lactation*, and *Females and Males of Reproductive Potential* subsections.

BACKGROUND

Regulatory History

- On July 15, 2020, the applicant submitted an original BLA for Bimzelx (bimekizumab-bkzx). Bimekizumab-bkzx is a humanized interleukin-17A and F antagonist. The proposed indication for Bimzelx is for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy or phototherapy.
- On November 20, 2020, the Agency sent the applicant an information request (IR) for an updated review and summary of all available pregnancy and lactation cases with reported exposure to bimekizumab-bkzx during the clinical development program.
- On December 10, 2020, the applicant submitted the requested information.

High-Level Summary of Drug Characteristics[3]

- *Description:* bimekizumab-bkzx, an interleukin-17 A and F antagonist, is a recombinant humanized full-length monoclonal antibody of the IgG1 sub-class, expressed in a genetically engineered Chinese Hamster Ovary cell line.
- *Mechanism of action:* a humanized immunoglobulin IgG1/κ monoclonal antibody, with two identical antigen binding regions that selectively bind to human interleukin 17A (IL-17A), IL-17F, and IL-17-AF cytokines, and inhibits their interaction with the IL-17RA/IL-17RC receptor complex. IL-17A and IL-17F are naturally occurring cytokines that are involved in normal inflammatory and immune responses.
- *Dosage and administration:* 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 some patients, a dose of 320 mg every 4 weeks after week 16 may be considered.
- *Contraindications:* none
- *Warnings and Precautions:* may increase the risk of infections; evaluate patients for tuberculosis prior to initiating treatment; consider completion of all age appropriate immunizations according to current immunization guidelines prior to initiating therapy and avoid the use of live vaccines; risk of new onset and exacerbation of inflammatory bowel disease.

[3] Bimzelx (bimekizumab-bkzx) (BLA 761151), proposed package insert.

- *Adverse Reactions:* upper respiratory tract infections, oral candidiasis, headache, injection site reactions, acne, oropharyngeal candidiasis, folliculitis, gastroenteritis, tinea pedis, fatigue, and oral herpes.
- *Absolute bioavailability:* 70% following subcutaneous administration.
- *Mean terminal elimination half-life:* 23 days

Psoriasis and Pregnancy

Psoriasis affects 2% to 3% of the population, men and women equally.[4] Psoriasis commonly starts during a woman's reproductive years. The disease activity during pregnancy is unpredictable and, therefore, it is possible that treatment may be needed.[5] Based on limited safety data, clinical guidelines for management of psoriasis during pregnancy and lactation recommend the following:

- First line: moisturizers and topical steroids (preferably low-medium potency)
- Second line: ultraviolet B phototherapy
- Third line: tumor necrosis factor inhibitors and cyclosporine.[4]

Reviewer's Comment

The 2020 Joint American Academy of Dermatology (AAD) and National Psoriasis Foundation (NPF) Guidelines of Care for the Management and Treatment of Psoriasis with Biologics conclude there is limited evidence regarding pregnancy and lactation for many of the newer biological products.[6] The guidelines state TNF-α inhibitors are safe in pregnancy and during lactation as well as in men attempting conception with their partners. However, due to transplacental drug delivery to the fetus, neonates and infants should be considered immunosuppressed for at least 1-3 months (depending on the TNF inhibitor) postpartum in mothers who have been on TNF-inhibitors. There is a greater theoretical risk with use during the third trimester of pregnancy owing to transplacental transfer of TNF-α inhibitors (with the exception of certolizumab pegol which has shown minimal to no placental transfer).

The AAD-NPF Guidelines further state that the safety of other newer biological products (including IL-12, IL-17, and IL-23 inhibitors) during pregnancy and lactation is unknown. Specifically, for IL-17 inhibitors (including secukinumab, ixekizumab, and brodalumab), the guidelines include the following information regarding use during pregnancy and lactation:

- *There are no studies in human pregnancy.*
- *Animal studies with secukinumab have shown no harm to the developing fetus.*
- *Animal studies with ixekizumab at higher doses than recommended have shown no harm to the developing fetus, but higher neonatal deaths were observed.*
- *Animal studies with brodalumab at higher doses than recommended have shown no harm to the developing fetus.*
- *All IL-17 inhibitors are likely acceptable for men attempting conception with their partner.*

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[4] Bae Y, Van Voorhees A, Hsu S, et al. Review of treatment options for psoriasis in pregnant or lactating women: Medical Board of the National Psoriasis Foundation. J Am Acad Dermatol vol 67, Number 3:459-477. 2012.

[5] Bangsgaard N, Rørbye C, Skov L et al. Treating Psoriasis During Pregnancy: Safety and Efficacy of Treatments. Am J Clin Dermatol. 2015 Oct; 16(5):389-98.

[6] Menter A, et al. Joint AAD-NPF Guidelines of Care for the Management and Treatment of Psoriasis with Biologics. J Am Acad Dermatol, Volume 80, Number 4: 1029-1072. April 2019.

- *The presence of IL-17 inhibitors in excreted human milk has not been studied.*

Thus, pending further study of other biological products, anti-TNF therapies are generally considered the preferred treatment for psoriasis in the pregnant population.[7]

REVIEW

PREGNANCY

Nonclinical Experience[3]

In an enhanced peri- and postnatal development study in the cynomolgus monkey, bimekizumab-bkzx showed no effects on gestation, parturition, infant survival, fetal and postnatal development when administered throughout organogenesis until parturition at dose resulting in 27 times the human exposure at 320 mg every 4 weeks based on AUC. At birth, serum bimekizumab-bkzx concentrations in infant monkeys were comparable to those of mothers. For additional details, refer to the Nonclinical Review by Jill Merrill, PhD.

Reviewer's Comment

DPMH discussed with the Nonclinical Review Team whether or not there is a potential concern for immunosuppression in infants exposed to bimekizumab-bkzx in utero.[8] *Important considerations include the anticipated transplacental transfer of this monoclonal antibody as pregnancy progresses and the nonclinical study findings described above in which serum drug concentrations in infant monkeys at birth were comparable to those of mothers. The Nonclinical Review Team stated the following in their response:*

"The applicant has completed blood (CD3+ T cells, CD3+CD8+ cytotoxic T cells, CD3+CD4+ T helper cells, CD20+ B cells, CD16+ NK cells, CD14+ monocytes) and tissue immunophenotyping. Although there was high inter-individual variability, the data do not indicate a treatment-related effect. There was no change in B cell percentages in the spleen or lymph node and no effect on the numbers of CD34+ progenitor cells of CD138+ cells in the bone marrow. They have also evaluated the immune response after antigenic challenge and [monkey] infants were able to mount a recall response after KLH immunization. Thus, based on the nonclinical studies performed there is no potential concern for immunosuppression."

Clinical Trials

Pregnant women were excluded from clinical trials with Bimzelx. A total of 11 pregnancy exposure cases have been reported to the UCB Global Safety Database as of the 120-Day Safety Update clinical cutoff date of April 15, 2020. Per protocol, study medication was stopped as soon as the pregnancy was discovered. Thus, bimekizumab-bkzx exposure was limited to a maximum of 1 dose during the first trimester (see Table 1-1 Appendix A for details).

Pregnancy outcomes (n=11 total) included:

- 6 normal livebirths (gestational age at delivery not reported)
- 2 spontaneous abortions (both occurred 1st trimester)
- 1 induced abortion (due to unintended pregnancy)

[7] Pomeranz M, et al. "Management of Psoriasis in Pregnancy." UpToDate. Literature review current through Nov 2020. www.uptodate.com. Accessed January 4, 2020.

[8] Personal Communication with Jill Merrill, PhD dated December 22, 2020.

- 2 unknown outcomes (lost to follow-up)

No congenital anomalies or major maternal complications were reported. One serious treatment emergent adverse event (TEAE) of hemorrhage in pregnancy was reported; however, the outcome was unknown and no further information was available as this participant was lost to follow-up. The applicant concluded, "no safety signals emerged from the very limited number of pregnancies reported throughout the clinical development program."

Reviewer's Comment
This reviewer agrees with the applicant's conclusion above. Overall, the available data are limited to a small number of bimekizumab exposures early in the 1st trimester followed by immediate discontinuation upon the diagnosis of pregnancy. In addition, there are no available data regarding use in women who continue to take Bimzelx chronically throughout pregnancy.

Applicant's Review of Published Literature
The applicant did not submit a literature review related to Bimzelx use during pregnancy.

DPMH's Review of Published Literature
This Reviewer performed a search in PubMed, Embase, Micromedex[9], TERIS[10], Reprotox[11], and Briggs[12] to find relevant articles related to the use of Bimzelx during pregnancy. Search terms included "bimekizumab" AND "pregnancy," "pregnant women," "birth defects," "congenital malformations," "stillbirth," "spontaneous abortion," OR "miscarriage." No relevant articles were identified.

LACTATION
Nonclinical Experience
Animal lactation studies have not been conducted with bimekizumab-bkzx.

Applicant's Review of Published Literature
The applicant did not submit a literature review related to Bimzelx use during lactation.

DPMH's Review of Published Literature
This Reviewer performed a search in *Medications and Mother's Milk*[13], LactMed[14], Micromedex[9], Reprotox[11], Briggs[12], PubMed, and Embase to find relevant articles related to the use of Bimzelx during lactation. Search terms included "bimekizumab" AND "lactation" OR

[9] Truven Health Analytics information, http://www micromedexsolutions.com/. Accessed 12/21/20.
[10] TERIS database, Truven Health Analytics, Micromedex Solutions, Accessed 12/21/20.
[11] Reprotox® Website: www.Reprotox.org. REPROTOX® system was developed as an adjunct information source for clinicians, scientists, and government agencies. Accessed 12/21/20.
[12] Briggs, GG. Freeman, RK. & Yaffe, SJ. (2017). Drugs in pregnancy and lactation: A reference guide to fetal and neonatal risk. Philadelphia, Pa, Lippincott Williams & Wilkins.
[13] Hale, Thomas (2020) Medication's and Mother's Milk. https://www.halesmeds.com Accessed 12/21/20.
[14] http://toxnet nlm nih.gov/cgi-bin/sis/htmlgen?LACT. The LactMed database is a National Library of Medicine (NLM) database with information on drugs and lactation geared toward healthcare practitioners and nursing women. The LactMed database provides information when available on maternal levels in breast milk, infant blood levels, any potential effects in the breastfed infants if known, alternative drugs that can be considered and the American Academy of Pediatrics category indicating the level of compatibility of the drug with breastfeeding. Accessed 12/21/20.

