CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

BLA761151Orig1s010

Name: BIMZELX® (bimekizumab-bkzx) injection, for subcutaneous use

Sponsor: UCB, Inc.

Approval Date: November 19, 2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761151Orig1s010

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APPROVAL LETTER

BLA 761151/S-010

SUPPLEMENT APPROVAL

UCB, Inc.
Attention: Susan Tegtmeyer
Associate Director
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

Dear Susan Tegtmeyer:

Please refer to your supplemental biologics license application (sBLA), dated and received January 19, 2024, and your amendments, submitted under section 351(a) of the Public Health Service Act for Bimzelx (bimekizumab-bkzx) injection, for subcutaneous use.

This Prior Approval supplemental biologics license application provides for the additional indication of the treatment of adults with moderate to severe hidradenitis suppurativa (HS).

APPROVAL & LABELING

We have completed our review of this application, as amended. It is approved, effective on the date of this letter, for use as recommended in the enclosed agreed-upon labeling.

WAIVER OF HIGHLIGHTS ½ PAGE LENGTH REQUIREMENT FOR HIGHLIGHTS

Please note that we have previously granted a waiver of the requirements of 21 CFR 201.57(d)(8) regarding the length of Highlights of Prescribing Information.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, via the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at FDA.gov,[1] that is identical to the enclosed labeling (text for the Prescribing Information, and Medication Guide) and include the labeling changes proposed in any pending "Changes Being Effected" (CBE) supplements.

[1] http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm

Information on submitting SPL files using eLIST may be found in the guidance for industry *SPL Standard for Content of Labeling Technical Qs and As*.[2]

The SPL will be accessible via publicly available labeling repositories.

Also, within 14 days, amend all pending supplemental applications that include labeling changes for this BLA, including pending "Changes Being Effected" (CBE) supplements, for which FDA has not yet issued an action letter, with the content of labeling [21 CFR 601.12(f)] in Microsoft Word format that includes the changes approved in this supplemental application, as well as annual reportable changes. To facilitate review of your submission(s), provide a highlighted or marked-up copy that shows all changes, as well as a clean Microsoft Word version. The marked-up copy should provide appropriate annotations, including supplement number(s) and annual report date(s).

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We are waiving the pediatric study requirement for ages 0 to less than 12 years of age because necessary studies are impossible or highly impracticable. This is because the prevalence of moderate to severe HS is low in this population.

We are deferring submission of your pediatric study for ages 12 to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric study has not been completed.

Your deferred pediatric study required by section 505B(a) of the Federal Food, Drug, and Cosmetic Act are required postmarketing study. The status of this postmarketing study must be reported annually according to 21 CFR 601.28 and section 505B(a)(4)(B) of the Federal Food, Drug, and Cosmetic Act. This required study is listed below.

4704-1 Conduct a multicenter, open-label clinical trial to evaluate the pharmacokinetic and safety of bimekizumab in pediatric patients including those 12 years of age and older with moderate to severe hidradenitis suppurativa.

Final Protocol Submission: 07/2025

[2] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Interim Report:	02/2029
Study Completion:	05/2031
Final Report Submission:	11/2031

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[3]

Submit the protocol(s) to your IND 134700, with a cross-reference letter to this BLA. Reports of this required pediatric postmarketing study must be submitted as a BLA or as a supplement to your approved BLA with the proposed labeling changes you believe are warranted based on the data derived from this study. When submitting the reports, please clearly mark your submission "**SUBMISSION OF REQUIRED PEDIATRIC ASSESSMENTS**" in large font, bolded type at the beginning of the cover letter of the submission.

POSTMARKETING REQUIREMENTS (PMR) UNDER 505(o)

Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (FDCA) authorizes FDA to require holders of approved drug and biological product applications to conduct postmarketing studies and clinical trials for certain purposes, if FDA makes certain findings required by the statute.

We have determined that an analysis of spontaneous postmarketing adverse events reported under subsection 505(k)(1) of the FDCA will not be sufficient to identify an unexpected serious risk of unexpected serious risk of adverse pregnancy, fetal, infant and fetal outcomes.

Furthermore, the active postmarket risk identification and analysis system as available under section 505(k)(3) of the FDCA will not be sufficient to assess these serious risks.

Therefore, based on appropriate scientific data, FDA has determined that you are required to conduct the following studies:

4704-2 Conduct a prospective pregnancy exposure registry/registries in pregnant patients with hidradenitis suppurativa.

You can use the registry required under PMR 4268-3 issued in the BLA 761151 Approval letter dated October 17, 2023.

[3] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The timetable you submitted on November 6, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2025
Study Completion: 06/2034
Final Report Submission: 06/2035

4704-3 Conduct a retrospective pregnancy cohort study in patients with hidradenitis suppurativa using claims or electronic health record data with medical chart validation.

You can use the registry required under PMR 4268-4 issued in the BLA 761151 Approval letter dated October 17, 2023.

The timetable you submitted on November 6, 2024, states that you will conduct this study according to the following schedule:

Final Protocol Submission: 06/2025
Study Completion: 12/2034
Final Report Submission: 12/2035

FDA considers the term *final* to mean that the applicant has submitted a protocol, the FDA review team has sent comments to the applicant, and the protocol has been revised as needed to meet the goal of the study or clinical trial.[4]

Submit clinical protocol(s) to your IND 134700 with a cross-reference letter to this BLA. Submit nonclinical and chemistry, manufacturing, and controls protocols and all final report(s) to your BLA. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission, as appropriate: **REQUIRED POSTMARKETING PROTOCOL UNDER 505(o), REQUIRED POSTMARKETING FINAL REPORT UNDER 505(o), REQUIRED POSTMARKETING CORRESPONDENCE UNDER 505(o).**

Section 505(o)(3)(E)(ii) of the FDCA requires you to report periodically on the status of any study or clinical trial required under this section. This section also requires you to periodically report to FDA on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Section 506B(a)(1) of the FDCA, as well as 21 CFR 601.70 requires you to report annually on the status of any postmarketing commitments or required studies or clinical trials.

FDA will consider the submission of your annual report under section 506B(a)(1) and 21 CFR 601.70 to satisfy the periodic reporting requirement under section

[4] See the guidance for Industry *Postmarketing Studies and Clinical Trials—Implementation of Section 505(o)(3) of the Federal Food, Drug, and Cosmetic Act (October 2019).* https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

505(o)(3)(E)(ii) provided that you include the elements listed in 505(o) and 21 CFR 601.70. We remind you that to comply with 505(o), your annual report must also include a report on the status of any study or clinical trial otherwise undertaken to investigate a safety issue. Failure to submit an annual report for studies or clinical trials required under 505(o) on the date required will be considered a violation of FDCA section 505(o)(3)(E)(ii) and could result in enforcement action.

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling. For information about submitting promotional materials, see the final guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs.*[5]

You must submit final promotional materials and Prescribing Information, accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at FDA.gov.[6] Information and Instructions for completing the form can be found at FDA.gov.[7]

REPORTING REQUIREMENTS

We remind you that you must comply with reporting requirements for an approved BLA (in 21 CFR 600.80 and in 21 CFR 600.81).

Your product is a Part 3 combination product (21 CFR 3.2(e)); therefore, you must also comply with postmarketing safety reporting requirements for an approved combination product (21 CFR 4, Subpart B). Additional information on combination product postmarketing safety reporting is available at FDA.gov.

[5] For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/media/128163/download.
[6] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf
[7] http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf

If you have any questions, contact Strother D. Dixon, Senior Regulatory Project Manager, at strother.dixon@fda.hhs.gov or (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, MD
Associate Director for Therapeutic Review
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURES:

- Content of Labeling
  - Prescribing Information
  - Medication Guide

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/

GORDANA DIGLISIC
11/19/2024 01:59:59 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use BIMZELX safely and effectively. See full prescribing information for BIMZELX.

BIMZELX® (bimekizumab-bkzx) injection, for subcutaneous use
Initial U.S. Approval: 2023

----------RECENT MAJOR CHANGES----------

Indications and Usage (1.2, 1.3, 1.4, 1.5)	11/2024
Dosage and Administration (2.3, 2.4, 2.5, 2.6, 2.7)	11/2024
Warnings and Precautions (5.1, 5.2)	11/2024

----------INDICATIONS AND USAGE----------

BIMZELX is a humanized interleukin-17A and F antagonist indicated for the treatment of:

- Moderate to severe **plaque psoriasis (PSO)** in adults who are candidates for systemic therapy or phototherapy. (1.1)
- Adults with active **psoriatic arthritis (PsA)**. (1.2)
- Adults with active **non-radiographic axial spondyloarthritis** (**nr-axSpA**) with objective signs of inflammation. (1.3)
- Adults with active **ankylosing spondylitis** (**AS**). (1.4)
- Adults with moderate to severe **hidradenitis suppurativa (HS)**. (1.5)

----------DOSAGE AND ADMINISTRATION----------

- Prior to treatment: (2.1)
  - Evaluate patients for tuberculosis infection.
  - Test liver enzymes, alkaline phosphatase, and bilirubin.
  - Complete all age-appropriate vaccinations as recommended by current immunization guidelines.
- **Plaque Psoriasis**
  - Administer 320 mg by subcutaneous injection at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. For patients weighing 120 kg or more, consider a dose of 320 mg every 4 weeks after Week 16. (2.2)
- **Psoriatic Arthritis**
  - Administer 160 mg by subcutaneous injection every 4 weeks. (2.3)
  - For patients with coexisting moderate to severe plaque psoriasis, use the dosage and administration for plaque psoriasis. (2.2)
- **Non-Radiographic Axial Spondyloarthritis**
  - Administer 160 mg by subcutaneous injection every 4 weeks. (2.4)
- **Ankylosing Spondylitis**
  - Administer 160 mg by subcutaneous injection every 4 weeks. (2.5)
- **Hidradenitis Suppurativa**
  - Administer 320 mg by subcutaneous injection at Week 0, 2, 4, 6, 8, 10, 12, 14 and 16, then every 4 weeks thereafter. (2.6)
- See full prescribing information for recommendations regarding missed doses, preparation and administration instructions. (2.7, 2.8, 2.9)

----------DOSAGE FORMS AND STRENGTHS----------

- Injection: 160 mg/mL in a single-dose prefilled syringe or single-dose prefilled autoinjector. (3)
- Injection: 320 mg/2 mL (160 mg/mL) in a single-dose prefilled syringe or single-dose prefilled autoinjector. (3)

----------CONTRAINDICATIONS----------

None. (4)

----------WARNINGS AND PRECAUTIONS----------

- Suicidal Ideation and Behavior (SI/B): May increase risk of SI/B. Advise patients, their caregivers, and families to monitor for the emergence or worsening of depression, suicidal ideation, or other mood changes. If such changes occur, instruct patients to promptly seek medical attention or call the National Suicide and Crisis Lifeline at 988. Carefully weigh risks and benefits of treatment with BIMZELX in patients with a history of severe depression and/or suicidal ideation or behavior. (5.1)
- Infections: May increase risk of infection. Instruct patients to seek medical advice if signs or symptoms of clinically important infection occur. If such an infection develops, do not administer BIMZELX until the infection resolves. (5.2)
- Tuberculosis (TB): Avoid use in patients with active TB. Initiate treatment of latent TB prior to BIMZELX treatment. (5.3)
- Liver Biochemical Abnormalities: Elevated serum transaminases were reported in clinical trials. Test liver enzymes, alkaline phosphatase, and bilirubin at baseline and according to routine patient management. Permanently discontinue use of BIMZELX in patients with causally - associated combined elevations of transaminases and bilirubin. (5.4)
- Inflammatory Bowel Disease (IBD): Cases of IBD were reported in clinical trials with IL-17 inhibitors, including BIMZELX. Avoid use of BIMZELX in patients with active IBD. Monitor patients for signs and symptoms of IBD and discontinue treatment if new onset or worsening of signs and symptoms occurs. (5.5)
- Immunizations: Avoid the use of live vaccines in patients treated with BIMZELX. (5.6)

----------ADVERSE REACTIONS----------

Most common adverse reactions are:

- Psoriasis and Hidradenitis Suppurativa (incidence ≥ 1%): upper respiratory tract infections, oral candidiasis, headache, injection site reactions, tinea infections, gastroenteritis, Herpes simplex infections, acne, folliculitis, other candida infections, and fatigue. (6.1)
- Psoriatic Arthritis (incidence ≥ 2%): upper respiratory tract infections, oral candidiasis, headache, diarrhea, and urinary tract infection. (6.1)
- Non-Radiographic Axial Spondyloarthritis (incidence ≥ 2%): upper respiratory tract infections, oral candidiasis, headache, diarrhea, cough, fatigue, musculoskeletal pain, myalgia, tonsilitis, transaminase increase, and urinary tract infection. (6.1)
- Ankylosing Spondylitis (incidence ≥ 2%): upper respiratory tract infections, oral candidiasis, headache, diarrhea, injection site pain, rash and vulvovaginal mycotic infection. (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact UCB, Inc. at 844-599-2273 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 11/2024

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FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

1.1 Plaque Psoriasis

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

1.2 Psoriatic Arthritis

BIMZELX is indicated for the treatment of adults with active psoriatic arthritis.