"breastfeeding." No relevant articles were identified.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience[3]

In cynomolgus monkey, bimekizumab-bkzx subcutaneous weekly doses of up to 200 mg/kg for up to 26 weeks (dose resulting in 109 times the human exposure at 320 mg every 4 weeks based on AUC) produced no organ toxicity, no effects on blood immunophenotyping or T-cell dependent antibody response and no effects on reproductive organs, menstrual cycle or sperm. For additional details, refer to the Nonclinical Review by Jill Merrill, PhD.

Applicant's Review of Published Literature

The applicant did not submit a literature review related to Bimzelx effects on fertility.

DPMH's Review of Published Literature

This Reviewer performed a search in PubMed, Embase, and Reprotox[11] to find relevant articles related to the use of Bimzelx and effects on fertility. Search terms included "bimekizumab" AND "fertility," "contraception," "oral contraceptives," OR "infertility." No relevant articles were identified.

DISCUSSION and CONCLUSIONS

Pregnancy

Pregnant women were excluded from clinical trials with Bimzelx. Available data from the 11 reported cases of inadvertent pregnancy exposure during the clinical development program (of which only 9 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.

Considering bimekizumab-bkzx is an IgG1 monoclonal antibody, DPMH recommends subsection 8.1 of labeling include a statement that human IgG antibody is known to cross the placental barrier; therefore, Bimzelx may be transmitted from the mother to the developing fetus. As noted above, DPMH discussed with the Nonclinical Review Team whether there is a potential concern for immunosuppression in the *in utero* exposed infant considering the anticipated transplacental transfer of this monoclonal antibody as pregnancy progresses and the nonclinical study finding of serum bimekizumab-bkzx concentrations in infant monkeys at birth that were comparable to those of mothers. The Nonclinical Review Team concluded based on the nonclinical studies performed that there is no evidence of immunosuppression in the *in utero* exposed monkeys.

Plaque psoriasis is common in females of reproductive potential, and therefore unintended and intended exposures to bimekizumab-bkzx in pregnancy are likely to occur. The applicant is planning to perform two postapproval pregnancy studies (both a pregnancy exposure registry and a retrospective cohort study) to evaluate the safety of Bimzelx use during pregnancy. DPMH agrees with applicant's proposal and recommends these pregnancy safety studies be issued as postmarketing requirements (PMRs). See below for DPMH suggested PMR language.

Lactation

Lactating women were excluded from clinical trials with Bimzelx and no lactation exposures were reported. Overall, there are no available data on the presence of bimekizumab-bkzx in human or animal milk, the effects on the breastfed infant, or the effects on milk product. Maternal IgG antibody is known to be present in human milk. The effects of local gastrointestinal exposure and limited systemic exposure to bimekizumab-bkzx on the breastfed infant are unknown.

Based on the lack of available data and the anticipated use of Bimzelx in females of reproductive potential including lactating women, DPMH also recommends issuing a PMR for a clinical lactation study (milk only) to assess concentration of bimekizumab-bkzx in human milk and to assess the effects on the breastfed infant. See below for DPMH suggested PMR language.

Females and Males of Reproduction Potential

DPMH recommends omitting subsection 8.3 of Bimzelx labeling. There are no available human data regarding the effects of Bimzelx on male or female fertility. Animal studies do not suggest an adverse effect on fertility. Pregnancy testing and contraception subheadings are not applicable because there are no available data to suggest Bimzelx use is associated with embryo-fetal toxicity.

RECOMMENDATIONS

DPMH recommends the following:

1. DPMH agrees with the applicant's proposed plan for a pregnancy exposure registry. The following PMR language is suggested:

   > 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.

2. DPMH also agrees with the applicant's proposed plan for a retrospective cohort study. The following PMR language is suggested:

   > 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.

3. The applicant should also conduct a lactation trial in Bimzelx treated patients, using a validated assay, in order to inform the lactation subsection of labeling. The following PMR language is suggested:

   > 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.

4. DPMH updated subsections 8.1 and 8.2 and section 17 of labeling for compliance with the PLLR (see below). DPMH discussed the below labeling recommendations with DDD at the labeling meeting on January 14, 2021. DPMH refers to the final BLA action for final labeling.

DPMH Proposed Bimzelx (bimekizumab-bkzx) Pregnancy and Lactation Labeling

(b) (4)

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APPENDIX A

Table 1-1: Details of maternal bimekizumab exposure pregnancies during the PSO clinical development program

Study participant narrative	Timing of exposure in pregnancy (LMP date)	BKZ dose at pregnancy Last BKZ dose date	Reported pregnancy complications / adverse events / maternal outcomes	Pregnancy outcome	Infant / fetal outcomes
PS0011- (b) (6) (b) (6)	First trimester (b) (6)	160mg Q4W (b) (6)	C-Section due to breech presentation No complications	Live birth	Healthy baby (male) No abnormalities reported Apgar score: 9 (at min 1) / 10 (at min 5)
PS0008- (b) (6) (b) (6)	First trimester (b) (6)	320mg Q4W (b) (6)	Pregnancy with contraceptive device (condom) No complications	Spontaneous abortion (5 weeks 3 days of gestation)	Not applicable
PS0008- (b) (6) (b) (6)	Pregnancy during SFU period (b) (6)	320mg Q4W (b) (6)	None reported	Live birth	Healthy baby (gender unk) No abnormalities reported Apgar score: unk
PS0008- (b) (6) (b) (6)	Pregnancy during SFU period (b) (6)	320mg Q4W (b) (6)	None reported	Lost to follow up	None reported
PS0009- (b) (6) (b) (6)	First trimester (b) (6)	320mg Q4W (b) (6)	None reported	Live birth	Healthy baby (female) No abnormalities reported Apgar score: 9 (no further details)
PS0009- (b) (6) (b) (6)	Pregnancy during SFU period (b) (6)	320mg Q4W (b) (6)	Pregnancy on contraceptive Hospitalized due to bleeding during pregnancy (no further information)	Lost to follow-up	None reported

Study participant narrative	Timing of exposure in pregnancy (LMP date)	BKZ dose at pregnancy Last BKZ dose date	Reported pregnancy complications / adverse events / maternal outcomes	Pregnancy outcome	Infant / fetal outcomes
PS0009 (b) (6) (b) (6)	Pregnancy during SFU period (b) (6)	320mg Q4W	No complications	Live birth	Healthy baby (female) No abnormalities reported Apgar score: unk
PS0014 (b) (6) (b) (6)	First trimester (b) (6)	320mg Q8W	No complications	Live birth	Healthy baby (female) No abnormalities reported Apgar score: unk
PS0014 (b) (6) (b) (6)	First trimester (unk)[a]	320mg Q4W (b) (6)	Concurrent viral infection with fever was reported as possible risk factor No complications reported	Spontaneous abortion (8 weeks of gestation)	Not applicable
PS0014 (b) (6) (b) (6)	First trimester (unk)[b]	320mg Q4W (b) (6)	Unintended pregnancy on oral contraceptive None reported	Induced abortion	Not applicable
PS0014 (b) (6) (b) (6)	First trimester (b) (6)	320mg Q4W	None reported	Live birth[c]	Healthy baby (male) No abnormalities reported Apgar score: unk

BKZ=bimekizumab; LMP=last menstruation period; unk=unknown; SFU=Safety Follow-Up

[a] first positive serum pregnancy test results: (b) (6)

[b] first pregnancy test positive at home: (b) (6)

[c] pregnancy outcome received after 120-Day Safety update cutoff date

Source: UCB Global Safety Database

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CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #11834

Consultant Reviewer:	Shamir N. Kalaria, PharmD, PhD, Clinical Reviewer, OND-ON-DP
Consultation Requestor:	Strother D. Dixon, RPM, OND-OII-DDD Kevin Clark, MD, Clinical Reviewer, OND-OII-DDD
Subject of Request:	BLA 761151 / IND 128707 (bimekizumab subcutaneous injection)
Date of Request:	8/4/2020
Date Received:	8/4/2020
Desired Completion Date:	3/12/2021

I. Executive Summary

The Applicant, UCB Inc., submitted a new biological licensing application (BLA) currently under review by the Division of Dermatology and Dentistry (DDD) for bimekizumab for the indication of treatment of moderate to severe plaque psoriasis (PSO) in adults. During the development program, the Applicant's neuropsychiatric safety assessments included the Hospital Anxiety and Depression Scale Depression (HADS) scale during two phase 2 trials and the Patients' Health Questionnaire 9 (PHQ-9) during three phase 3 trials. In addition, the Applicant utilized the electronic Columbia Suicide Severity Rating Scale (eC-SSRS) during the development program to evaluate suicidal ideation and behavior (SI/B). DDD previously requested consultation with the Division of Psychiatry (DP) to evaluate the adequacy of inclusion and exclusion criteria, safety monitoring, and stopping criteria submitted under IND 128707 (PS0008, PS0009, PS0010, PS0013, PS0015, and PS0016) and (b) (4) (HS0001). DDD has consulted DP again to review the data from the BLA submitted on July 15, 2020, to provide input on safety concerns about psychiatric adverse effects associated with bimekizumab, and to recommend appropriate language for labeling.

The objectives of this analysis was to pool clinical trial data from two phase 2 studies (PS0010 and PS0016) and three phase 3 studies (PS0008, PS0009, and PS0013) to evaluate psychiatric AEs, SI/B, depression and anxiety. We analyzed data available from long-term extension safety studies separately due to the lack of a control arm. Because of differences in trial design, dosing regimens, and trial duration, we also analyzed data based on specific treatment period (i.e., initial, maintenance, and open-label extension). Overall, the incidence of psychiatric events was numerically low (< 2%) in bimekizumab-treated patients during the initial placebo- or active-controlled treatment period. Analysis of the eC-SSRS suggested an SI/B incidence of ≤ 2% for bimekizumab (exposure-adjusted incidence rate for adjudicated SI/B: 0.07 per 100 patient years), similar to the background incidence for SI/B in this patient population. We observed no SI/B-related deaths or suicidal behavior events in any patient and no significant association for an increased risk of depression and anxiety with bimekizumab.

Based on this thorough review of clinical trial data, we do not recommend specific psychiatric warning language in the bimekizumab label at this time. We continue to recommend that any future study protocol under the bimekizumab development program should include, when necessary, prospective assessment for SI/B and psychiatric disorders given the history of possible SI/B signals in this drug class and in this patient population.

II. Background

Bimekizumab is a humanized, monoclonal antibody of the immunoglobulin G1 (IgG1) subclass that selectively binds and neutralizes human interleukin-17A (IL-17A) and interlukin-17F (IL-17F). Non-clinical studies suggest that bimekizumab is also highly selective in inhibiting interlukin-6 (IL-6) secretion, inhibiting migration of monocytes and neutrophils induced by activated human dermal fibroblasts, and inhibiting the expression of several inflammatory genes in epidermal keratinocytes and dermal fibroblasts. The Applicant, UCB Inc., is developing bimekizumab for the treatment of moderate to severe plaque psoriasis (PSO) in adults. The Applicant proposes to administer bimekizumab subcutaneously with a dosing regimen of 320 mg every 4 weeks for 16 weeks, followed by a maintenance dose of 320 mg every 8 weeks.

The Applicant is also developing parallel programs in the inflammatory disease of psoriatic arthritis, axis spondylarthritis (b) (4) and hidradenitis suppurativa (b) (4)). Based on the adult PSO program, the Applicant also plans to conduct two studies in pediatric patients (age 6 to 17 years) with moderate to severe plaque PSO. Several additional monoclonal antibodies intended to either neutralize IL-17 (including ixekizumab and secukinumab) or inhibit IL-17 receptors (brodalumab) are developed or are in development for the treatment of PSO.

Patients with psoriasis are at higher risk for depression and suicide than the general public, although it is unclear if the rates are mainly due to an immune-mediated cause, high psychosocial burden of the illness, or a combination of both factors.[1] There have been growing concerns for increased depression and suicidal behaviors in response to IL-17- based treatments. Other psoriasis systemic therapies that target other various receptors (e.g., IL-12, IL-23, IL-17, and Tumor Necrosis Factor-α) are associated with downstream psychiatric effects and are theorized to modulate neurotransmission. Increasing evidence suggests that cytokines are key mediators in the pathophysiology of major depressive disorder (possibly via hypothalamic-pituitary-adrenal (HPA) axis effects) and other psychiatric disorders like schizophrenia. Animal studies suggest that when IL-17 signaling was altered, mice exhibited various behavioral changes.[2] Other clinical studies have also noted altered cytokine levels (i.e., IL-6 elevations, IL-2, IL-4 and Transforming Growth Factor-β) in the cerebrospinal fluid of suicide attempters and completers compared to non-suicidal subjects.[3,4] However, a clear mechanism explaining the relationship between biological inflammatory markers and psychiatric events is not established.

[1] 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.

[2] Moynihan J, et al. Psychoneuroimmunology: the example of psoriasis. *G Ital Dermatol Venereol.* 2010;145(2): 221-8

[3] Gananca L, et al. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology*. 2016;63:296-310.

[4] Ducasse D, et al. A meta-analysis of cytokines in suicidal behavior. *Brain, Behavior, and Immunity*. 2015;46:203-11

III. Review of Clinical Data

a. Selection of Relevant Clinical Trials

Table 1: Subject Population, Placebo/Active-Controlled Trials

Trial	Trial Design*	Trial Duration	Treatment Group	Number of Subjects
PS0010	R, DB, PLB controlled, parallel-group, dose-ranging study	12 weeks	PLB every 4 weeks	42
			BKZ 64 mg every 4 weeks	39
			BKZ 160 mg every 4 weeks	43
			BKZ 320 mg every 4 weeks	43
			BKZ 480 mg every 4 weeks	43
			BKZ 320 mg loading dose then BKZ 160 mg every 4 weeks	40
PS0016	R, DB, PLB controlled, parallel group pharmacodynamic response study	28 weeks	BKZ 320 mg at baseline, week 4, and PLB at week 16	32
			BKZ 320 mg at baseline, week 4, and week 16	17
PS0008	R, DB, active-controlled, parallel-group study	56 weeks for BKZ; 24 weeks for ADA	BKZ 320 mg every 4 weeks	158
			BKZ 320 mg every 4 weeks until week 16, then 320 mg every 8 weeks through week 52	161
			ADA 80 mg loading dose and 400 mg every 2 weeks after week 1 until week 24, then BKZ 320 mg every 4 weeks through week 52	159
PS0009	R, DB, PLB and active-controlled, parallel-group, study	52 weeks	BKZ 320 mg every 4 weeks	321
			USK 45 mg or 90 mg at baseline and 4 weeks later, then every 12 weeks	163
			Placebo every 4 weeks until week 16, then BKZ 320 mg every 4 weeks through week 48	83
PS0013	R, DB, PLB controlled, withdrawal study	56 weeks (16 week initial period)	Initial Period: BKZ 320 mg every 4 weeks	349
			Initial Period: PLB every 4 weeks	86

R: randomized; DB: double-blind; PLB: placebo; BKZ: bimekizumab; USK: ustekinumab; ADA: adalimumab
*population: adults with moderate to severe PSO who were eligible for systemic therapy and/or phototherapy
Source: Reviewer's table

As noted in Table 1, two phase 2 studies (PS0010 and PS0016) and three phase 3 studies (PS0008, PS0009, and PS0013) are included in this analysis to evaluate psychiatric safety-related AEs, SI/B, depression, and anxiety. Study PS00013 is a randomized withdrawal study that included an initial treatment period of 16 weeks where patients received either subcutaneous bimekizumab (320 mg every 4 weeks) or placebo. Patients receiving bimekizumab that achieved a PASI90 response were re-randomized to continue bimekizumab every 4 weeks or every 8 weeks, or switch to placebo treatment. Data captured during the controlled initial treatment period, maintenance/withdrawal treatment period, and open-label extension period was leveraged in this analysis.

Table 2: Subject Population, Open-Label Extension Studies

Trial	Trial Design*	Trial Duration	Treatment Group	Number of Subjects
PS0011	Open-label extension study using patients from study PS0010	48 weeks	BKZ 64 mg every 4 weeks	15
			BKZ 160 mg every 4 weeks	111
			BKZ 320 mg every 4 weeks	91
PS0018	Open-label extension study using patients from study PS0016	48 weeks	BKZ 320 mg every 4 weeks (PLB group at week 16)	28
			BKZ 320 mg every 4 weeks	15
PS0014	Open-label extension study using patients from study PS0008, PS0009, PS0013	144 weeks	BKZ 320 mg every 4 weeks	15 (currently ongoing)
			BKZ 320 mg every 8 weeks	51 (currently ongoing)

PLB: placebo; BKZ: bimekizumab
*patient population consisted of adult subjects with moderate to severe plaque psoriasis who were candidates for systemic PSO therapy and/or phototherapy.
Source: Reviewer's table

Trial characteristics for the three long term extension studies (PS0011, PS0018, PS0014) are provided in Table 2. We analyzed data available from long-term extension safety studies separately due to the lack of a control arm. The Applicant also noted that a phase 3b active controlled study using secukinumab was still blinded and ongoing at the time of clinical cut-off date, and thus not included in the initial regulatory submission.

b. Psychiatric Inclusion and Exclusion Criteria

Table 3: Inclusion, Exclusion, and Withdrawal Criteria for Placebo/Active-Controlled Trials

Trial	Exclusion Criteria	Withdrawal Criteria
PS0010 PS0016	• Presence of significant uncontrolled neuropsychiatric disorder, active suicidal ideation, or positive suicide behavior using the "Baseline" version of the eC-SSRS and the HADS with either of the following criteria: o a lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or has suicidal ideation in the past 6 months as indicated by a positive response to either Question 4 or Question 5 of the eC-SSRS at screening. o HADS-D score >10 or HADS-A score ≥15	• Active suicidal ideation as indicated by positive response to Question 4 or 5 or to the suicidal behavior questions using the "Since Last Visit" version of the eC-SSRS • HADS-D score ≥15 (a patient that experiences a HADS-D score > 10 should be referred to a mental mealthcare provider for potential withdrawal)
PS0008 PS0009 PS0013	• Presence of active suicidal ideation or positive suicidal behavior using the "Screening" version of the eC-SSRS and with either of the following criteria: o history of suicide attempt within the past 5 years prior to screening o 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	• Active suicidal ideation as indicated by positive response to Question 4 or 5 or to the suicidal behavior questions using the "Since Last Visit" version of the eC-SSRS • Severe major depression as indicated by a PHQ-9 score ≥20 (study PS0013 only: patients with moderately severe major depression as indicated by a PHQ-9 score of 15-19 if this represent an increase of 3 points compared to the last visit must be referred to a mental healthcare provider for potential withdrawal)

eC-SSRS: electronic Columbia Suicide Severity Rating Scale; HADS: Hospital Anxiety and Depression Scale; HADS-D: Hospital Anxiety and Depression Scale – Depression Score ; HADS-A: Hospital Anxiety and Depression Scale – Anxiety Score ; PHQ-9: Patient Health Questionnaire 9
Source: Reviewer's table