1.3 Non-Radiographic Axial Spondyloarthritis

BIMZELX is indicated for the treatment of adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.

1.4 Ankylosing Spondylitis

BIMZELX is indicated for the treatment of adults with active ankylosing spondylitis.

1.5 Hidradenitis Suppurativa

BIMZELX is indicated for the treatment of adults with moderate to severe hidradenitis suppurativa.

2 DOSAGE AND ADMINISTRATION

2.1 Recommended Evaluations and Immunization Prior to Treatment Initiation

- Evaluate patients for tuberculosis (TB) infection prior to initiating treatment with BIMZELX *[see Warnings and Precautions (5.3)]*.
- Test liver enzymes, alkaline phosphatase and bilirubin prior to initiating treatment with BIMZELX *[see Warnings and Precautions (5.4)]*.
- Complete all age-appropriate vaccinations as recommended by current immunization guidelines *[see Warning and Precautions (5.6)]*.

2.2 Recommended Dosage for Plaque Psoriasis

The recommended dosage is 320 mg by subcutaneous injection at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. For patients weighing 120 kg or more, consider a dosage of 320 mg every 4 weeks after Week 16 *[see Clinical Pharmacology (12.3)]*.

2.3 Recommended Dosage for Psoriatic Arthritis

The recommended dosage is 160 mg by subcutaneous injection every 4 weeks.

For psoriatic arthritis patients with coexistent moderate to severe plaque psoriasis, use the dosing regimen for adult patients with plaque psoriasis *[see Dosage and Administration (2.2)]*.

2.4 Recommended Dosage for Non-Radiographic Axial Spondyloarthritis

The recommended dosage is 160 mg by subcutaneous injection every 4 weeks.

2.5 Recommended Dosage for Ankylosing Spondylitis

The recommended dosage is 160 mg by subcutaneous injection every 4 weeks.

2.6 Recommended Dosage for Hidradenitis Suppurativa

The recommended dosage is 320 mg by subcutaneous injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks thereafter.

2.7 Missed Doses

If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regularly scheduled interval.

2.8 Preparation Instructions

- Before injecting, remove the carton with BIMZELX from the refrigerator and allow BIMZELX to reach room temperature (30 to 45 minutes) without removing the prefilled syringes or autoinjectors from the carton to protect from light.

- Inspect visually for particulate matter and discoloration prior to administration, whenever solution and container permit. BIMZELX injection is clear to slightly opalescent, and colorless to pale brownish- yellow. Do not use if the solution contains visible particles, is discolored or cloudy.

2.9 Administration Instructions

- BIMZELX is intended for use under the guidance and supervision of a healthcare professional. Patients may self-inject after training in subcutaneous injection technique. Provide proper training to patients and/or caregivers on the subcutaneous injection technique of BIMZELX according to the "Instructions for Use" *[see Instructions for Use]*.

- If two separate 160 mg injections are used to achieve the recommended dose, administer each injection subcutaneously at a different anatomic location (such as thighs, abdomen or back of upper arm). Discard the syringes or autoinjectors after use. Do not reuse.

- Do not inject BIMZELX within 2 inches (5 cm) of the navel or into areas where the skin is tender, bruised, red, hard, thick, scaly, or affected by psoriasis. Administration of BIMZELX in the upper, outer arm may only be performed by a healthcare professional or caregiver. Rotate the injection site with each injection.

3 DOSAGE FORMS AND STRENGTHS

- Injection (1 mL): 160 mg/mL clear to slightly opalescent, and colorless to pale brownish-yellow solution in a single-dose prefilled syringe or single-dose prefilled autoinjector.
- Injection (2 mL): 320 mg/2 mL (160 mg/mL) clear to slightly opalescent, and colorless to pale brownish-yellow solution in a single-dose prefilled syringe or single-dose prefilled autoinjector.

4 CONTRAINDICATIONS

None.

5 WARNINGS AND PRECAUTIONS

5.1 Suicidal Ideation and Behavior

An increased incidence of new onset or worsening suicidal ideation and behavior was observed in subjects treated with BIMZELX. A causal association between treatment with BIMZELX and increased risk of suicidal ideation and behavior has not been definitively established.

Suicidal ideation and behavior were prospectively monitored using the Columbia Suicide Severity Rating Scale (C-SSRS) in clinical trials. The C-SSRS is an interview-based instrument used to monitor for the presence and severity of suicidal ideation (ranging from "none" to "active suicidal ideation with specific plan and intent") and behaviors (rating the injury and potential lethality of self-injury, if present).

Plaque Psoriasis

During the two 16-week, placebo-controlled periods of Trials Ps-1 and Ps-2, higher rates of suicidal ideation as assessed by C-SSRS were reported in BIMZELX-treated subjects than in subjects receiving

placebo. Pooled analysis of C-SSRS data indicated that 12/670 (1.8%) BIMZELX-treated subjects and 1/169 (0.6%) subjects receiving placebo reported passive suicidal ideation with an estimated relative risk of 3.0 (95% confidence interval: 0.39, 22.74). Subjects without a prior history of SI/B treated with BIMZELX also reported a higher rate of new onset suicidal ideation on the C-SSRS than subjects receiving placebo (1.3% vs 0.6%). During the open-label extension trial, one completed suicide was reported in a BIMZELX-treated subject *[see Adverse Reactions (6.1)]*.

Psoriatic Arthritis
Pooled analysis of C-SSRS data from the two 16-week, placebo-controlled periods of Trials PsA-1 and PsA-2 indicated that 2/698 (0.3%) BIMZELX-treated subjects and 3/413 (0.7%) subjects receiving placebo reported passive suicidal ideation with an estimated relative risk of 0.35 (95% confidence interval: 0.05, 2.29) *[see Adverse Reactions (6.1)]*.

Non-Radiographic Axial Spondyloarthritis
Analysis of C-SSRS data from a 16-week, placebo-controlled period of Trial nr-axSpA-1 indicated that no subjects, being treated either with BIMZELX or placebo, reported suicidal ideation *[see Adverse Reactions (6.1)]*.

Ankylosing Spondylitis
Analysis of C-SSRS data from a 16-week, placebo-controlled period of Trial AS-1 indicated that no subjects, being treated either with BIMZELX or placebo, reported suicidal ideation *[see Adverse Reactions (6.1)]*.

Hidradenitis Suppurativa
During the two 16-week, placebo-controlled periods of Trials HS-1 and HS-2, higher rates of suicidal ideation as assessed by C-SSRS were reported in BIMZELX-treated subjects than in subjects receiving placebo. Based on a pooled analysis of the first 16 weeks of the placebo controlled clinical trials, 16/861 subjects in the BIMZELX group (1.9 %) reported suicidal ideation on the C-SSRS compared to 1/146 subjects in the placebo group (0.7%) with an estimated relative risk of 2.70 (95% confidence interval: 0.36, 20.12). Subjects without a prior history of SI/B treated with BIMZELX also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects treated with placebo (0.9% vs. 0%). *[see Adverse Reactions 6.1]*.

Consider the potential risks and benefits before prescribing BIMZELX to patients with a history of severe depression or suicidal ideation or behavior. Advise patients, their caregivers, and families to monitor for the emergence or worsening of depression, suicidal ideation, or other mood changes. If such changes occur, instruct patients to promptly seek medical attention or call the National Suicide and Crisis Lifeline at 988 *[see Patient Counseling Information (17)]*. Refer BIMZELX-treated patients with new or worsening symptoms of depression or suicidal ideation and/or behavior to a mental health professional, as appropriate. Re-evaluate the risks and benefits of continuing treatment with BIMZELX if such events occur.

5.2 Infections
BIMZELX may increase the risk of infections, including serious infections.

Do not initiate treatment with BIMZELX in patients with any clinically important active infection until the infection resolves or is adequately treated.

In patients with a chronic infection or a history of recurrent infection, consider the risks and benefits prior to prescribing BIMZELX. Instruct patients to seek medical advice if signs or symptoms of clinically

important infection occur. If a patient develops such an infection or is not responding to standard therapy, monitor the patient closely and discontinue BIMZELX until the infection resolves.

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

5.4 Liver Biochemical Abnormalities
Treatment with BIMZELX was associated with increased incidence of liver enzyme elevations compared to treatment with placebo in randomized clinical trials. Liver serum transaminase elevations > 3 times the upper limit of normal were reported in subjects treated with BIMZELX *[see Adverse Reactions (6.1)]*. Elevated liver serum transaminases resolved after discontinuation of BIMZELX.

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

5.5 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.

5.6 Immunizations
Prior to initiating therapy with BIMZELX, complete all age-appropriate vaccinations according to current immunization guidelines. Avoid the use of live vaccines in patients treated with BIMZELX. Limited data are available regarding coadministration of BIMZELX with non-live vaccines *[see Clinical Pharmacology (12.2)]*.

6 ADVERSE REACTIONS
The following adverse reactions have been observed with BIMZELX and are discussed in greater detail in other sections of the labeling:
- Suicidal Ideation and Behavior *[see Warnings and Precautions (5.1)]*
- Infections *[see Warnings and Precautions (5.2)]*
- Liver Biochemical Abnormalities *[see Warnings and Precautions (5.4)]*
- Inflammatory Bowel Disease *[see Warnings and Precautions (5.5)]*

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Plaque Psoriasis Clinical Trials
In clinical trials, a total of 1,789 subjects with plaque psoriasis were treated with BIMZELX. Of these, 1,073 subjects were exposed to BIMZELX for at least one year.

The safety of BIMZELX was evaluated in two placebo-controlled trials (Ps-1 and Ps-2), an active-controlled trial (Ps-3), and an open-label extension trial. Data from Trials Ps-1 and Ps-2 in 839 subjects (mean age 45 years, 72% male, 84% White) were pooled to evaluate the safety of BIMZELX in comparison to placebo up to 16 weeks after treatment initiation. A total of 670 subjects were treated during this initial period with BIMZELX 320 mg at Weeks 0, 4, 8, 12, and 16. Table 1 summarizes the adverse reactions that occurred at a rate of 1% or greater and at a higher rate in the BIMZELX group than the placebo group.

Table 1: Adverse Reactions Occurring in ≥1% of Subjects with Plaque Psoriasis in the BIMZELX Group and More Frequently than in the Placebo Group in Trials Ps-1 and Ps-2

	BIMZELX N=670 n (%)	**Placebo N=169 n (%)**
URI[a]	102 (15)	24 (14)
Oral Candidiasis[b]	61 (9)	0 (0)
Headache	22 (3)	0 (0)
Injection Site Reactions[c]	19 (3)	2 (1)
Tinea Infections[d]	18 (3)	1 (1)
Gastroenteritis[e]	12 (2)	0 (0)
Herpes Simplex Infections[f]	9 (1)	0 (0)
Acne	8 (1)	0 (0)
Folliculitis	8 (1)	0 (0)
Other Candida Infections[g]	7 (1)	1 (1)
Fatigue	7 (1)	0 (0)

[a] Upper Respiratory Infections include nasopharyngitis, upper respiratory tract infection, pharyngitis, rhinitis, viral upper respiratory tract infection, tonsillitis, sinusitis, pharyngitis streptococcal, pharyngitis bacterial, peritonsillar abscess, viral rhinitis, and influenza

[b] Oral Candidiasis includes oral candidiasis, oropharyngeal candidiasis, oral fungal infection, fungal pharyngitis, and oropharyngitis fungal

[c] Injection Site Reactions include injection site reaction, injection site erythema, injection site pain, injection site edema, injection site bruising, and injection site swelling

[d] Tinea Infections include tinea pedis, fungal skin infection, tinea versicolor, tinea cruris, tinea infection, body tinea, and onychomycosis

[e] Gastroenteritis includes Enterovirus infection, gastroenteritis, gastroenteritis bacterial, and gastroenteritis viral

[f] Herpes Simplex Infections include herpes simplex and oral herpes

[g] Other Candida Infections include vulvovaginal candidiasis, vulvovaginal mycotic infection, skin candida, and genital candidiasis.

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the BIMZELX group and at a higher rate than in the placebo group through Week 16 were neutropenia, eczema, otitis externa, otitis media, and pyrexia.

The safety of BIMZELX was evaluated in another active-controlled trial (Ps-4) in 743 adult subjects who received BIMZELX 320 mg every 4 weeks or every 8 weeks through Week 48.

Specific Adverse Reactions

Suicidal Ideation and Behavior: The study populations of Trial Ps-1, Trial Ps-2, Trial Ps-3 and Trial Ps-4 excluded subjects with active suicidal ideation, suicidal ideation within the month prior to screening, a

history of suicide attempt within the past 5 years prior to screening, or moderately severe to severe major depression (i.e., score of ≥15 on the screening Patient Health Questionnaire-9 (PHQ-9)).

Analysis of pooled C-SSRS data from the first 16 weeks of placebo-controlled clinical trials indicated that 12/670 (1.8%) BIMZELX-treated subjects and 1/169 (0.6%) subjects receiving placebo reported passive suicidal ideation with an estimated relative risk of 3.0 (95% confidence interval: 0.39, 22.74). Subjects without a prior history of SI/B treated with BIMZELX also reported a higher rate of new onset suicidal ideation on the C-SSRS than subjects receiving placebo (1.3% vs 0.6%).