c. Psychiatric Monitoring

Table 4: Neuropsychiatric Scales used for Safety Monitoring

Trial	Neuropsychiatric Safety Monitoring
PS0010	• ***HADS:*** screening, baseline, week 4, week 8, week 12, study withdrawal, and safety follow-up (20 weeks after last dose) • ***eC-SSRS:*** screening, baseline, week 1, week 2, week 4, week 6, week 8, week 12, study withdrawal, and safety follow-up (20 weeks after last dose)
PS0016	• ***HADS:*** screening, baseline, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 36, study withdrawal, and safety follow-up (20 weeks after last dose) • ***eC-SSRS:*** screening, baseline, week 1, week 2, week 4, week 6, week 8, week 12, week 16, week 20, week 24, week 28, week 36, study withdrawal, and safety follow-up (20 weeks after last dose)
PS0008	• ***PHQ-9:*** screening, baseline, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, week 48, week 52, week 56, study withdrawal, and safety follow-up (20 weeks after last dose) • ***eC-SSRS:*** screening, baseline, weeks 1-5, week 7-9, week 11-13, week 15-17 , week 19-21, week 23-24, week 28, week 32, week 36, week 40, week 44, week 48, week 52, week 56, study withdrawal, and safety follow-up (20 weeks after last dose)
PS0009	• ***PHQ-9:*** screening, baseline, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, week 48, week 52, study withdrawal, and safety follow-up (20 weeks after last dose) • ***eC-SSRS:*** screening, baseline, week 1, week 2, week 4, week 8, week 12, week 16, week 20, week 24 week 28, week 32, week 36, week 40, week 44, week 48, week 52, study withdrawal, and safety follow-up (20 weeks after last dose)
PS0013	• ***PHQ-9:*** screening, baseline, week 4, week 8, week 12, week 16, week 20, week 24, week 28, week 32, week 36, week 40, week 44, week 48, week 52, week 56, study withdrawal, and safety follow-up (20 weeks after last dose) • ***eC-SSRS:*** screening, baseline, week 1, week 2, week 4, week 8, week 12, week 16, week 20, week 24 week 28, week 32, week 36, week 40, week 44, week 48, week 52, week 56, study withdrawal, and safety follow-up (20 weeks after last dose)

eC-SSRS: electronic Columbia Suicide Severity Rating Scale; HADS: Hospital Anxiety and Depression Scale; PHQ-9: Patient Health Questionnaire 9
Source: Reviewer's table

d. Coding of Psychiatric Adverse Events

We summarized AEs across all studies based on MedDRA-coded terms (MedDRA version 19.0) and reviewed the Applicant's submitted *adae.xpt* dataset for coding accuracy between AETERMs and AEDECODs. We determined that coding accuracy was satisfactory from a psychiatric AE perspective. AEs listed under the Injury, Poisoning, and Procedural Complications system organ classifications (SOC) suggested no obvious miscodings of hidden psychiatric events. The events were likely accidental and non-psychiatric in nature based on the limited information provided, except for the events that were coded already as psychiatric.

Psychiatric AE terms were found under AEBODSYS category for Psychiatric Disorder SOC. Under AEDECOD (preferred terms) they were as follows:

PS0010— anxiety, sleep disorder
PS0016— none listed
PS0008— adjustment disorder, affective disorder, alcohol abuse, anxiety, confusional state, depression, insomnia, initial insomnia, somnambulism
PS0009— acute psychosis, aggression, alcoholism, anxiety, attention deficit/hyperactivity disorder, bipolar disorder, depression, generalized anxiety disorder, insomnia, mood swings, schizoaffective disorder, substance abuse, suicide attempt
PS0013— alcohol abuse, anxiety, bipolar disorder, depressed mood, depression, drug abuse, initial insomnia, insomnia, sleep disorder, stress
PS0011— affect lability, anxiety, cyclothymic disorder, depression, insomnia
PS0018— insomnia,
PS0014—alcohol abuse, alcohol withdrawal syndrome, bipolar disorder, depression, generalized anxiety disorder, insomnia, panic attack, tension

There were also 140 cases (out of 440 total AE cases) coded under fatigue or tiredness. These events were not included in this analysis due to difficulties in determining the etiology from both the underlying medical condition of psoriasis and possible systemic drug effects versus any depressive etiology.

e. Method of Review

For the purpose of this analysis, we evaluated neuropsychiatric safety by specific pools of studies or individually. Due to differences in trial design, dosing regimens, and trial duration, we created three different collections of trials.

Pool 1 consists of the combined data from the initial treatment period for phase 2 studies PS0010 and PS0016 and phase 3 studies PS0008, PS0009, and PS0013 with study participants exposed to bimekizumab for up to 16 weeks in the phase 3 studies and up to 12 weeks in phase 2 studies. Pool 2 consists of the combined data from the maintenance treatment period for phase 3 studies PS0008, PS0009, and PS0013 (includes withdrawal period). Pool 3 consists of the combined data from the open-label extension studies PS0011, PS0018, PS0014 with study participants exposed to bimekizumab for up to an additional 48 weeks.

IV. Review of Safety

a. Psychiatric Adverse Events

Table 5: Number of Patients Experiencing Psychiatric AEs in Phase 2 and 3 Trials during the Placebo Controlled, Initial Treatment Phase (Until End of Week 16 for PS0009, PS0008, PS0013, End of Week 12 for PS0016, and End of Week 8 for PS00010) – Pool 1

Study	Placebo (N=211)	Adalimumab (N=159)	Ustekinumab (N=163)	BKZ Total (N=1,246)
PS0016	0	-	-	0
PS0010	0	-	-	3
PS0008	-	1	0	2
PS0009	0	0	1	6
PS0013	0*	-	-	6
Total	(0%)	1 (0.6%)	1 (0.6%)	17 (1.3%)

*One event was listed by the Applicant to have occurred in a placebo treated patient. However, this event occurred on Day 114 (16.2 weeks)
Source: Reviewer's table

Table 6: Number of Patients Experiencing Psychiatric AEs in Phase 2 and 3 Trials during the Maintenance Treatment Phase (Until End of Week 52 for PS0008, PS0009, and PS0013) – Pool 2

Study	Ustekinumab (N=157)	BKZ Total (N=1,042)
PS0008	0	6
PS0009	3	5
PS0013	0	9
Total	3 (1.9%)	20 (1.9%)

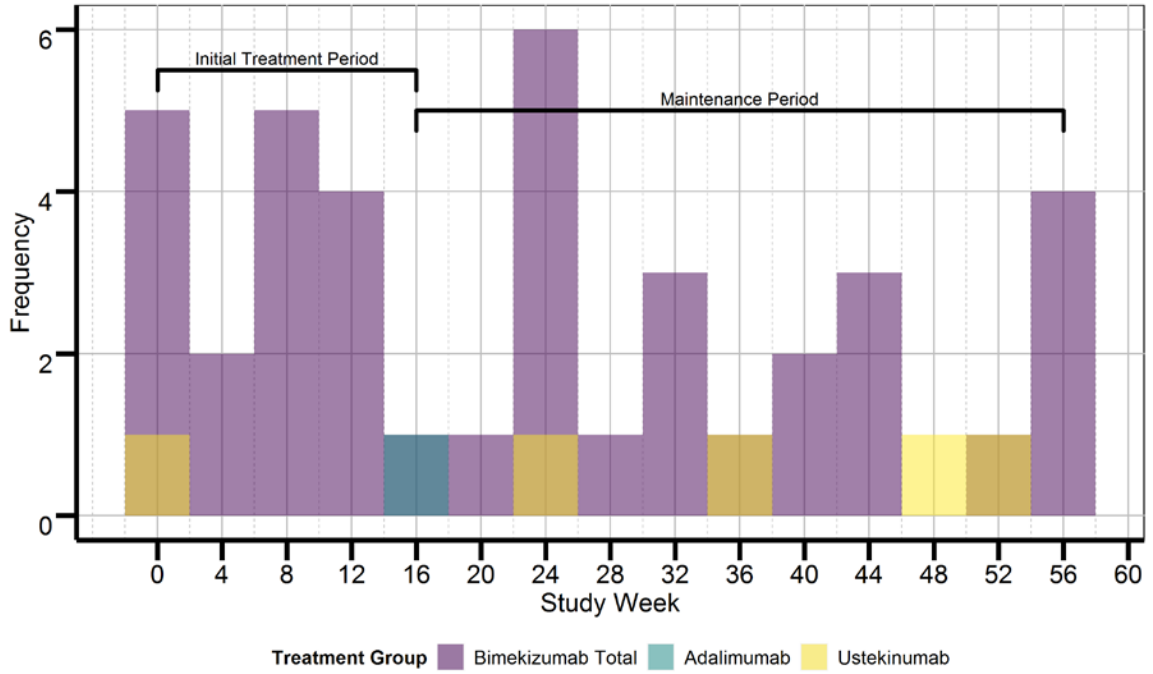
Source: Reviewer's table

The total number of patients experiencing a psychiatric safety-related AE was numerically higher in the bimekizumab-treated group compared to the control groups. White patients aged 40 to 65 years from North American trial sites contributed to a majority of the psychiatric AEs reported. Although two patients receiving placebo reported sleeping difficulties during the screening and withdrawal period in PS0013, no new psychiatric AEs were reported in any patient receiving placebo. During the maintenance phase, there were 20 patients (1.9%) that experienced a psychiatric AE while receiving bimekizumab treatment. Three patients receiving ustekinumab (1.9%) also experienced a psychiatric AE during the maintenance phase.