During the course of the clinical trials for plaque psoriasis, there was 1 completed suicide in the open label extension trial after 718 days of treatment (1/2,480; 0.01/100 patient-years). The completed suicide was reported in a subject without a past reported psychiatric history. There were also 3 suicide attempts (3/2,480; 0.04/100 patient-years); 2 of these subjects had a history of prior suicide attempts.

Infections: During the placebo-controlled period of Trials Ps-1 and Ps-2, infections were reported in 36% of subjects (141.7 per 100 patient-years) treated with BIMZELX compared with 23% of subjects (84.6 per 100 patient-years) receiving placebo. Serious infections occurred in 0.3% of subjects (1.0 per 100 patient-years) treated with BIMZELX and 0% subjects receiving placebo.

The most common infections were upper respiratory tract infections and Candida infections, including oral candidiasis (oral candidiasis, oropharyngeal candidiasis, oral fungal infection, fungal pharyngitis, and oropharyngitis fungal) occurring in 9% (30.6 per 100 patient-years) of subjects treated with BIMZELX and other Candida infections (vulvovaginal candidiasis, vulvovaginal mycotic infection, skin candida, and genital candidiasis) in 1% (3.4 per 100 patient-years) of subjects treated with BIMZELX compared to 0% and 1%, respectively, of subjects receiving placebo.

During the combined initial, maintenance, and open-label extension treatment periods of trials Ps-1, Ps-2, Ps-3, and the open-label extension trial, infections were reported in 63% of subjects treated with BIMZELX (120.4 per 100 patient-years). Serious infections were reported in 1.5% of subjects treated with BIMZELX (1.6 per 100 patient-years).

Inflammatory Bowel Disease: In clinical trials in subjects with plaque psoriasis, subjects with active inflammatory bowel disease were excluded. In these trials, which included 2,480 subjects exposed to BIMZELX accounting for 5,830 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.

Liver Biochemical Abnormalities: During the placebo-controlled period of Trials Ps-1 and Ps-2, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.0% of subjects treated with BIMZELX versus 0.6% of subjects receiving placebo. The time to onset of these adverse reactions varied between 28 and 198 days after starting BIMZELX treatment. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

Safety through Week 56
During the maintenance period (Week 16 through Week 52 of Trial Ps-1 and Week 56 of Trial Ps-2), adverse reactions were consistent with those observed during the initial 16 weeks of treatment with BIMZELX. During the maintenance treatment periods of Trial Ps-2 and Trial Ps-3, the rates of adverse reactions were similar between subjects treated with BIMZELX 320 mg every four week and every eight weeks, after the initial 16 weeks of treatment.

Safety through Week 128
During the open-label extension trial, including data from Week 56 through Week 128, new adverse reactions of suicide attempt and a completed suicide occurred [described above in *Suicidal Ideation and Behavior*].

Additional Safety Data
In an active-controlled clinical trial (Trial Ps-4), 691 subjects with plaque psoriasis were treated with BIMZELX for up to 144 weeks. Adverse reactions were consistent with those observed during the initial 16 weeks of treatment and with the overall safety profile of BIMZELX.

Psoriatic Arthritis Clinical Trials
The safety of BIMZELX was evaluated in two placebo-controlled trials (PsA-1 and PsA-2). Data from Trials PsA-1 and PsA-2 in 1,111 subjects (mean age 49 years, 47% male, 96% White) were pooled to evaluate the safety of BIMZELX in comparison to placebo up to 16 weeks after treatment initiation. A total of 698 subjects were treated during this initial period with BIMZELX 160 mg at Weeks 0, 4, 8, 12, and 16. Table 2 summarizes the adverse reactions that occurred at a rate of 2% or greater and at a higher rate in the BIMZELX group than the placebo group.

Table 2: Adverse Reactions Occurring in ≥2% of Subjects with Psoriatic Arthritis in the BIMZELX Group and More Frequently than in the Placebo Group in Trials PsA-1 and PsA-2

	BIMZELX N=698 n (%)	**Placebo N=413 n (%)**
URI[a]	99 (14)	41 (10)
Headache	25 (4)	7 (2)
Diarrhea	19 (3)	8 (2)
Urinary Tract Infection	14 (2)	7 (2)
Oral Candidiasis	16 (2)	0

[a]Upper Respiratory Tract Infections (URI) includes: nasopharyngitis, upper respiratory tract infection, pharyngitis, sinusitis, and rhinitis.

Adverse reactions that occurred in < 2% but > 1% of subjects in the BIMZELX group and at a higher rate than in the placebo group through Week 16 included neutropenia (placebo: n=0; BIMZELX: n=8 (1.1%)), stomatitis (placebo: n=0; BIMZELX: n=8 (1.1%)), bronchitis (placebo: n=1 (0.2%); BIMZELX: n=11 (1.6%)), and oropharyngeal pain (placebo: n=0; BIMZELX: n=9 (1.3%)).

Specific Adverse Reactions

Suicidal Ideation and Behavior: The neuropsychiatric inclusion/exclusion criteria in PsA trials were the same as in PSO.

Based on a pooled analysis of the first 16 weeks of the placebo controlled clinical trials, 2 of the 698 subjects in the BIMZELX group (0.3%) reported passive suicidal ideation on the C-SSRS compared to 3 of 413 subjects in the placebo group (0.7%).

During the entire clinical trial program for PsA (2,664 patient-years), there were 2 cases of suicidal ideation (2/1413; 0.08/100 patient-years) and 1 suicide attempt (1/1413; 0.04/100 patient-years); all reported in BIMZELX-treated subjects with pre-existing psychiatric conditions.

Infections: During the placebo-controlled period of Trials PsA-1 and PsA-2, infections were reported in 27% of subjects (100.7 per 100 patient-years) treated with BIMZELX compared with 18% of subjects (62.8 per 100 patient-years) treated with placebo. Serious infections occurred in 0.4% of subjects (1.4 per 100 patient-years) treated with BIMZELX and 0% treated with placebo.

The most common infections were upper respiratory tract infections, nasopharyngitis, urinary tract infection and Candida infections, including oral candidiasis (oral candidiasis, oral fungal infection, and tongue fungal infection), occurring in 3.2% (10.2 per 100 patient-years) of subjects treated with BIMZELX and other Candida infections (skin candida, vulvovaginal candidiasis, and vulvovaginal mycotic infection) in 0.6% (1.8 per 100 patient-years) of subjects treated with BIMZELX compared to 0% and 1%, respectively, of subjects treated with placebo.

During the combined placebo-controlled, maintenance and open-label extension treatment periods of Trials PsA-1 and PsA-2, infections were reported in 58% of subjects treated with BIMZELX (58.5 per 100 patients-years). Serious infections were reported in 2% of subjects treated with BIMZELX (1.3 per 100 patient-years).

Inflammatory Bowel Disease: In clinical trials in subjects with psoriatic arthritis, subjects with active inflammatory bowel disease were excluded. In these trials, which included 1,413 subjects exposed to BIMZELX accounting for 2,664 patient-years, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC) and IBD) occurred in 2 subjects (0.08 per 100 patient-years); one of these cases was serious and none resulted in discontinuation of therapy.

Liver Biochemical Abnormalities: During the placebo-controlled period of Trials PsA-1 and PsA-2, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.3% of subjects treated with BIMZELX versus 0% of subjects receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

Safety through Week 52
During the maintenance period (Week 16 through Week 52 of Trial PsA-1), adverse reactions were consistent with those observed during the initial 16 weeks of treatment and with the overall safety profile of BIMZELX.

Non-Radiographic Axial Spondyloarthritis Clinical Trials
BIMZELX was evaluated in a placebo-controlled trial (Trial nr-axSpA-1) in subjects with non-radiographic axial spondyloarthritis (128 subjects on BIMZELX and 126 subjects on placebo). The safety profile observed in subjects with non-radiographic axial spondyloarthritis treated with BIMZELX was overall similar to the safety profile seen in subjects with psoriatic arthritis, except for cough, musculoskeletal pain, myalgia, tonsilitis, transaminase increase (placebo: n=0; BIMZELX: n=3 (2.3%) for each), and fatigue (placebo: n=1 (0.8%); BIMZELX: n=3 (2.3%)).

Specific Adverse Reactions

Suicidal Ideation and Behavior: The neuropsychiatric inclusion/exclusion criteria were the same in non-radiographic axial spondyloarthritis trials as in PSO.

During the first 16 weeks of the placebo controlled clinical trial (Trial nr-axSpA-1), no subjects in the BIMZELX or placebo group reported suicidal ideation on the C-SSRS. During the entire clinical trial program for nr-axSpA (398 patient-years), there were no cases of suicidal ideations. One suicide attempt (1/244; 0.25/100 patient-years) was reported in a BIMZELX-treated patient with pre-existing psychiatric conditions and recent life stressors.

Infections: During the placebo-controlled period of Trial nr-axSpA-1, infections were reported in 36% of subjects (144.8 per 100 patient-years) treated with BIMZELX compared with 25% of subjects (94.4 per 100 patient-years) receiving placebo. There were no reports of serious infections reported during the placebo-controlled period of the trial.

During the combined 52 week treatment period of Trial nr-axSpA-1, and subsequent open-label treatment, infections were reported in 68% of subjects treated with BIMZELX (78.0 per 100 patient-years). Serious infections were reported in 1.6% of subjects treated with BIMZELX (1.0 per 100 patient-years).

Inflammatory Bowel Disease: In the clinical trial in subjects with non-radiographic axial spondyloarthritis, subjects with active inflammatory bowel disease were excluded. In placebo-controlled, maintenance, and open label treatment periods of this trial, which included 244 subjects exposed to BIMZELX accounting for 397 patient-years, adjudicated cases of new onset of inflammatory bowel disease occurred in 1 subject (Ulcerative Colitis; 0.26 per 100 patient-years); this case of ulcerative colitis was nonserious and did not result in discontinuation of therapy.

Liver Biochemical Abnormalities: During the placebo-controlled period of Trials nr-axSpA-1, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.6% of subjects treated with BIMZELX versus 0.8% of subjects receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

Safety through Week 52
During the maintenance period (Week 16 through Week 52 of Trial nr-axSpA-1), adverse reactions were consistent with those observed during the initial 16 weeks of treatment and with the overall safety profile of BIMZELX.

Ankylosing Spondylitis Clinical Trials
BIMZELX was evaluated in a placebo-controlled trial (Trial AS-1) in subjects with ankylosing spondylitis (221 subjects on BIMZELX and 111 subjects on placebo). The safety profile observed in subjects with ankylosing spondylitis treated with BIMZELX was overall similar to the safety profile seen in subjects with psoriatic arthritis, except for injection site pain, rash (placebo: n=1 (0.9%); BIMZELX: n=6 (2.7%), for each) and vulvovaginal mycotic infection (placebo: n=0; BIMZELX: n=5 (2.3%)).

Specific Adverse Reactions

Suicidal Ideation and Behavior: The neuropsychiatric inclusion/exclusion criteria were the same in AS trials as in PSO.

During the first 16 weeks of the placebo controlled clinical Trial AS-1, no subjects in the BIMZELX or placebo group reported suicidal ideation on the C-SSRS. During the entire clinical trial program for AS (1,844 patient-years), there was 1 case of suicidal ideation (1/684; 0.05/100 patient-years) reported in a subject with pre-existing psychiatric conditions.

Infections: During the placebo-controlled period of Trial AS-1, infections were reported in 28% of subjects (110.3 per 100 patient-years) treated with BIMZELX compared with 23% of subjects (83.7 per 100 patient-years) receiving placebo. Serious infections occurred in 1 (0.5%) subject (1.5 per 100 patient-years) treated with BIMZELX and 1 (0.9%) subject (2.9 per 100 patient-years) receiving placebo.

During the combined 52 week treatment period of Trial AS-1, and subsequent open-label treatment, infections were reported in 62% of subjects treated with BIMZELX (58.8 per 100 patient-years). Serious infections were reported in 2.7% of subjects treated with BIMZELX (1.5 per 100 patient-years).

Inflammatory Bowel Disease: In clinical trials in subjects with AS, subjects with active inflammatory bowel disease were excluded. In these phase 2/3 trials, which included 593 subjects exposed to BIMZELX accounting for 1,599 patient-years, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC), Crohn's disease (CD) and IBD-undetermined) occurred in 6 subjects (0.38 per 100 patient-years); 4 cases were serious, and 3 cases resulted in discontinuation of therapy.

Liver Biochemical Abnormalities: During the placebo-controlled period of Trial AS-1, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.4% of subjects treated with BIMZELX versus 1.8% of subjects receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

Safety through Week 52
During the maintenance period (Week 16 through Week 52 of Trial AS-1), adverse reactions were consistent with those observed during the initial 16 weeks of treatment and with the overall safety profile of BIMZELX.