Figure 1 provides a graphical summary with regards to the timing of the event across the initial and maintenance treatment periods. There was no apparent time-trends observed among psychiatric events in patients enrolled into any treatment arm. Characterization of AEs are provided in Table 7 and Table 8 by treatment phase. The majority of AEs were related to anxiety in patients receiving bimekizumab during the initial and maintenance treatment period. Given that no events occurred in patients receiving placebo, we did not conduct an informal statistical analysis to compare the incidences of psychiatric events. Although the incidence of psychiatric events were numerically greater in the bimekizumab treated patients versus active control treated patients, the limited sample size in the active control group would not allow for an effective statistical

comparison. Because approximately 90% of patients were receiving bimekizumab 320 mg every 4 weeks, determination of dosing-regimen-dependent analysis was also not feasible.

Figure 1: Distribution of AEs across Phase 2 and 3 Studies (Pool 1 and 2)



Source: Reviewer's figure

Table 7: Psychiatric AEs in Phase 2 and 3 Trials during the Placebo Controlled, Initial Treatment Phase (Until End of Week 16 for PS0009, PS0008, PS0013, End of Week 12 for PS0010, and End of Week 8 for PS00016) – Pool 1

Adverse Event	Placebo (N=211)	Adalimumab (N=159)	Ustekinumab (N=163)	BKZ Total (N=1,246)
Aggression	0	0	0	1
Alcohol abuse	0	1	0	1
Anxiety	0	0	0	5
Attention deficit/hyperactivity disorder	0	0	0	1
Bipolar disorder	0	0	0	1
Confusional state	0	0	0	1
Depression	0	0	1	2
Insomnia	0	0	0	1
Mood swings	0	0	0	1
Sleep disorder	0	0	0	1
Somnambulism	0	0	0	1
Stress	0	0	0	1
ALL Psychiatric AEs	0*	1 (0.6%)	1 (0.6%)	17 (1.3%)

*One event was listed by the Applicant to have occurred in a placebo treated patient. However, this event occurred on Day 114 (16.2 weeks)
Source: Reviewer's table

Table 8: Psychiatric AEs in Phase 2 and 3 Trials during the Maintenance Treatment Phase (Until End of Week 52 for PS0008, PS0009, and PS0013) – Pool 2

Adverse Event	Ustekinumab (N=157)	BKZ Total (N=1,042)
Acute psychosis	0	1
Adjustment disorder	0	1
Affective disorder	0	1
Alcoholism	0	1
Anxiety	1	4
Attention deficit/ hyperactivity disorder	0	1
Depression	1	2*
Drug abuse	0	1
Insomnia	0	7
Sleep disorder	0	1
Suicide attempt	1	0
ALL Psychiatric AEs	3 (1.9%)	20 (1.9%)

*One patient receiving bimekizumab 320 mg every 8 weeks experienced a depressive episode on Day 175 and was later reported to have worsening depression on Day 220. For this analysis, the two events were combined and was coded as one single event. The total number of events reported by the Applicant was 21 in patients treated with bimekizumab.
Source: Reviewer's table

Table 9: Psychiatric AEs in Phase 2 and 3 Trials during the Open-Label Extension Phase (PS0011, PS0014, and PS0018) – Pool 3

Adverse Event	BKZ 160 mg every 4 weeks (N=111)	BKZ 320 mg every 4 weeks (N=149)	BKZ 320 mg every 8 weeks (N=51)	BKZ Total* (N=326)
Affect lability	1	0	0	1
Alcohol abuse	0	1	0	1
Alcohol withdrawal syndrome	0	1	0	1
Anxiety	3	2	0	5
Bipolar disorder	0	2	0	2
Cyclothymic disorder	1	0	0	1
Depression	1	2	0	3
Insomnia	1	5	1	7
Panic attack	0	0	1	1
Tension	0	1	0	1
ALL Psychiatric AEs	7 (6.3%)	14 (9.4%)	2 (3.9%)	23 (7.1%)

*Fifteen patients received bimekizumab 64 mg every 4 week and no AEs were observed
Source: Reviewer's table

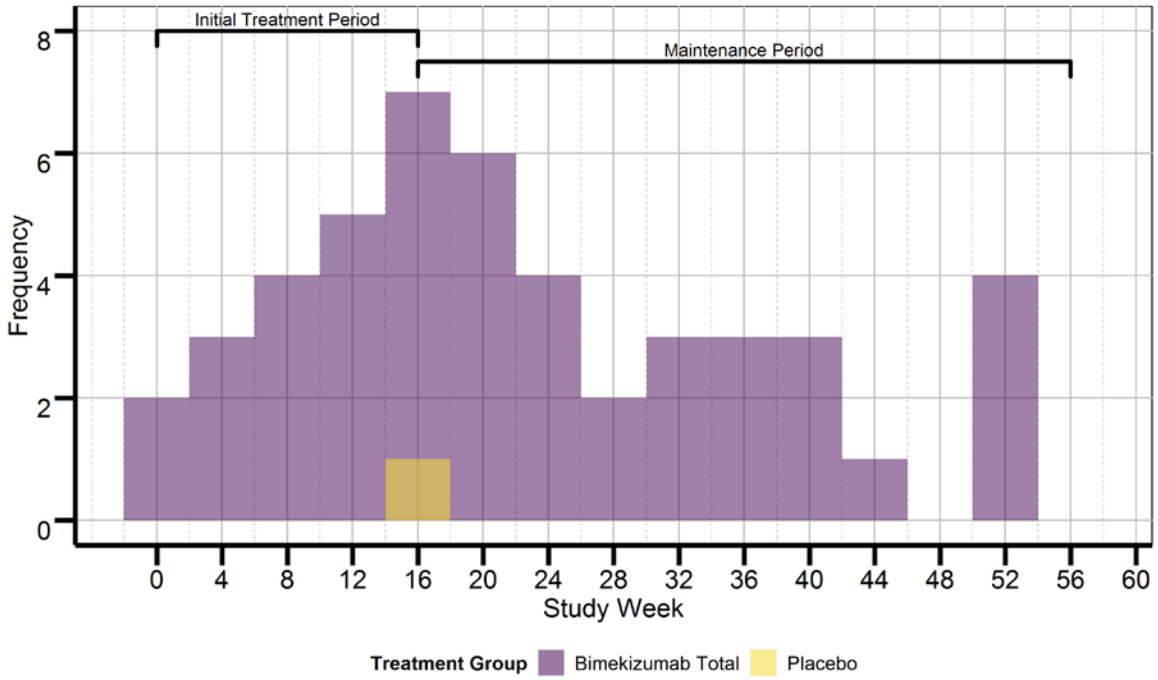
During the open-label extension, the number of AEs reported in patients receiving bimekizumab was numerically higher than the incidences observed during the initial or maintenance treatment phase. The most common AEs reported were anxiety and insomnia. The combination of all the different treatment phases yielded approximately 60 total psychiatric AEs. If we considered one additional depression AE observed in the maintenance phase (two events reported for the same episode by the Applicant), the incidences reported by the reviewer and the Applicant are identical. The Applicant reported a total of four AEs (0.2%) observed in patients receiving bimekizumab as treatment-emergent AEs that led to study discontinuation. The applicant did not categorize any of

the AEs as serious. One limitation of the presented analysis is acknowledging differences in drug exposure time and not reporting exposure-time adjusted rates of psychiatric AEs. Because dropout rates were relatively low (all-cause dropout rate reported by the Applicant was 11.8% in patients receiving bimekizumab in phase 2 and 3 trials; 7.7% versus 4.4% in patients receiving placebo and bimekizumab during the initial treatment period, respectively), percent incidence is reasonably reliable to interpret psychiatric related-risks. However, the Applicant's exposure-adjusted incidence rate (EAIR) analysis demonstrated that there was no difference in patients experiencing a psychiatric AE between placebo (EAIR: 1.9; 95% CI: 0-10.9) and bimekizumab (EAIR: 3.4; 95% CI: 2.6-4.4).

b. Suicidal Ideation and Behavior (SI/B) Events per eC-SSRS

Due to differences in the methods of eC-SSRS data collection used across phase 2 and phase 3 studies, eC-SSRS data from phase 2 studies were not pooled with data from phase 3 studies. Individual study results from the PS0010 and PS0016 studies are reported separately. Data for study participants who completed the wrong questionnaire at a visit (for example, the "since last visit" assessment was completed at the Screening visit) were not pooled. We summarized the incidence of study participants with suicidal ideation, suicidal behavior, suicidal ideation or behavior, and self-injurious behavior by treatment group for the initial and maintenance treatment periods for phase 3 studies in Pool 1 (PS0008, PS009, PS0013). Because patients could experience multiple SI/B events that may arise from an identical episode, we summarized the maximum severity of SI/B. We have provided a separate summary of SI/B events for patients enrolled in the open-label extension period. We defined lifetime history of SI/B as a positive SI/B event prior to receiving treatment (lifetime history plus baseline record).

Figure 2: Distribution of SI/B Events across the Initial and Maintenance Treatment Period for Studies PS0008, PS009, and PS0013



Source: Reviewer's figure

Figure 2 suggests that the majority of SI/B events occurred within 6 months of study enrollment. There was no clear pattern in the timing of SI/B events relative to treatment initiation. The summarized initial treatment period data describes that suicidal ideation contributed to the majority of SI/B events, and all of the ideation events were mild in severity (all but one was C-CASA level 1, and one was C-CASA level 2). The one suicidal behavior event recorded was apparently an error. The number of events did not increase over time during the maintenance or open-label periods; the events' ongoing occurrence even in those periods indicate no clear relationship to initiation of drug treatment. These observations further highlight the lack of an evidence of a causal relationship between bimekizumab and SI/B events.

Table 10: Incidence of Suicidal Ideation and Behavior using the eC-SSRS (Initial Treatment Period Until End of Week 16 for PS0009, PS0008, PS0013) – Pool 1

		eC-SSRS / C-CASA Categories				Total Events (yes/no)	
		Lifetime N (%)		Maximum – Treatment Phase N (%)		Lifetime N (%)	Maximum- Treatment Phase N (%)
Treatment Arm	Category	SI	SB	SI	SB	SI/B	SI/B
Bimekizumab (N=975)	0	903 (92.6)	974 (99.9)	959 (98.3)	975 (100)	73 (7.5)	18 (1.8)
	1	42 (4.3)	1 (0.1)	16 (1.6)	0		
	2	17 (1.7)	0	1	0		
	3	10 (1.0)	0	0	0		
	4	0	0	0	1* (0.1)		
	5	3 (0.3)	0	0	0		
Placebo (N=169)	0	159 (94.0)	167 (98.8)	168 (99.4)	169 (100)	12 (7.1)	1 (0.6)
	1	5 (3.0)	1 (0.6)	1 (0.6)	0		
	2	1 (0.6)	0	0	0		
	3	3 (1.8)	0	0	0		
	4	0	1 (0.6)	0	0		
	5	1 (0.6)	0	0	0		

eC-SSRS: electronic Columbia Suicide Severity Rating Scale; C-CASA: Columbia Classification Algorithm of Suicide Assessment ; SI: suicidal ideation; SB: suicidal behavior
*One suicidal behavior (interrupted attempt) response was noted, but confirmed after the cut-off date to be a data entry error (Study participant PS0009 (b) (6))
Source: Reviewer's table

We did not report any SI/B-related deaths during the initial treatment period (Table 10). Although we observed very few SI/B events per C-SSRS during the initial treatment period, the number of

SI/B events in the bimekizumab treatment group was still numerically greater than the placebo-control group (18 SI/B events vs. 1 SI/B event), although any statistical significance for this difference cannot be determined. The lifetime history for SI/B was comparable between both groups. Only four patients (22%) that received bimekizumab and experienced an SI/B event during the initial treatment period reported a lifetime history for suicidal ideation. Therefore, the majority of cases can be thought of as an "initial-onset" of SI/B.

The Applicant only reported two AEs among patients reporting a positive response on the eC-SSRS. Patient PS0009-[redacted] (b) (6) and PS0013-[redacted] (b) (6) reported AEs of "bipolar affective disorder" and "worsening bipolar disorder", respectively. The Applicant also submitted a neuropsychiatric-adjudicated narrative for patient receiving ustekinumab in study PS0009-[redacted] (b) (6) for suicidal behavior.

Table 11: Incidence of Suicidal Ideation and Behavior using the eC-SSRS (Maintenance Treatment Period) – Pool 2

		eC-SSRS / CASA Categories				Total Events (yes/no)	
		Lifetime N (%)		Maximum – Treatment Phase N (%)		Lifetime N (%)	Maximum-Treatment Phase N (%)
Treatment Arm	Category	SI	SB	SI	SB	SI/B	SI/B
Bimekizumab (N=1,027)	0	977 (95.1)	1026 (99.9)	1011 (98.4)	1027 (100)	51 (5.0)	16 (1.6)
	1	31 (3.0)	1 (0.1)	13 (1.3)	0		
	2	14 (1.4)	0	1 (0.1)	0		
	3	4 (0.4)	0	1 (0.1)	0		
	4	0	0	1 (0.1)	0		
	5	1 (0.1)	0	0	0		

eC-SSRS: electronic Columbia Suicide Severity Rating Scale; C-CASA: Columbia Classification Algorithm of Suicide Assessment ; SI: suicidal ideation; SB: suicidal behavior
Source: Reviewer's table

Table 12: Incidence of Suicidal Ideation and Behavior using the eC-SSRS (Open Label Extension Period) – Pool 3

		eC-SSRS / CASA Categories				Total Events (yes/no)	
		Lifetime N (%)		Maximum – Treatment Phase N (%)		Lifetime N (%)	Maximum-Treatment Phase N (%)
Treatment Arm	Category	SI	SB	SI	SB	SI/B	SI/B
Bimekizumab (N=450)	0	376 (83.6)	448 (99.6)	441 (98.0)	450 (100)	16 (3.6)	9 (2)
	1	7 (1.6)	1 (0.2)	7 (1.6)	0		
	2	1 (0.2)	0	0	0		
	3	5 (1.1)	0	2 (0.4)	0		
	4	0	1 (0.2)	0	0		
	5	1 (0.2)	0	0	0		

eC-SSRS: electronic Columbia Suicide Severity Rating Scale; C-CASA: Columbia Classification Algorithm of Suicide Assessment ; SI: suicidal ideation; SB: suicidal behavior
Source: Reviewer's table

The incidence for a positive SI/B event during the maintenance and open-label extension period (25 events) was also low and similar to the incidence observed during the initial treatment period (Table 11 and Table 12). The majority of positive responses were limited to question 1 (20 patients) in the bimekizumab treatment group. Only one patient receiving bimekizumab (PS0009-[(b) (6)]) was adjudicated as SI/B by the Neuropsychiatric Adjudication Committee. Investigators recorded a suicidal ideation event during the initial treatment period (C-CASA level 1) and then later captured another event in the same patient during the maintenance period (C-CASA level 4). This patient had schizoaffective disorder-bipolar type diagnosed after the SI/B event and a medical history of a suicide attempt identified only during the study. Two out of 16 patients (12.5%) in the maintenance period and four out of nine patients (44.4%) in the open-label extension period that experienced a positive SI/B signal were also reported to have a lifetime history of SI/B per the eC-SSRS.

We noted three patients receiving bimekizumab (3/208; 1.4%) to have a positive response to question 1 for suicidal ideation (wish to be dead) during the post-baseline treatment period in study PS0010. It is unclear why the Applicant did not report the three events (Applicant reported 0 SI/B events for this study). In agreement with the Applicant, we also did not report any SI/B events in patients enrolled in study PS0016. No completed suicides occurred at any period to date in the PSO program. Assuming the lifetime history of SI/B reflects the risk in the background population, there does not appear to be an increased risk with bimekizumab treatment.

c. Depression and Anxiety

The Applicant used the HADS to prospectively measure changes in anxiety (HADS-A) and depression (HADS-D) in study PS0010 and PS0016. The total score for both scales range from 0 to 21, with higher scores indicating a worse state. A summary of the mean change from baseline in HADS-A and HADS-D is provided in Table 13 for both studies. At baseline, mean HADS-A and HADS-D scores were low and generally similar in all treatment groups. A score below 8 or less is considered to be normal. Study protocols indicated that patients with a HADS-A or HADS-D score of greater than 15 would require study withdrawal.

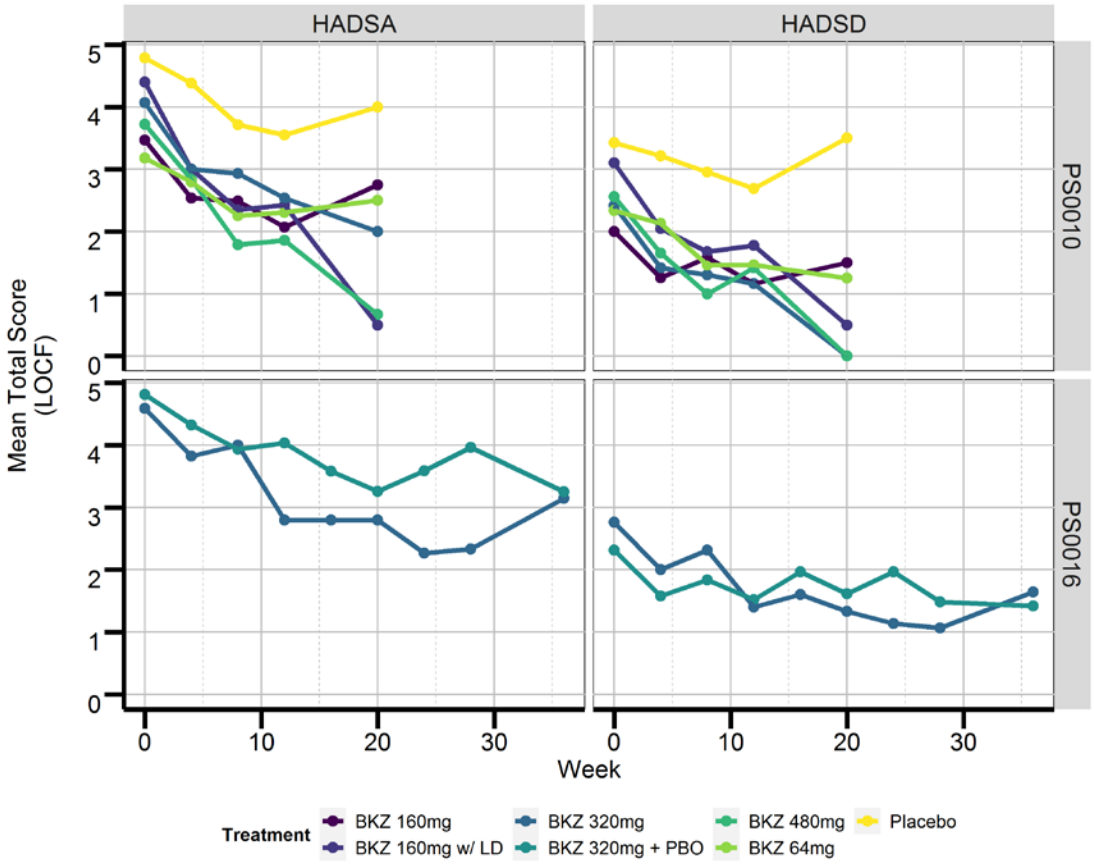
Table 13: Analysis of HADS-A and HADS-D for Study PS0010 and PS0016

			HADS-A		HADS-D	
Study	**Treatment Arm**	**Week**	**Mean CFB (SE)***	**# of patients Total Score > 8**	**Mean CFB (SE)***	**# of patients Total Score > 8**
PS0010	Placebo	12	-1.3 (0.4)	2/42	-0.7 (0.3)	5/42
	BKZ 64 mg	12	-0.8 (0.4)	1/39	-0.9 (0.3)	1/39
	BKZ 160 mg	12	-1.4 (0.3)	1/43	-0.8 (0.3)	1/43
	BKZ 160 mg w/ LD	12	-1.9 (0.5)	2/40	-1.3 (0.5)	1/40
	BKZ 320 mg	12	-1.6 (0.4)	2/43	-1.3 (0.4)	0/43
	BKZ 480 mg	12	-1.9 (0.4)	0/43	-1.2 (0.5)	2/43
PS0016	BKZ 320 mg + PLB	28	-1.3 (0.4)	4/27	-1.0 (0.3)	0/27
	BKZ 320 mg	28	-2.1 (0.5)	1/15	-1.7 (0.6)	0/15

CFB: change from baseline; SE: standard error; LD: loading dose; PLB: placebo
*Missing data controlled for by using multiple imputation method reported by the Applicant
Source: adapted from Applicant's submitted tables for PS0010 and PS0016

Small improvements were observed in HADS-A and HADS-D total scores across all treatment groups compared to placebo treated patients. Average treatment effects observed for anxiety and depressive symptoms were similar across all bimekizumab treatment groups. The number of patients that were observed to have a HADS-A or HADS-D total score greater than 8 was relatively low and similar across treatment groups. No patients met the HADS withdrawal criteria. Figure 3 provides a longitudinal visualization of average total HADS-A and HADS-D total scores for both studies.