Hidradenitis Suppurativa Clinical Trials
BIMZELX was evaluated in two placebo-controlled trials (Trial HS-1 and Trial HS-2) in 1,007 adult subjects with moderate to severe hidradenitis suppurativa (861 BIMZELX-treated subjects and 146 subjects receiving placebo) *[see Clinical Studies (14.5)]*. The safety profile observed in subjects with hidradenitis suppurativa treated with BIMZELX was overall similar to the safety profile seen in subjects with PSO treated with BIMZELX.

Upon completion of both trials, a total of 657 subjects enrolled in a long-term extension treatment period for up to an additional 188 weeks.

Specific Adverse Reactions

Suicidal Ideation and Behavior: The neuropsychiatric inclusion/exclusion criteria were the same in HS trials as in PSO.

Analysis of pooled C-SSRS data from the first 16 weeks of the placebo-controlled clinical trials indicated that 16/861 (1.9%) BIMZELX-treated subjects and 1/146 (0.7%) subjects receiving placebo reported suicidal ideation with an estimated relative risk of 2.70 (95% confidence interval: 0.36, 20.12). Subjects without a prior history of SI/B treated with BIMZELX also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects treated with placebo (0.9% vs. 0%).

There were 2 reported cases of suicidal ideation that were adjudicated as suicide attempts (2/1,041; 0.15/100 patient-years). Both subjects had a history of neuropsychiatric disorders.

Infections: During the placebo-controlled period of Trials HS-1 and HS-2, infections were reported in 33% of subjects (132.2 per 100 patient-years) treated with BIMZELX compared with 21% of subjects (76.4 per 100 patient-years) receiving placebo. Serious infections occurred in 0.1% of subjects (0.4 per 100 patient-years) treated with BIMZELX and 0% of subjects receiving placebo.

The most commonly reported infections were comparable to those reported in subjects with PSO. Oral candidiasis occurred in 7.8% of subjects (26.7 per 100 patient years) treated with BIMZELX 320 mg Q2W, 3.9% of subjects (12.9 per 100 patient-years) treated with BIMZELX 320 mg Q4W, and 0 subjects receiving placebo. Other candida infections occurred in 3.6% of subjects (12.2 per 100 patient-years) treated with BIMZELX 320 mg Q2W, 6.7% of subjects (22.6 per 100 patient-years) treated with BIMZELX 320 mg Q4W, and 0 subjects receiving placebo. Tinea infections occurred in 3.1% of subjects (10.4 per 100 patient-years) treated with BIMZELX 320 mg Q2W, 2.5% of subjects (8.1 per 100 patient-years) treated with BIMZELX 320 mg Q4W, and 0.7% (2.3 per 100 patient-years) receiving placebo.

During the combined placebo-controlled, maintenance treatment periods and open-label extension treatment periods of Trials HS-1 and HS-2, infections were reported in 68% of subjects treated with BIMZELX (104.7 per 100 patient-years). Serious infections were reported in 2.1% of subjects treated with BIMZELX (1.7 per 100 patient-years).

Inflammatory Bowel Disease: In clinical trials in subjects with hidradenitis suppurativa, subjects with active inflammatory bowel disease were excluded. During the combined placebo-controlled, maintenance, and open-label extension treatment periods of Trials HS-1 and HS-2, which included 995 subjects exposed to BIMZELX accounting for 1,272 patient-years, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC), Crohn's disease (CD) and undetermined) occurred in 5 subjects (0.39 per 100 patient-years); 3 of these cases were serious, all of which resulted in discontinuation of therapy. Additionally, flares of pre-existing IBD occurred in 2 subjects, which resulted in discontinuation of BIMZELX in both.

Liver Biochemical Abnormalities: During the placebo-controlled period of Trials HS-1 and HS-2, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.2% of subjects treated with BIMZELX versus 0% of subjects receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

Safety through Week 48
During the maintenance period (Week 16 through Week 48 of Trials HS-1 and HS-2), adverse reactions were consistent with those observed during the initial 16 weeks of treatment and with the overall safety profile of BIMZELX.

6.2 Postmarketing Experience
The following adverse reactions have been reported during post-approval use of BIMZELX. Because they are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Infections: conjunctivitis, esophageal candidiasis

7 DRUG INTERACTIONS
CYP450 Substrates
The formation of CYP450 enzymes can be altered by increased levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Treatment with BIMZELX may modulate serum levels of some cytokines.

Therefore, upon initiation or discontinuation of BIMZELX in patients who are receiving concomitant drugs which are CYP450 substrates, particularly those with a narrow therapeutic index, consider monitoring for effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) and consider dosage modification of the CYP450 substrate.

Population pharmacokinetic (PK) data analyses indicated that the clearance of BIMZELX was not impacted by concomitant administration of cDMARDs including methotrexate, or by prior exposure to biologics.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIMZELX during pregnancy. 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 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 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. 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.

8.4 Pediatric Use
The safety and effectiveness of BIMZELX in pediatric patients have not been established.

8.5 Geriatric Use
Of the 1,789 subjects with plaque psoriasis that were exposed to BIMZELX, a total of 153 subjects were 65 years of age or older, and 18 subjects were 75 years of age or older. Although no differences in safety or effectiveness were observed between subjects 65 years of age or older and younger adult subjects, clinical trials in PSO did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

Of the 1,197 subjects with PsA that were exposed to BIMZELX, a total of 148 were 65 years of age and older. Although no differences in safety or effectiveness were observed between subjects 65 years of age or older and younger adult subjects, clinical trials in PsA did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

Of the 244 subjects with nr-axSpA that were exposed to BIMZELX, a total of 6 were 65 years of age and older. Although no differences in safety or effectiveness were observed between subjects 65 years of age or older and younger adult subjects, the clinical trial in nr-axSpA did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

Of the 330 subjects with AS that were exposed to BIMZELX, a total of 11 were 65 years of age and older. Although no differences in safety or effectiveness were observed between subjects 65 years of age or older and younger adult subjects, the clinical trial in AS did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

Of the 995 subjects with hidradenitis suppurativa that were exposed to BIMZELX, a total of 18 were 65 years of age and older. Although no differences in safety or effectiveness were observed between subjects 65 years of age or older and younger adult subjects, clinical trials in HS did not include sufficient numbers of subjects aged 65 years and over to determine whether they respond differently from younger adult subjects.

11 DESCRIPTION
Bimekizumab-bkzx, an interleukin-17 A and F antagonist, is a recombinant humanized immunoglobulin G1 (IgG1) monoclonal antibody. Bimekizumab-bkzx is produced by recombinant DNA technology in Chinese Hamster Ovary cells, and has an approximate molecular weight of 150 kDa.

BIMZELX (bimekizumab-bkzx) injection is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale brownish-yellow solution for subcutaneous use.

Each BIMZELX 1 mL (160 mg/mL) prefilled syringe or prefilled autoinjector delivers 1 mL containing 160 mg bimekizumab-bkzx, glacial acetic acid (1.23 mg), glycine (16.5 mg), polysorbate 80 (0.4 mg), sodium acetate (2.83 mg), and Water for Injection, USP at pH 5.1.

Each BIMZELX 2 mL (160 mg/mL) prefilled syringe or prefilled autoinjector delivers 2 mL containing 320 mg bimekizumab-bkzx, glacial acetic acid (2.46 mg), glycine (33.0 mg), polysorbate 80 (0.8 mg), sodium acetate (5.65 mg), and Water for Injection, USP at pH 5.1.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Bimekizumab-bkzx 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-17 receptor complex. IL-17A and IL-17F are naturally occurring cytokines that are involved in normal inflammatory and immune responses. Bimekizumab-bkzx inhibits the release of proinflammatory cytokines and chemokines.

12.2 Pharmacodynamics

Elevated levels of IL-17A and IL-17F are found in lesional psoriatic skin, and lesional skin in HS. Bimekizumab-bkzx exposure-response relationships to serum biomarkers, including IL-17A and IL-17F, and the time course of such pharmacodynamic responses are unknown.

Immune Response to Inactivated or Non-Live Vaccines

Healthy individuals who received a single 320 mg dose of BIMZELX two weeks prior to vaccination with an inactivated seasonal influenza vaccine had similar antibody responses compared to individuals who did not receive BIMZELX prior to vaccination. The effectiveness of inactivated seasonal influenza vaccines and other inactivated and non-live vaccines has not been evaluated in patients treated with BIMZELX.

12.3 Pharmacokinetics

Bimekizumab-bkzx pharmacokinetics are comparable in adult patients with moderate to severe plaque psoriasis, psoriatic arthritis, non-radiographic axial spondyloarthritis, and ankylosing spondylitis.

The median peak plasma concentration of bimekizumab-bkzx was 25 (range: 12-50) µg/mL and was reached in 3-4 days. Bimekizumab-bkzx exhibited dose-proportional pharmacokinetics in patients with plaque psoriasis over a dose range of 64 mg to 480 mg (0.2 to 1.5 times the approved recommended dosage) following subcutaneous administration.

The median steady-state trough concentration of bimekizumab-bkzx was approximately 40% lower in HS subjects than that of PSO subjects.

Absorption

The absolute bioavailability of bimekizumab-bkzx was 70% in healthy subjects.

Distribution

The median volume of distribution at steady state was 11.2 L in subjects with moderate to severe plaque psoriasis. The volume of distribution in subjects with moderate to severe hidradenitis suppurativa was estimated to be approximately 18% higher than in subjects with moderate to severe plaque psoriasis.

Elimination

The median (coefficient of variation %) clearance (CL/F) of bimekizumab-bkzx was 0.337 L/day (32.7%). The mean terminal elimination half-life was 23 days, with clearance independent of dose. The apparent clearance in subjects with moderate to severe hidradenitis suppurativa was estimated to be approximately 31% higher than in subjects with moderate to severe plaque psoriasis.

Metabolism: Bimekizumab-bkzx is expected to be degraded into small peptides by catabolic pathways.

Specific Populations

No significant differences in the pharmacokinetics of bimekizumab-bkzx were observed based on age (≥18 years).

Body Weight: The average plasma concentration in adult subjects weighing ≥120 kg was predicted to be at least 30% lower than those weighing < 120 kg (median of 87 kg) *[see Dosage and Administration (2.2)]*.

12.6 Immunogenicity

The observed incidence of anti-drug antibodies (ADA) is highly dependent on the sensitivity and specificity of the assay. Differences in assay methods preclude meaningful comparisons of the incidence of ADA in the studies described below with the incidence of ADA in other studies, including those of BIMZELX or of other bimekizumab products.

Across the pivotal trials in all indications, there was no identified clinically significant effect of anti-bimekizumab-bkzx antibodies, including neutralizing anti-drug antibodies, on safety or effectiveness of BIMZELX.

Plaque Psoriasis

During the 52–56-week treatment period in Trial Ps-1, Trial Ps-2, and Trial Ps-3 *[see Clinical Studies (14.1)],* 116/257 (45%) of BIMZELX-treated subjects (at the recommended dosage) developed anti-bimekizumab-bkzx antibodies (also referred to as ADA). Of the BIMZELX-treated subjects who developed ADA in these trials, approximately 16% had neutralizing antibodies.

Psoriatic Arthritis

During the 52-week treatment period in Trial PsA-1 *[see Clinical Studies (14.2)]*, 201/431 (47%) of subjects treated with BIMZELX had ADA, and 18% had neutralizing ADA.

Non-Radiographic Axial Spondyloarthritis

During the 52-week treatment period in Trial nr-axSpA-1 *[see Clinical Studies (14.3)],* 68/119 (57%) of BIMZELX-treated subjects had anti-bimekizumab-bkzx ADA, and approximately 25% had neutralizing ADA.

Ankylosing Spondylitis

During the 52-week treatment period in Trial AS-1 *[see Clinical Studies (14.4)],* 86/194 (44%) of BIMZELX-treated subjects had anti-bimekizumab-bkzx ADA, and approximately 20% had neutralizing ADA.

Hidradenitis Suppurativa

During the 48-week treatment period in Trials HS-1 and HS-2 *[see Clinical Studies (14.5)],* 171/291 (59%) of BIMZELX-treated subjects had anti-bimekizumab-bkzx ADA, and of those who developed ADA, approximately 63% had neutralizing ADA.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity and mutagenicity studies have not been conducted with bimekizumab-bkzx.

No effects on fertility parameters such as effects on reproductive organs, menstrual cycle length, or sperm analysis were observed in sexually mature cynomolgus monkeys that were subcutaneously administered 200 mg/kg/week bimekizumab-bkzx (150 times the MRHD, based on mg/kg comparison) for 26 weeks. The monkeys were not mated to evaluate fertility.

14 CLINICAL STUDIES

14.1 Plaque Psoriasis

Three multicenter, randomized, double-blind trials [Trial Ps-1 (NCT03370133), Trial Ps-2 (NCT03410992), and Trial Ps-3 (NCT03412747)] enrolled a total of 1,480 subjects 18 years of age and older with moderate to severe plaque psoriasis who had a body surface area (BSA) involvement of ≥10%, an Investigator's Global Assessment (IGA) score of ≥3 ("moderate") in the overall assessment of psoriasis on a severity scale of 0 to 4, and a Psoriasis Area and Severity Index (PASI) score ≥12.

In Trial Ps-1, 567 subjects were randomized to receive either BIMZELX 320 mg by subcutaneous injection every 4 weeks, ustekinumab (for subjects weighing ≤100kg, 45 mg initially and 4 weeks later, then every 12 weeks; for subjects weighing >100kg, 90 mg initially and 4 weeks later, then every 12 weeks), or placebo through Week 52. At Week 16, subjects originally randomized to placebo received BIMZELX 320 mg every 4 weeks through Week 52.

In Trial Ps-2, 435 subjects were randomized to either BIMZELX 320 mg by subcutaneous injection every 4 weeks or placebo. At Week 16, subjects who achieved a PASI 90 response continued into a 40-week randomized withdrawal period. Subjects originally randomized to BIMZELX 320 mg every 4 weeks were re-randomized to either BIMZELX 320 mg every 4 weeks or BIMZELX 320 mg every 8 weeks or placebo. Subjects originally randomized to placebo continued to receive placebo if they were PASI 90 responders. Subjects who did not achieve a PASI 90 response at week 16 entered an open-label escape arm and received BIMZELX 320 mg every 4 weeks for 12 weeks. Subjects who relapsed, defined as having a less than PASI 75 response compared to baseline, during the randomized withdrawal period also entered the 12-week escape arm.

In Trial Ps-3, 478 subjects were randomized to receive either BIMZELX 320 mg by subcutaneous injection every 4 weeks through week 56, BIMZELX 320 mg every 4 weeks through week 16 followed by BIMZELX every 8 weeks through week 56, or adalimumab (80 mg as an initial dose followed by 40 mg every other week starting 1 week after initial dose through Week 24) followed by BIMZELX 320 mg every 4 weeks through Week 56.

In Trial Ps-1, Trial Ps-2, and Trial Ps-3, 71% of the subjects were male and 84% of the subjects were White, with a mean age of 45 years and a mean weight of 89 kg. At baseline, subjects had a median baseline PASI score of 18, median baseline for BSA of 20%, and baseline IGA score of 4 ("severe") in 33% of subjects. A total of 93% subjects had psoriasis of the scalp (Scalp IGA score of ≥1) and a total of 26% of subjects had a history of psoriatic arthritis. Additionally, 38% had received prior biologic therapy.

Clinical Response at Week 16 (Trial Ps-1 and Trial Ps-2)

Trial Ps-1 and Trial Ps-2 responses at Week 16 compared to placebo for the two co-primary endpoints:

- The proportion of subjects who achieved an IGA score of 0 ("clear") or 1 ("almost clear") with at least a 2-grade improvement from baseline
- The proportion of subjects who achieved at least a 90% reduction from baseline PASI (PASI 90)

Secondary endpoints included the proportion of subjects who achieved PASI 100, IGA 0, and Scalp IGA response (defined as Scalp IGA score of 0 [clear] or 1 [almost clear] with at least 2-grade of improvement from baseline) at Week 16, and PASI 75 at Week 4. In addition, secondary endpoints included assessment of psoriasis symptoms (itching, pain, and scaling) measured by the Patient Symptom Diary (PSD) at Week 16.

The proportion of subjects who achieved IGA 0 or 1, PASI 90, IGA 0, and PASI 100 response at Week 16 are presented in Table 3.

Table 3: Efficacy Results at Week 16 in BIMZELX or Placebo-Treated Adults with Plaque Psoriasis in Trial Ps-1 and Trial Ps-2

	Trial Ps-1		Trial Ps-2	
	BIMZELX 320 mg every 4 weeks (N=321) n (%)	**Placebo (N=83) n (%)**	**BIMZELX 320 mg every 4 weeks (N=349) n (%)**	**Placebo (N=86) n (%)**
IGA 0 or 1 ("clear" or "almost clear") [a]	270 (84%)	4 (5%)	323 (93%)	1 (1%)
Difference (95% CI)	79% (73%, 85%)		91% (88%, 95%)	
PASI 90[a]	273 (85%)	4 (5%)	317 (91%)	1 (1%)
Difference (95% CI)	80% (74%, 86%)		90% (86%, 93%)	
IGA 0 ("clear")	188 (59%)	0 (0%)	243 (70%)	1 (1%)
Difference (95% CI)	59% (53%, 64%)		69% (64%, 74%)	
PASI 100	188 (59%)	0 (0%)	238 (68%)	1 (1%)
Difference (95% CI)	59% (53%, 64%)		67% (62%, 73%)	

[a] Co-primary endpoints

Examination of age, gender, race, baseline IGA score and previous treatment with systemic or biologic agents did not identify differences in response to BIMZELX among these subgroups at Week 16.

A greater proportion of subjects randomized to BIMZELX achieved PASI 75 at Week 4 in both trials compared to placebo. In Trial Ps-1, 77% of subjects treated with BIMZELX achieved PASI 75 compared to 2% treated with placebo. In Trial Ps-2, 76% of subjects treated with BIMZELX achieved PASI 75 compared to 1% treated with placebo.

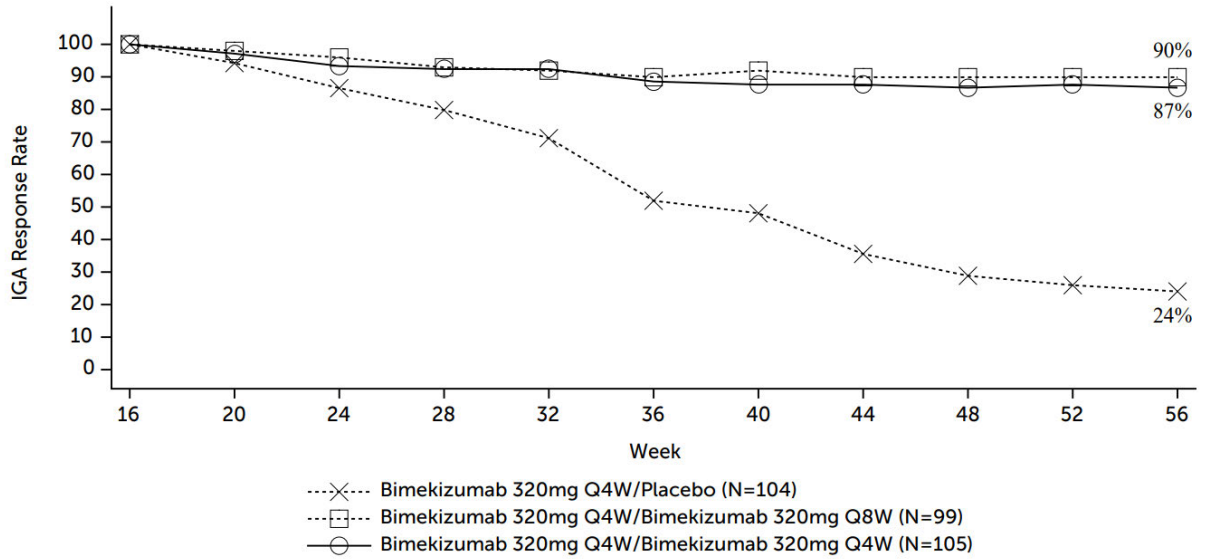
Among subjects with Scalp IGA score of at least 2 at baseline, a greater proportion of subjects randomized to BIMZELX achieved Scalp IGA response at Week 16 in both trials compared to placebo. In Trial Ps-1, 84% (240/285) of subjects treated with BIMZELX achieved Scalp IGA response compared to 15% (11/72) of placebo treated subjects. In Trial Ps-2, 92% (286/310) of subjects treated with BIMZELX achieved Scalp IGA response compared to 7% (5/74) of placebo treated subjects.

Maintenance and Durability of Response

In Trial Ps-2, subjects randomized to BIMZELX every 4 weeks at Week 0 and who were PASI 90 responders at Week 16 were re-randomized to either continue treatment with BIMZELX every 4 weeks, switched to BIMZELX every 8 weeks, or be withdrawn from therapy (i.e., received placebo).

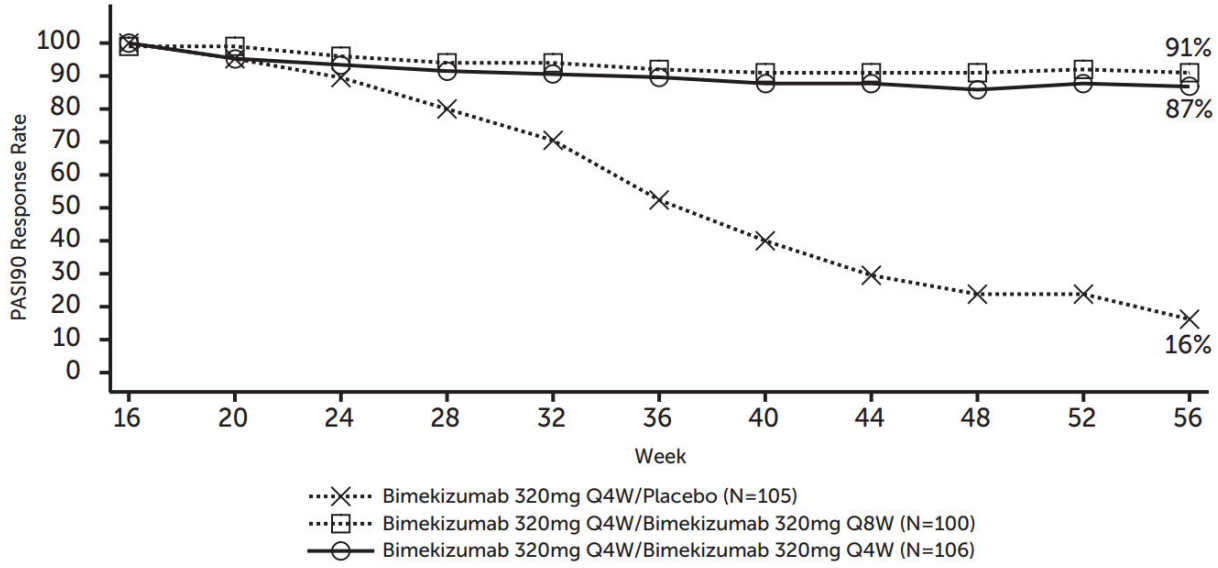
Figure 1 and Figure 2 present the percentage of subjects maintaining IGA score of 0 ("Clear") or 1 ("Almost Clear") and PASI 90, respectively, through Week 56 after re-randomization at Week 16.

Figure 1: Percentage of Subjects Maintaining IGA 0 or 1 through Week 56 after Re-Randomization at Week 16



For IGA 0 or 1 responders at Week 16 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of IGA 0 or 1 response was approximately 24 weeks. Among these subjects with IGA score of 2 at retreatment, 58% (14/24) achieved IGA score of 0 within 12 weeks of restarting treatment with BIMZELX 320 mg every 4 weeks. Among these subjects with IGA score ≥ 3 at retreatment, 87% (34/39) regained IGA 0 or 1 response with at least 2-grade improvement from retreatment within 12 weeks of restarting treatment with BIMZELX 320 mg every 4 weeks.

Figure 2: Percentage of Subjects Maintaining PASI 90 through Week 56 after Re-Randomization at Week 16



For PASI 90 responders at Week 16 who were re-randomized to treatment withdrawal (i.e., placebo), the median time to loss of PASI 90 response was approximately 24 weeks.

Patient Reported Outcomes

Greater improvements in itch, pain, and scaling at Week 16 with BIMZELX compared to placebo were observed in both trials as measured by the Patient Symptom Diary (PSD).

14.2 Psoriatic Arthritis

The safety and efficacy of BIMZELX were assessed in 1,112 subjects in two multicenter, randomized, double-blind, placebo-controlled studies [Trial PsA-1 (NCT 03895203) and Trial PsA-2 (NCT 03896581)] in subjects 18 years and older with active psoriatic arthritis (PsA).

Subjects in these studies had a diagnosis of PsA of at least 6 months based on Classification Criteria for Psoriatic Arthritis (CASPAR), a median duration of 4.6 years at baseline, and active disease with ≥3 tender joint count and ≥3 swollen joint count. Subjects with each subtype of PsA were enrolled in these studies, including polyarticular symmetric arthritis (63.5%), oligoarticular asymmetric arthritis (25.9%), distal interphalangeal joint predominant (4.4%), spondylitis predominant (4.2%), and arthritis mutilans (1.5%). At baseline, 56% of subjects had ≥3% Body Surface Area (BSA) with active plaque psoriasis. At baseline across both studies, 32% and 12% of subjects had enthesitis and dactylitis, respectively, 58% of subjects had psoriatic nail disease, and 53% of subjects were receiving concomitant methotrexate.