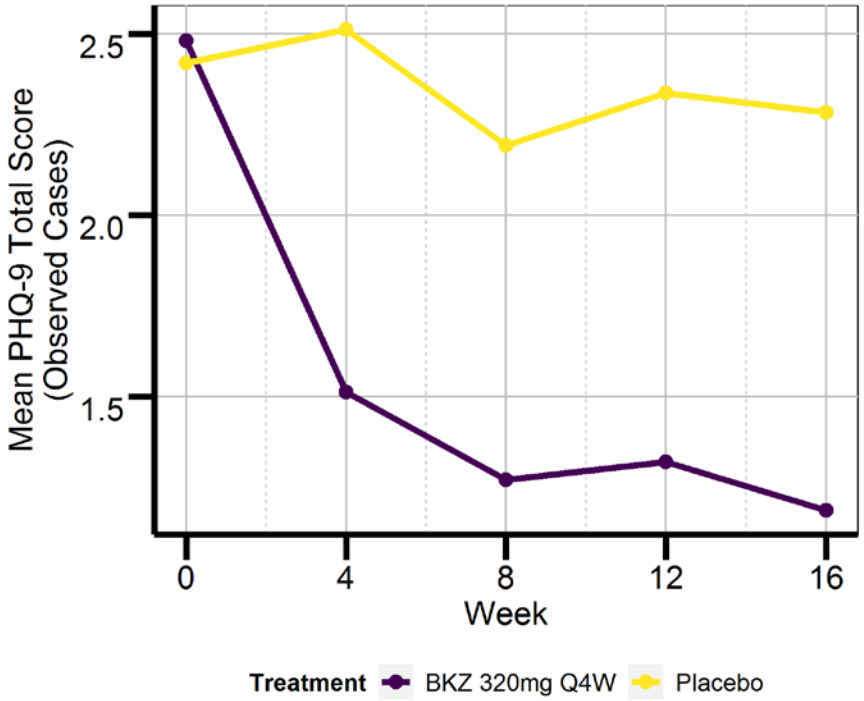
Figure 3: Average Total Scores in HADS-A and HADS-D over Time in All Treatment Groups for Studies PS0010 and PS0016



Source: Reviewer's figure

The PHQ-9 is a multipurpose instrument for measuring the severity of depression. The Applicant used the PHQ-9 in studies PS0008, PS009, and PS0013. Scores range from 0 to 27 with higher scores indicating a worse state. A score of 5 to 9 indicates minimal symptoms of depression. A score of 10 to 14 indicates minor depression, dysthymia, or mild major depression. A score of 15 to 19 indicates moderately severe major depression and a score ≥20 indicates severe major depression. Figure 4 provides a visual summary of the average PHQ-9 total score during the initial treatment period. At Baseline, mean PHQ-9 total scores were low and similar in the bimekizumab 320 mg Q4W group (2.45 points) and the placebo group (2.60 points). At Week 16, mean change from baseline in total PHQ-9 scores was numerically favorable in the bimekizumab 320mg Q4W group (-1.27 points) compared to the placebo group (-0.26 points).

Figure 4: Mean PHQ-9 Total Score during the Initial Treatment Period



Source: Reviewer's figure

The number of patients that had a PHQ-9 total score ≥ 15 during the initial treatment phase was greater in the bimekizumab treatment group versus placebo (15 vs. 7 patients). Only one patient treated with bimekizumab (PS0013-[redacted] (b) (6)) was recorded to have a total score ≥ 20 and subsequently withdrawn from the study. This patient was noted to have a positive SI/B event recorded using the eC-SSRS and a reported AE for worsening bipolar disorder. A total of three patients with a PHQ-9 total score ≥ 15 reported an AE. When combining the initial, maintenance, and open-label extension periods, the number of patients with a total score ≥ 15 and ≥ 20 was 18 (1.2%) and 3 (0.2%) patients, respectively. No clear association is evident between bimekizumab and the development or worsening of anxiety and depression when evaluating AEs using placebo-controlled data.

Analysis of changes in depression and anxiety symptoms from other psoriasis studies (i.e., brodalumab and secukinumab) described similar results.[5,6,7] The observed treatment effect on depression and anxiety should be interpreted with caution due to potential confounding (e.g., change in depression and/or anxiety because of improved psoriasis symptoms).

[5] Koo J, et al. Depression and suicidality in psoriasis and clinical studies of brodalumab: a narrative review. *Cutis.* 2019;104(6):361-5.
[6] Wu CY, et al. Depression and insomnia in patients with psoriasis and psoriatic arthritis taking tumor necrosis factor antagonists. *Medicine (Baltimore).* 2016;95:e3816.
[7] Strober B, et al. Depressive symptoms, depression, and the effect of biologic therapy among patients in Psoriasis Longitudinal Assessment and Registry (PSOLAR). *J Am Acad Dermatol.* 2018;78:70-80.

d. Case Summaries

Brief case summaries and World Health Organization (WHO)-based causality assessments of the two SI/B events and other severe psychiatric AEs from phase 2 and 3 studies were as follows:

Table 14: Bimekizumab Program Psychiatric Case Summaries

Subject ID	Study	Event Type	Original Treatment Arm	Summary	Causality Assessment
(b) (6)	PS0009	Positive eC-SSRS response	Bimekizumab 320 every 4 weeks	36-year-old Japanese male with a past medical history of mental health problems, including an attempted suicide 16 years prior to study enrollment At week 20, patient had a positive response to question 4 of the eC-SSRS and was referred to a mental healthcare provider and was subsequently diagnosed with schizoaffective and bipolar affective disorder (also reported as adverse events).	Unlikely, due to previous suicidal behavior and concurrent psychiatric diagnosis.
(b) (6)	PS0009	Suicide Attempt	Ustekinumab 45 mg at baseline and week 4; Ustekinumab every 12 weeks	25-year-old white male with a medical history of a bullet removal from the right lung, alcohol use within past 6 months, and previous tobacco use (10 pack years). No medical history of anxiety, depression, or other psychiatric disorder. Patient attempted suicide 352 days after study drug initiation and 73 days after the most recent injection. The day of the attempt, the patient was intoxicated due to heavy alcohol consumption and use of marijuana. He became violent, started arguing, and attempted suicide by running into traffic.	Unlikely, due to temporality and likely confounded by concurrent alcohol and recreational drug use.
(b) (6)	PS0013	Elevated PHQ-9 score	Bimekizumab 320 every 4 weeks; placebo during randomized withdrawal period	43-year-old white male with Gilbert syndrome and oral herpes. No history of mental health issues. Patient had an elevated PHQ-9 score that was considered severe in severity and not related to the	Unlikely, due to worsening underlying disease that is a known risk factor

Subject ID	Study	Event Type	Original Treatment Arm	Summary	Causality Assessment
				study drug. Patient had a recent flare in psoriasis and was concerned that he might be on placebo.	
(b) (6)	PS0013	Elevated PHQ-9 score	Bimekizumab 320 every 4 weeks	35-year-old white male with a medical history of epilepsy treated with valproic acid. Patient had an elevated PHQ-9 score that was considered mild in intensity after randomization to placebo and 29 days after the most recent study drug injection.	Unable to assess, insufficient information but likely not drug related due to temporality
(b) (6)	PS0013	Elevated PHQ-9 score	Bimekizumab 320 every 4 weeks	52-year-old white male with a medical history of bipolar disorder, depression, anxiety, and gout. Relevant concomitant medications include quetiapine, duloxetine, and oxazepam. Patient reported a falling out with a co-worker and had to take stress leave from work. This contributed to worsening depression and patient asked to be withdrawn from the study. An adverse event of worsening bipolar disorder was reported, and the patient met withdrawal criteria due to an elevated PHQ-9 score after Day 112.	Unlikely, due to pre-existing psychiatric condition and outside stressors
(b) (6)	PS0009	Alcoholism	Bimekizumab 320 every 4 weeks	76-year-old Japanese male with a history of age-related macular degeneration, alcohol use within past 6 months (3 units/week), and tobacco use (0.5 pack/day). Patient experienced alcoholism 283 days after study drug initiation, and 3 days after the most recent injection. Patient reported violent and offensive conversation toward his wife. Patient reported no suicidal ideation or behavior.	Unlikely, due to temporality and outside stressors

Subject ID	Study	Event Type	Original Treatment Arm	Summary	Causality Assessment
(b) (6)	PS0014	Elevated PHQ-9 score	Bimekizumab 320 every 4 weeks	35-year-old white male with back pain, cervicobrachial syndrome, alcohol use (3 units/week) over the past 6 months. Patient had an elevated PHQ-9 score after 278 days since the first study drug injection. The event was considered mild in intensity and not related to the study drug. On the same day, patient reported an AE for depression	Unlikely, due to temporality and presence of known risk factors.

V. Medical History and Concomitant Medications

Medical history data across phase 2 and 3 studies are based on the MedDRA coded terms (MedDRA version 19.0). Psychiatric disorder terms identified under the MHBODSYS category for Psychiatric Disorder SOC are presented in Table 15. The incidence of previous or ongoing medical history were generally similar between the placebo and bimekizumab treatment group, although incidence of depression and anxiety were numerically higher. The observed incidences for depression and anxiety are similar to background incidences reported in patients with psoriasis.[8] Patients with a psychiatric medical history and receiving placebo did not report any AEs. Out of all the AEs reported in patients receiving bimekizumab, patients with a positive psychiatric medical history reported 36 AEs (59%) throughout the initial, maintenance, or open-label extension period. We also recorded one patient with a positive psychiatric medical history and receiving placebo to have mild suicidal ideation (C-CASA level 1). Out of all patients with a positive SI/B signal, 9 patients (20%) with a positive psychiatric medical history and receiving bimekizumab also reported mild suicidal ideation (8 patients with C-CASA level 1; 1 patient with C-CASA level 2).

Table 15: Previous or Ongoing Psychiatric Medical History from Patients Enrolled in Phase 2 and 3 Studies

Psychiatric Disorder	Placebo (N=211) N(%)	Bimekizumab Total (N=1,789) N (%)
Depression	12 (5.7)	122 (6.8)
Anxiety	10 (4.7)	93 (5.2)
Insomnia	3 (1.4)	46 (2.6)
Attention Deficit/Hyperactivity Disorder	0	19 (1.1)
Alcoholism	0	9 (0.5)
Bipolar disorder	1 (0.4)	6 (0.3)
Tobacco Abuse	2 (0.9)	6 (0.3)

[8] 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.

Psychiatric Disorder	Placebo (N=211) N(%)	Bimekizumab Total (N=1,789) N (%)
Post-traumatic stress disorder	0	6 (0.3)
Sleep disorder	4 (1.8)	7 (0.4)
Obsessive-compulsive disorder	0	5 (0.3)
Suicide Attempt	1 (0.4)	4 (0.2)
Adjustment disorder	0	3 (0.2)
Adjustment disorder with depressed mood	0	3 (0.2)
Alcohol abuse	0	3 (0.2)
Drug Abuse	0	4 (0.2)

Source: adapted from Applicant's ISS clinical study report

Although the percentage of patients receiving psychotropic medications was low, the Applicant described that percentages were similar across all treatment arms. Approximately 7% of patients received an antidepressant or an antipsychotic for at least one day in common with the study medication. These results may further suggest similar incidences of baseline psychiatric morbidity between treatment groups. Exposure to non-biologic systemic immunomodulators (known to adversely affect mood, sleep, and anxiety) was also similar across treatment groups at baseline (approximately 53%).

VI. Findings from Previous Consults

In the United states, IL-17 pathway modulators approved for the treatment of psoriasis. include secukinumab (IL-17 antagonist), ustekinumab (thought to indirectly reduce IL-17), ixekizumab (IL-17A antagonist), and brodalumab (IL-17 receptor antagonist). Other drugs including tildrakizumab and guselkumab are also thought to antagonize other interleukin pathways (e.g., IL-23). Previous consults note no clear association of SI/B, depression, or anxiety with approved treatments for PSO. However, the intensity of the signals varied across different treatments.

The prescribing information for brodalumab address concerns related to a potentially increased risk for SI/B. During development, the Applicant reported 11 events classified as suicidal behavior, including seven suicide attempts and four completed suicides in patients with psoriasis treated with the active drug. FDA's review of the clinical trial data confirmed no completed suicides during the 12-week placebo-controlled period. DP and the Division of Epidemiology I (DEPI) concluded that brodalumab-treated patients with a history of SI/B or depression are at greater risk for SI/B as compared to patients without such a history. Therefore, a causal association for increased risk for SI/B was not established. The previous DP consult review also indicated a beneficial effect on depression and anxiety based on findings from study 2012-0102. The analysis suggested a numerical improvement in the severity of depression and anxiety using the HADS questionnaire. This current review for the bimekizumab program also notes no SI/B related deaths and only one brodalumab-treated patient with a positive signal for suicidal behavior (C-CASA=1) after the initial treatment period (miscoded by the Applicant). This review also highlights a similar beneficial treatment effect on the HADS-A and HADS-D in patients receiving bimekizumab enrolled in study PS0010 and PS0016.

There is no language in the prescribing information that describes an increased risk for SI/B or psychiatric disorders with secukinumab, ixekizumab, guselkumab, or ustekinumab. In most

programs, approximately 1% of patients reported depression as an AE. In the tildrakizumab development program, the Applicant did not report any SI/B- related deaths during the base study period. The previous consult indicated two completed suicides during the extension phase in patients with a positive psychiatric medical history. Although the previous reviewer discussed three SI/B events during study P011 in patients receiving the active drug, two ideation events during the extension phase were unlikely to be drug-related given the length of drug exposure. A previous DP consult review for guselkumab, a monoclonal antibody with a similar mechanism of action to tildrakizumab, also concluded no increased risk for SI/B and psychiatric AEs. The review indicated no suicidal behavior events and only one patient receiving active drug with suicidal ideation during the placebo-controlled phase. Retrospective C-CASA adjudication of SI/B events only noted an incidence rate of 0.10 per 100 subject-years for guselkumab. Although the previous review confirmed no completed suicides for ixekizumab, 10 instances of attempted suicide occurred in the ixekizumab group (0.14 per 100 patient years) and none in the placebo group. Previous DEPI consults evaluated SI/B in clinical trials for other biologics for moderate to severe psoriasis and identified similar rates with other drugs (Table 16).

The Applicant reports 46 total suicidal ideation events (reviewer's analysis of maximum SI/B severity revealed 42 patients) in bimekizumab-treated patients enrolled in phase 2 and 3 trials (1,461 exposure-years). The calculated exposure-adjusted incidence rate for suicidal ideation is 3.15 per 100 patient-years. Given that most of the previous clinical trials did not utilize the eC-SSRS to evaluate SI/B, comparison of suicidal ideation rates is limited. DEPI's previous consult review for brodalumab noted that the "incidence of suicidal behavior and ideation was likely to have been underestimated prior to use of the eC-SSRS. Ordinarily one would expect that the rate of suicide attempts would be considerably higher than the rate of completed suicide, and the rate of suicidal ideation to be higher still, as was seen in FDA's meta-analysis of antidepressant clinical trials. Based on data from the CDC's Web-based Injury Statistics Query and Reporting System (WISQARS), it is estimated that there are 12 attempted suicides for every completed suicide, though that ratio varies by age and gender. The ratio of the suicidal behavior rate to the completed suicide rate was 1.8 before the eC-SSRS, and 5.0 after the eC-SSRS, consistent with improved ascertainment of suicide attempts. Thus, implementation of the eC-SSRS monitoring appears to have improved detection of not only suicidal ideation but probably of suicide attempts also."

Previous analyses of antidepressant clinical trials note the high degree of sensitivity for suicidal ideation when using the eC-SSRS. This may explain the increased rate for suicidal ideation for bimekizumab as compared to other drugs (with most of the cases detected by eC-SSRS being mild in severity for this program). However, when using adjudicated AEs, only one patient experienced suicidal ideation. Therefore, it is likely that the incidence of suicidal ideation may be underestimated for other drugs due to incomplete ascertainment of events. It is also uncertain whether suicidal ideation is predictive of behavior.

In a recent meta-analysis by Loft et al., the percentage of patients experiencing depression after 52 weeks of treatment with IL-17 or IL-23 related products was 1.5% This was similar to the incidence of depression observed across phase 2 and 3 trials for bimekizumab. Overall, analysis

of current literature on IL-17 and association with any psychiatric effects remains limited and unremarkable.[9]

Table 16: Rates of SI/B in Clinical Trials for Psoriasis Treatments

Development Program	N	Completed Suicides, N	Suicide Attempts, N	Completed Suicides + Suicide Attempts, N (EAIR)	Suicidal Ideation, N (EAIR)	Adjudicated with C-CASA
Brodalumab*	4,464	3	3	6 (0.11)	3 (0.06)	No
Brodalumab**	3,823	1	5	5 (0.20)	15 (0.59)	Yes
Ixekizumab	4,209	0	9	9 (0.14)	0 (0)	Yes
Apremilast	2,401	1	2	3 (0.20)	2 (0.13)	Yes
Etanercept	1,807	0	1	1 (0.04)	2 (0.07)	No
Adalimumab	1,468	1	0	1 (0.02)	3 (0.07)	No
Secukinumab	3,928	0	1	1 (0.03)	1 (0.03)	Yes
Ustekinumab	3,117	1	0	1 (0.01)	0 (0)	No
Infliximab	1,564	0	3	3 (0.24)	0 (0)	No
Briakinumab	2,520	2	0	2 (0.07)	1 (0.03)	No
Bimekizumab***	1,495	0	1	1 (0.07)	46 (3.15)	Yes

EAIR: exposure-adjusted incidence rate per 100 patient years; C-CASA: Columbia Classification Algorithm of Suicide Assessment
*before implementation of eC-SSRS
**after implementation of eC-SSRS
***based on Applicants ISS Table 9.2 (eC-SSRS) and Table 4.2.1.1 (exposure-time)
Source: adapted from DEPI Consult Review for BLA 761032: Table 7

VII. 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 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.

Reviewer's Recommendation:

[9] Loft ND, et al. Adverse events with IL-17 and IL-23 inhibitors for psoriasis and psoriatic arthritis: a systematic review and meta-analysis of phase III studies. *JEADV*. 2020;34:1151-60.

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.

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/s/

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