The PsA-1 study evaluated 852 biologic-naïve subjects, who were treated with either BIMZELX 160 mg every 4 weeks up to Week 52, adalimumab 40 mg every 2 weeks up to Week 52 (active reference arm), or placebo. Subjects receiving placebo were switched to BIMZELX every 4 weeks at Week 16 to Week 52. In this study, 78% of subjects had received prior treatment with ≥ 1 conventional DMARDs (cDMARDs), and 22 % of subjects had no prior treatment with cDMARDs. At baseline, 58% of subjects were receiving concomitant methotrexate (MTX), 11% were receiving concomitant cDMARDs other than MTX, and 31% were receiving no cDMARDs. The PsA-2 study evaluated 400 anti-TNFα experienced subjects (inadequate response or intolerance to treatment), who were treated with BIMZELX 160 mg every 4 weeks or placebo up to Week 16. In this study, 43% of subjects were receiving concomitant MTX, 8% were receiving concomitant cDMARDs other than MTX, and 50% were receiving no cDMARDs.

For both studies, the primary endpoint was the proportion of subjects who achieved an America College of Rheumatology (ACR) 50 response at Week 16.

Clinical Response

In both studies, treatment with BIMZELX resulted in significant improvement in disease activity, as measured by ACR, compared to placebo at Week 16 (see Table 4). Responses in Trial PsA-2 (anti-TNF experienced) were similar to Trial PsA-1.

Table 4: Clinical Responses at Week 16 in Trial PsA-1 and Trial PsA-2

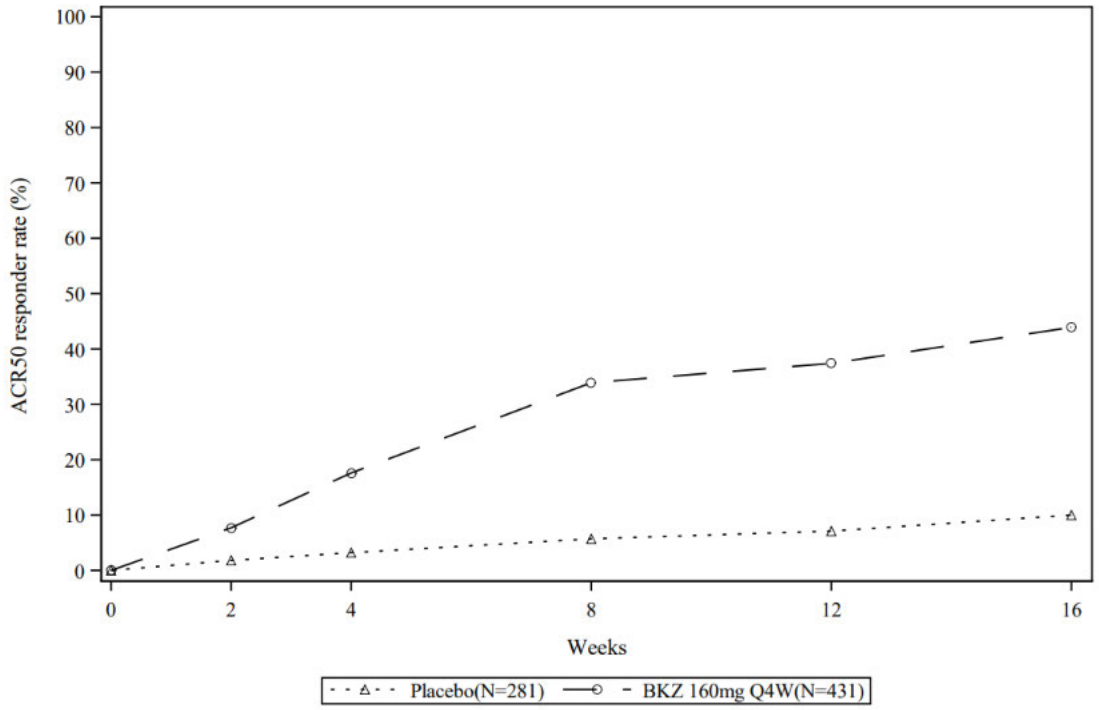
	Trial PsA-1 – bDMARD naïve			**Trial PsA-2 – anti-TNFα experienced**		
Endpoint	**BIMZELX 160 mg Q4W N=431 n (%)**	**Placebo N=281 n (%)**	**Difference from Placebo[**] (95% CI)**	**BIMZELX 160 mg Q4W N=267 n (%)**	**Placebo N=133 n (%)**	**Difference from Placebo[**] (95% CI)**
ACR 20 Response						
Week 16	268 (62.2)	67 (23.8)	38.3 (31.6, 45.1)	179 (67.0)	21 (15.8)	51.3 (42.9, 59.6)
ACR 50 Response						
Week 16	189 (43.9)[*]	28 (10.0)	33.9 (28.0, 39.7)	116 (43.4)[*]	9 (6.8)	36.7 (29.4, 44.0)
ACR 70 Response						
Week 16	105 (24.4)	12 (4.3)	20.1 (15.4, 24.8)	71 (26.6)	1 (0.8)	25.8 (15.6, 35.7)[***]

CI= confidence interval

* Multiplicity-controlled p<0.001
** 95% CI based on normal approximation
*** Exact 95% CI used

The percentage of subjects achieving ACR50 responses in Trial PsA-1 by visit through Week 16 is shown in Figure 3. Similar responses were seen in Trial PsA-2 up to Week 16.

Figure 3: Percent of Subjects Achieving ACR 50 Responses in Trial PsA-1 through Week 16



The results of the components of the ACR response criteria are shown in Table 5.

Table 5: Mean change from Baseline in ACR Component Scores at Week 16 in Trial PsA-1 and Trial PsA-2

	Trial PsA-1 – bDMARD naïve		Trial PsA-2 – anti-TNFα experienced	
	Placebo (N=281)	**BIMZELX 160 mg Q4W (N=431)**	**Placebo (N=133)**	**BIMZELX 160 mg Q4W (N=267)**
Number of Swollen Joints				
Baseline	9.5	9.0	10.3	9.7
Mean change at Week 16	-3.0	-6.6	-2.0	-7.0
Number of Tender Joints				
Baseline	17.1	16.8	19.3	18.4
Mean change at Week 16	-3.2	-10.0	-2.4	-10.9
Patient's Assessment of Pain				
Baseline	56.8	53.7	61.7	58.3
Mean change at Week 16	-6.2	-23.6	-4.5	-27.7

Patient's Global Assessment				
Baseline	58.6	54.4	63.0	60.5
Mean change at Week 16	-7.7	-26.3	-5.5	-31.8
Physician Global Assessment				
Baseline	57.3	57.2	57.7	59.3
Mean change at Week 16	-12.5	-37.4	-6.8	-49.4
Health Assessment Questionnaire- Disability Index (HAQ-DI)				
Baseline	0.9	0.8	1.0	1.0
Mean Change at Week 16	-0.1	-0.3*	-0.1	-0.4*
High Sensitivity C-reactive Protein (hsCRP) mg/L				
Baseline	11.4	8.7	11.6	12.4
Mean Change at Week 16	-2.4	-4.2	3.6	-7.0

Multiple Imputation (MI) is used for all endpoints presented in Table 5. *p<0.001 reference-based imputation versus placebo adjusted for multiplicity.

Treatment with BIMZELX resulted in improvement in dactylitis and enthesitis in subjects with pre-existing dactylitis or enthesitis, compared to placebo.

In subjects with coexistent plaque psoriasis receiving BIMZELX, the skin lesions of psoriasis improved with treatment, relative to placebo, as measured by the Psoriasis Area Severity Index (PASI 90) at Week 16.

Radiographic Response

In Trial PsA-1, inhibition of progression of structural damage was assessed radiographically and expressed as the change from baseline in the Van der Heijde modified total Sharp Score (vdHmTSS) and its components, the Erosion Score (ES) and the Joint Space Narrowing score (JSN), at Week 16 (see Table 6).

BIMZELX significantly inhibited the rate of progression of joint damage at Week 16 in the overall population compared to placebo. The change from Baseline in erosion subscores contributed more to the change from Baseline in vdHmTSS total score than the change from Baseline in joint narrowing subscore. The percentage of subjects with no radiographic joint damage progression (defined as a change from baseline in mTSS of ≤0.0) from randomization to Week 16 was 77% for BIMZELX and 69% for placebo in the overall population. Similar responses were achieved in the population with elevated hsCRP and/or at least 1 bone erosion (75% for BIMZELX and 67% for placebo).

Table 6: Change in vdHmTSS in PsA-1 at Week 16

	Placebo	**BIMZELX 160 mg Q4W**	**Difference from Placebo (95% CI)[a]**
Overall population	**(N=269)**	**(N=420)**	
Baseline mean (SE)	12.34 (1.37)	12.47 (1.46)	
Mean change from baseline at Week 16 (SE)	0.32 (0.09)	0.04 (0.04)*	-0.26 (-0.29, -0.23)

*p≤0.001 versus placebo. p-values are based on reference-based imputation using difference in LS Mean using an ANCOVA model with treatment, bone erosion at Baseline and region as fixed effects and Baseline score as a covariate.
a) Unadjusted differences are shown

Physical Function
In both studies, subjects treated with BIMZELX showed statistically significant improvement from baseline in physical function compared with placebo as assessed by HAQ-DI at Week 16 (see Table 5). In both studies, a greater proportion of subjects achieved a reduction of at least 0.35 in HAQ-DI score from baseline in the BIMZELX group compared with placebo at Week 16.

Other Health Related Outcomes
Fatigue was assessed by Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-Fatigue). Additionally, in both studies at Week 16, subjects treated with BIMZELX showed improvements in FACIT-Fatigue scores.

14.3 Non-Radiographic Axial Spondyloarthritis
The efficacy and safety were assessed in 254 patients in one randomized, double-blind, placebo-controlled study [Trial nr-axSpA-1 (NCT03928704)] in adult subjects 18 years of age and older with active non-radiographic axial spondyloarthritis. Subjects had to have objective signs of inflammation with elevated C-reactive protein (CRP) level and/or evidence of sacroiliitis on Magnet Resonance Imaging (MRI). Subjects met ASAS classification criteria for axial spondyloarthritis and have active disease as defined by BASDAI greater than or equal to 4, spinal pain of greater than or equal to 4 (0-10 numeric rating scale (NRS)), and no definitive radiographic evidence of structural damage in the sacroiliac joints. At baseline, 73% of subjects had enthesitis. Subjects also had a history of inadequate response to 2 different non-steroidal anti-inflammatory drugs (NSAIDs), or intolerance or contraindication to NSAIDs. Approximately 24% of subjects were on concomitant cDMARDs. Overall, 11% of subjects had received previous treatment (failed or were intolerant to) with anti-TNF alpha agents.

Subjects were randomized to receive BIMZELX 160 mg or placebo every 4 weeks up to the completion of Week 16 assessments. Starting at Week 16, all subjects received BIMZELX every 4 weeks up to Week 52. The primary endpoint was at least 40% improvement in Assessment of Spondyloarthritis International Society (ASAS 40) at Week 16.

Clinical Response
In Trial nr-axSpA-1, treatment with BIMZELX resulted in significant improvements in the measure of disease activity compared to placebo at Week 16 (Table 7).

Table 7: Clinical Response in Trial nr-axSpA-1 at Week 16

	BIMZELX 160 mg Q4W (N=128) n (%)	Placebo (N=126) n (%)	Difference from placebo (95% CI)**
ASAS 40 response	61 (47.7%)*	27 (21.4%)	26.2 (15.0, 37.5)
ASAS 20 response	88 (68.8%)*	48 (38.1%)	30.7 (19.0, 42.3)

NRI is used
CI= confidence interval
* Multiplicity-controlled p<0.001
**95% CI based on normal approximation

Similar responses were seen regardless of prior anti-TNF alpha therapy. Treatment with BIMZELX resulted in improvement in enthesitis in subjects with pre-existing enthesitis.

The results of the main components of the ASAS 40 response criteria and other measures of disease activity are shown in Table 8.

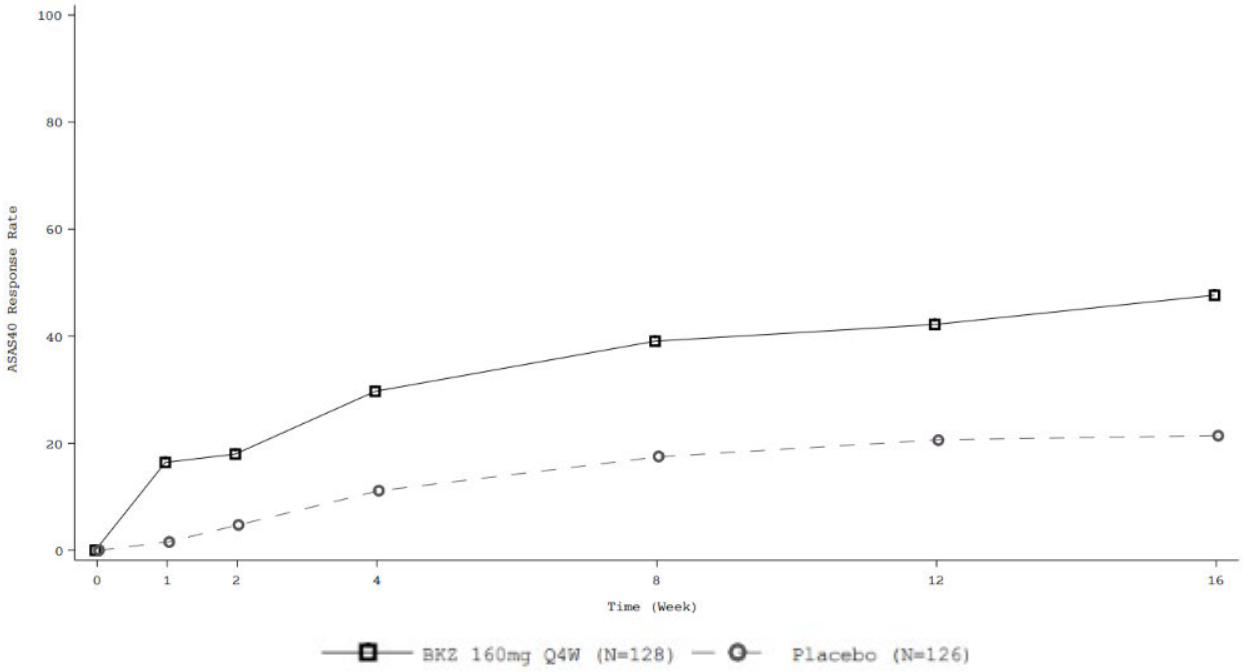
Table 8: Components of the ASAS 40 Response Criteria and Other Measures of Disease Activity in nr-axSpA Subjects at Baseline and Week 16 in Trial nr-axSpA-1

	BIMZELX 160 mg Q4W (N= 128)	Placebo (N=126)
ASAS Components		
- *Patient Global Assessment (0-10)*		
Baseline	7.1	6.9
Mean Change from Baseline	-3.2	-1.4
- *Total Spinal Pain (0-10)*		
Baseline	7.3	7.1
Mean Change from Baseline	-3.4	-1.7
- *BASFI (0-10)*		
Baseline	5.5	5.3
Mean Change from Baseline	-2.5*	-1.0
- *Inflammation (0-10)*[a]		
Baseline	7.0	6.9
Mean Change from Baseline	-3.6	-1.9
Other Measures of Disease Activity		
BASDAI Score		
Baseline	6.9	6.7
Mean Change from Baseline	-3.1*	-1.5
BASMI		
Baseline	2.9	3.0
Mean Change from Baseline	-0.4	-0.1
hsCRP (mg/L)		
Baseline	11.1	10.2
Mean Change from Baseline	-6.7	0.0

[a] Inflammation is the mean of patient-reported stiffness self-assessments (questions 5 and 6) in BASDAI
BASFI = Bath Ankylosing Spondylitis Functional Index
BASMI = Bath Ankylosing Spondylitis Metrology Index
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index
MI is used for all endpoints presented in Table 8
*Multiplicity-controlled $p<0.001$

The percentage of subjects achieving ASAS 40 responses in Trial nr-axSpA-1 by visit through Week 16 is shown in Figure 4.

Figure 4: Percent of Subjects Achieving ASAS 40 Responses in Trial nr-axSpA-1 Week 16



Health Related Quality of Life

BIMZELX treated subjects showed significantly greater improvement compared to subjects receiving placebo at Week 16 in health-related quality of life as measured by the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score.

14.4 Ankylosing Spondylitis

The efficacy and safety were assessed in 332 patients in one randomized, double-blind, placebo-controlled study [Trial AS-1 (NCT03928743)] in adult subjects 18 years of age and older with active ankylosing spondylitis. Subjects had to have documented radiologic evidence (x-ray) fulfilling the Modified New York criteria for AS. Subjects had active disease as defined by BASDAI ≥4 and spinal pain ≥4 on a 0 to 10 numeric rating scale (NRS) (from BASDAI Item 2). Subjects also had a history of inadequate response to 2 different non-steroidal anti-inflammatory drugs (NSAIDs), or intolerance or contraindication to NSAIDs. Approximately 20% of subjects were on concomitant cDMARDs. Overall, 16% of subjects had received previous treatment (failed or were intolerant to) with anti-TNF alpha agents.

Subjects were randomized 2:1 to receive BIMZELX 160 mg or placebo every 4 weeks up to the completion of Week 16 assessments. Starting at Week 16, all subjects received BIMZELX every 4 weeks up to Week 52. The primary endpoint was at least 40% improvement in Assessment of Spondyloarthritis International Society (ASAS 40) at Week 16.

Clinical Response

In Trial AS-1, treatment with BIMZELX resulted in significant improvements in the measure of disease activity compared to placebo at Week 16 (Table 9).

Table 9: Clinical Response in Trial AS-1 at Week 16

	BIMZELX 160 mg Q4W (N=221)	Placebo (N=111)	Difference from placebo (95% CI)**

	n (%)	n (%)	
ASAS 40 response	99 (44.8%)*	25 (22.5%)	22.3 (12.1, 32.4)
ASAS 20 response	146 (66.1%)*	48 (43.2%)	22.8 (11.7, 34.0)

NRI is used
CI= confidence interval
* Multiplicity-controlled p<0.001
**95% CI based on normal approximation

Similar responses were seen regardless of prior anti-TNF alpha therapy. Treatment with BIMZELX resulted in improvement in enthesitis in subjects with pre-existing enthesitis.

The results of the main components of the ASAS 40 response criteria and other measures of disease activity are shown in Table 10.

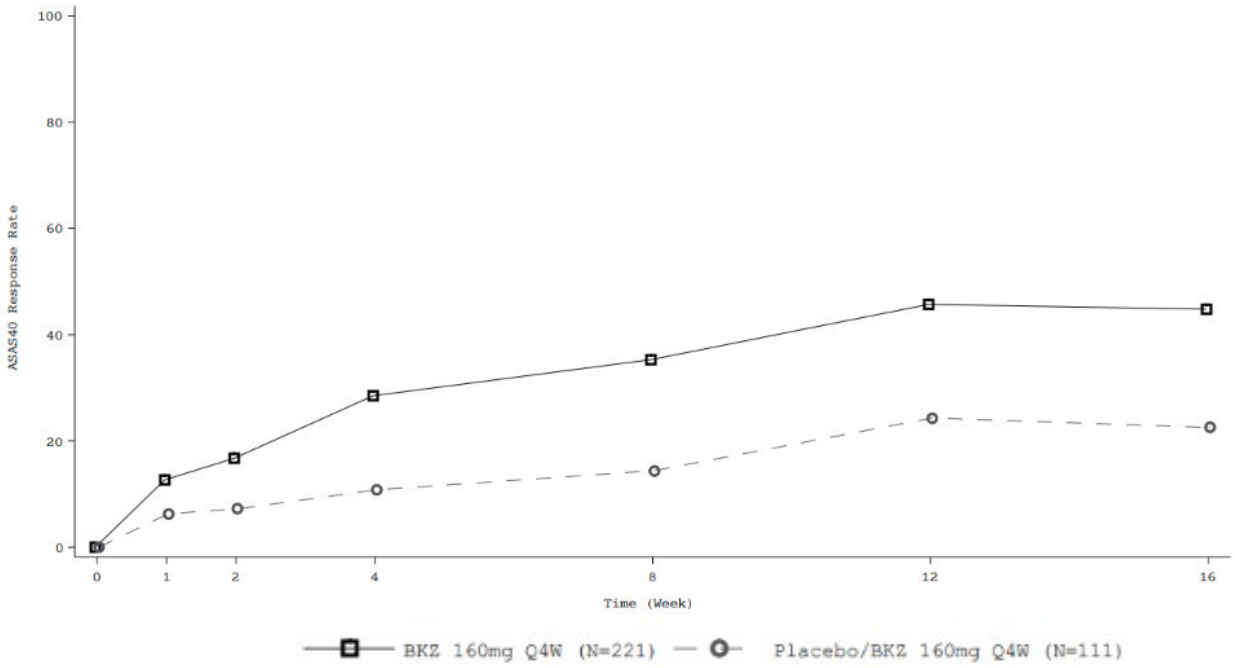
Table 10: Components of the ASAS 40 Response Criteria and Other Measures of Disease Activity in Ankylosing Spondylitis Subjects at Baseline and Week 16 in Trial AS-1

	BIMZELX 160 mg Q4W (N= 221)	Placebo (N=111)
ASAS Components		
- *Patient Global Assessment (0-10)*		
Baseline	6.6	6.7
Mean Change from Baseline	-2.7	-1.6
- *Total Spinal Pain (0-10)*		
Baseline	7.1	7.2
Mean Change from Baseline	-3.3	-1.9
- *BASFI (0-10)*		
Baseline	5.3	5.2
Mean Change from Baseline*	-2.2*	-1.1
- *Inflammation (0-10)*[a]		
Baseline	6.7	6.8
Mean Change from Baseline	-3.2	-2.1
Other Measures of Disease Activity		
BASDAI Score		
Baseline	6.4	6.5
Mean Change from Baseline	-2.9*	-1.9
BASMI		
Baseline	3.9	3.8
Mean Change from Baseline	-0.5**	-0.2
hsCRP (mg/L)		
Baseline	14.7	13.6
Mean Change from Baseline	-8.6	-2.2

[a] Inflammation is the mean of patient-reported stiffness self-assessments (questions 5 and 6) in BASDAI.;
BASFI = Bath Ankylosing Spondylitis Functional Index
BASMI = Bath Ankylosing Spondylitis Metrology Index
BASDAI = Bath Ankylosing Spondylitis Disease Activity Index
MI is used for all endpoints presented in Table 10
* Multiplicity-controlled p<0.001
**Multiplicity-controlled p<0.006

The percentage of subjects achieving ASAS 40 responses in Trial AS-1 by visit through Week 16 is shown in Figure 5.

Figure 5: Percent of Subjects Achieving ASAS 40 Responses in Trial AS-1 Through Week 16



Health Related Quality of Life

BIMZELX treated subjects showed significantly greater improvement compared to subjects receiving placebo at Week 16 in health-related quality of life as measured by the Ankylosing Spondylitis Quality of Life Questionnaire (ASQoL) score.

14.5 Hidradenitis Suppurativa

The safety and efficacy of BIMZELX were assessed in two Phase 3 multicenter, randomized, double-blind, placebo-controlled trials [Trial HS-1 (NCT04242446) and Trial HS-2 (NCT04242498)] in 1,014 adult subjects with moderate to severe HS of at least 6 months with Hurley Stage II or Hurley Stage III disease, and with ≥5 inflammatory lesions [i.e., number of abscesses plus number of inflammatory nodules (AN count)], and a history of inadequate response to a course of systemic antibiotics for the treatment of HS.

Subjects received BIMZELX 320 mg every 2 weeks (Q2W) for 48 weeks, or BIMZELX 320 mg every 4 weeks (Q4W) up to Week 48, or BIMZELX 320 mg Q2W to Week 16, followed by 320 mg Q4W up to Week 48, or placebo. At Week 16, subjects receiving placebo were switched to BIMZELX 320 mg Q2W to Week 48. Concomitant oral doxycycline, minocycline, or an equivalent systemic tetracycline for HS was allowed if the subject was on a stable dose regimen for 28 days prior to baseline.

In these trials, at baseline the mean age of all subjects was 37 years, 57% of subjects were female, 80% were White, 11% were Black or African American, and 4% were Asian; for ethnicity, 7% identified as Hispanic or Latino. Of the subjects enrolled in trials conducted in the United States, 33% were Black or African American. The mean BMI was 33, and 46% were current smokers. Subjects had a median disease duration of 5 years. Overall, 9% of subjects were receiving concomitant antibiotic therapy for HS, and 19% of subjects had received previous treatment with biologics. The proportion of Hurley Stage II and Stage III subjects were 56% and 44%, respectively. Additionally, the mean number of draining tunnels was 3.6 and mean AN count was 16.3.

The primary efficacy endpoint in both trials was the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16, defined by at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess or draining tunnel count relative to baseline. Secondary endpoints included the proportion of subjects who achieved HiSCR75 and HS-specific skin pain response as assessed by a 0 to 10 numeric rating scale (NRS).

Clinical Response at Week 16 (Trials HS-1 and HS-2)

In both trials, a higher proportion of BIMZELX-treated subjects achieved HiSCR50 and HiSCR75 compared to placebo (see Table 11).

Table 11: Efficacy Results in Adults with HS in Trials HS-1 and HS-2 at Week 16 [a]

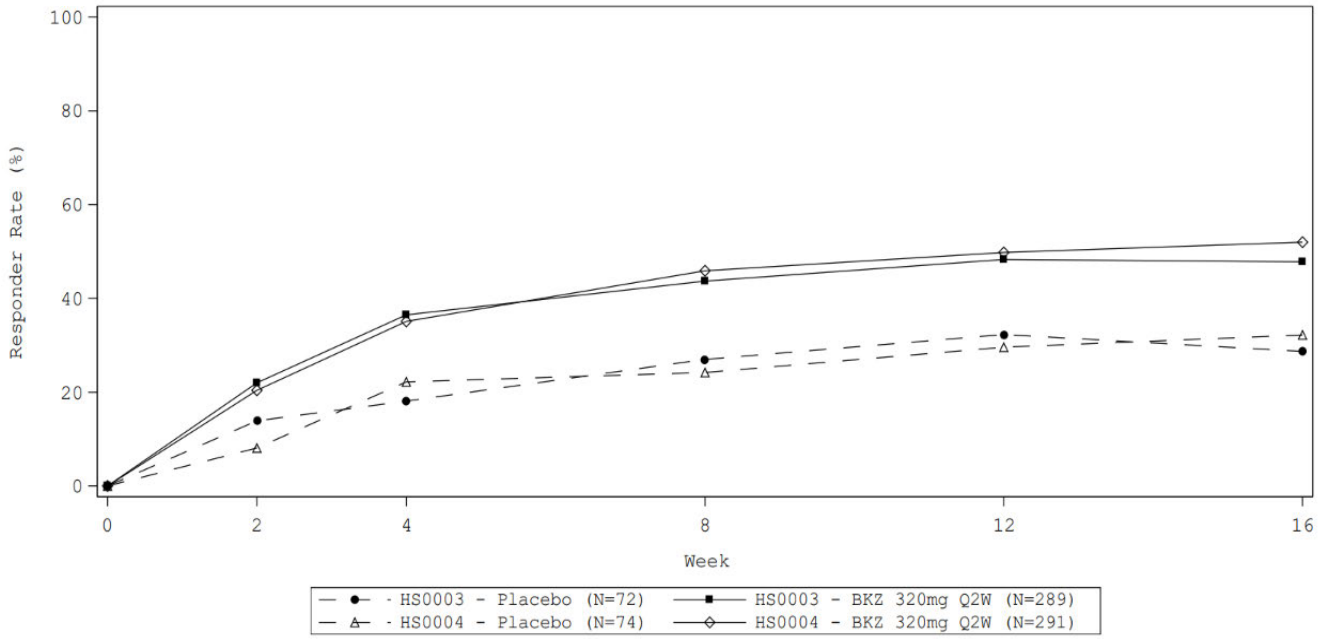
	Trial HS-1		Trial HS-2	
	BIMZELX 320mg Q2W (N=289)	**Placebo (N=72)**	**BIMZELX 320 mg Q2W (N=291)**	**Placebo (N=74)**
HiSCR50	48%	29%	52%	32%
Difference (95% CI)	18% (6%, 30%)		20% (8%, 32%)	
HiSCR75	33%	18%	36%	16%
Difference (95% CI)	15% (4%, 27%)		20% (10%, 31%)	

[a] Subjects who initiated systemic antibiotics (new antibiotic or change in the dose/type of current antibiotic) for any reason or who discontinued due to adverse event or lack of efficacy are treated as non-responders at all subsequent visits. Other missing data were imputed via multiple imputation.

Examination of age, gender, race, disease duration, weight, prior biologic therapy, systemic antibiotic use at baseline, Hurley stage, and smoking status did not identify meaningful differences in response to BIMZELX among these subgroups at Week 16.

Figure 6 presents the proportion of subjects achieving HiSCR50 response in Trials HS-1 and HS-2 by visit through Week 16.

Figure 6: HiSCR50 Response through Week 16 in Adults with HS in Trials HS-1 and HS-2



Subjects who initiated systemic antibiotics (new antibiotic or change in the dose/type of current antibiotic) for any reason through Week 16 or who discontinued due to adverse event or lack of efficacy are treated as non-responders at all subsequent visits. Other missing data were imputed via multiple imputation.

BIMZELX was associated with an improvement in patient-reported worst skin pain (lesion pain) based on the achievement of a reduction of at least 3 points (as measured on a 0 to 10 NRS) compared to placebo at Week 16.

16 HOW SUPPLIED/STORAGE AND HANDLING

How Supplied

BIMZELX (bimekizumab-bkzx) injection is a sterile, preservative-free, clear to slightly opalescent, and colorless to pale brownish-yellow solution. Each prefilled autoinjector or prefilled syringe contains 1 mL or 2 mL of a 160 mg/mL solution. The autoinjectors and prefilled syringes are not made with natural rubber latex. BIMZELX is supplied as:

BIMZELX 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.
- NDC 50474-781-84: Carton of one 160 mg/mL single-dose autoinjector. The prefilled autoinjector is fixed with a 27 gauge ½ inch needle.
- NDC 50474-782-84: Carton of one 320 mg/2 mL (160 mg/mL) single-dose autoinjector fixed with a 27 gauge ½ inch needle.

BIMZELX 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.
- NDC 50474-780-78: Carton of one 160 mg/mL single dose prefilled syringe. The prefilled syringe is fixed with a 27 gauge ½ inch needle with a needle guard.
- NDC 50474-783-78: Carton of one 320 mg/2 mL (160 mg/mL) single-dose prefilled syringe with a 27 gauge ½ inch needle.

Storage and Handling

Store cartons with BIMZELX 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. BIMZELX does not contain a preservative; discard any unused portion.

When necessary, BIMZELX 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 BIMZELX 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.

17 PATIENT COUNSELING INFORMATION

Advise the patient and/or caregiver to read the FDA-approved patient labeling (Medication Guide and Instructions for Use).

Administration Instructions

Instruct patients or caregivers to perform the first self-injection under the supervision and guidance of a qualified healthcare professional for proper training in subcutaneous injection technique *[see Dosage and Administration (2.9), Instructions for Use]*.

If two separate 160 mg injections are used to achieve the recommended dose, instruct patients or caregivers to administer each injection subcutaneously at a different anatomic location *[see Dosage and Administration (2.9)]*.

Instruct patients or caregivers in the technique of needle and syringe disposal *[see Instructions for Use]*.

Advise patients if they forget to take their dose of BIMZELX to inject their dose as soon as they remember. Instruct patients to then take their next dose at the appropriate scheduled time *[see Dosage and Administration (2.7)]*.

Suicidal Ideation and Behavior

Instruct patients and their caregivers to monitor for the emergence of suicidal ideation and behavior and promptly seek medical attention if the patient experiences suicidal ideation or behavior; or new onset or worsening depression, anxiety, or other mood changes. Instruct patients to call the National Suicide and Crisis Lifeline at 988 if they experience suicidal ideation or behavior *[see Warnings and Precautions (5.1)]*.

Infections

Inform patients that BIMZELX may lower the ability of their immune system to fight infections. Instruct patients of the importance of communicating any history of infections to the healthcare provider and contacting their healthcare provider if they develop any symptoms of an infection *[see Warnings and Precautions (5.2)]*.

Liver Biochemical Abnormalities

Inform patients that BIMZELX may increase the risk of elevated liver enzymes. Acute liver disease or cirrhosis may increase this risk. Advise patients that laboratory evaluation is needed prior to and periodically during treatment. Advise patients to hold the next dose of BIMZELX and call their healthcare provider right away, if signs or symptoms of liver dysfunction occur *[see Warnings and Precautions (5.4)]*.

Inflammatory Bowel Disease

Instruct patients to seek medical advice if they develop signs and symptoms of Crohn's disease or ulcerative colitis *[see Warnings and Precautions (5.5)]*.

Immunizations

Advise patients to avoid vaccination with live vaccines during BIMZELX treatment. Instruct patients to inform their healthcare practitioner that they are taking BIMZELX prior to a potential vaccination *[see Warnings and Precautions (5.6)]*.

Pregnancy

Advise patients that there is a pregnancy registry that monitors pregnancy outcomes in patients exposed to BIMZELX during pregnancy *[see Use in Specific Populations (8.1)]*.

Manufactured by:
UCB, Inc.
1950 Lake Park Drive Smyrna, GA 30080
US License No. 1736

MEDICATION GUIDE
BIMZELX® (bim zel'ex)
(bimekizumab-bkzx)
injection, for subcutaneous use

What is the most important information I should know about BIMZELX?

BIMZELX is a medicine that affects your immune system. BIMZELX may increase your risk of having serious side effects, including:

- **Suicidal thoughts and behavior. New or worsening suicidal thoughts and behavior have happened in some people treated with BIMZELX.** Get medical help right away or call the National Suicide and Crisis Lifeline at 988 if you, your caregiver or your family member notice in you any of the following symptoms:
  - new or worsening depression or anxiety
  - thoughts of suicide, dying, or hurting yourself
  - changes in behavior or mood
  - acting on dangerous impulses
  - attempt to commit suicide
- **Infections**. BIMZELX is a medicine that may lower the ability of your immune system to fight infections and may increase your risk of infections, including serious infections.
  - Your healthcare provider should check you for infections and tuberculosis (TB) before starting treatment with BIMZELX.
  - If your healthcare provider feels you are at risk for TB, you may be treated with medicine for TB before you begin treatment with BIMZELX and during your treatment with BIMZELX.
  - Your healthcare provider should watch you closely for signs and symptoms of TB during and after treatment with BIMZELX. **Do not take BIMZELX if you have an active TB infection.**

Before starting BIMZELX, tell your healthcare provider if you:

- are being treated for an infection
- have an infection that does not go away or keeps coming back
- have TB or have been in close contact with someone with TB
- think you have an infection or have symptoms of an infection such as:
  - fever, sweats, or chills
  - muscle aches
  - cough
  - shortness of breath
  - blood in your phlegm
  - weight loss
  - warm, red, or painful skin or sores on your body different from your psoriasis
  - diarrhea or stomach pain
  - burning when you urinate or urinating more often than normal

After starting BIMZELX, call your healthcare provider right away if you have any of the signs of infection listed above. Do not use BIMZELX if you have any signs of infection unless you are instructed to by your healthcare provider.

See "**What are the possible side effects of BIMZELX**?" for more information about side effects.

What is BIMZELX?

BIMZELX is a prescription medicine used to treat:

- adults with moderate to severe plaque psoriasis who may benefit from taking injections or pills (systemic therapy) or treatment using ultraviolet light alone or with pills (phototherapy).
- adults with active psoriatic arthritis.
- adults with active non-radiographic axial spondyloarthritis with objective signs of inflammation.
- adults with active ankylosing spondylitis.
- adults with moderate to severe hidradenitis suppurativa.

It is not known if BIMZELX is safe and effective in children.

Before using BIMZELX, tell your healthcare provider about all of your medical conditions, including if you:

- have any of the conditions or symptoms listed in the section **"What is the most important information I should know about BIMZELX?"**
- have a history of depression, or suicidal thoughts or behavior
- have liver problems

- have inflammatory bowel disease (Crohn's disease or ulcerative colitis)
- have recently received or are scheduled to receive an immunization (vaccine). You should avoid receiving live vaccines during treatment with BIMZELX. Tell all your healthcare providers that you are being treated with BIMZELX before receiving a vaccine.
- are pregnant or plan to become pregnant. It is not known if BIMZELX can harm your unborn baby.
  - If you become pregnant while taking BIMZELX, you are encouraged to enroll in the Pregnancy Registry. The purpose of the pregnancy registry is to collect information about the health of you and your baby. Talk to your healthcare provider or call 1-877-311-8972 to enroll in this registry or visit http://mothertobaby.org/pregnancy-studies/.
- are breastfeeding or plan to breastfeed. It is not known if BIMZELX passes into your breast milk. Talk to your healthcare provider about the best way to feed your baby during treatment with BIMZELX.

Tell your healthcare provider about all the medicines you take, including prescription and over the counter medicines, vitamins and herbal supplements.

How should I use BIMZELX?

See the detailed "Instructions for Use" that comes with your BIMZELX for information on how to prepare and inject a dose of BIMZELX, and how to properly throw away (dispose of) used BIMZELX autoinjectors and prefilled syringes.

- Use BIMZELX exactly as prescribed by your healthcare provider.
- If you miss your BIMZELX dose, inject a dose as soon as you remember. Then, take your next dose at your regular scheduled time. Call your healthcare provider if you are not sure what to do.

What are the possible side effects of BIMZELX?

BIMZELX may cause serious side effects, including:

- **See "What is important information I should know about BIMZELX?"**
- **Elevated liver enzyme levels.** Your healthcare provider will do blood tests to check your liver enzyme levels before starting treatment and during treatment with BIMZELX. Your healthcare provider may temporarily stop or permanently stop your treatment with BIMZELX if you develop liver problems. Call your healthcare provider right away if you develop any signs or symptoms of liver problems, including:
  - pain on the right side of your stomach-area
  - feeling very tired
  - loss of appetite
  - nausea and vomiting
  - itching
  - dark urine
  - light-colored stool
  - yellowing of your skin or the whites of your eyes
- **Inflammatory bowel disease.** New cases of inflammatory bowel disease or "flare-ups" have happened with BIMZELX. If you have inflammatory bowel disease (Crohn's disease or ulcerative colitis), tell your healthcare provider if you have worsening disease symptoms during treatment with BIMZELX or develop new symptoms of stomach pain or diarrhea. Your healthcare provider will stop treatment with BIMZELX if you develop new or worsening signs of Crohn's disease or ulcerative colitis.

The most common side effects of BIMZELX in people treated for Psoriasis and Hidradenitis Suppurativa include:

- upper respiratory tract infections
- headache
- herpes simplex infections (cold sores in or around the mouth)
- small red bumps on your skin
- feeling tired
- fungal infections (oral thrush or infections in the mouth, throat, skin, nails, feet or genitals)
- pain, redness or swelling at injection site
- stomach flu (gastroenteritis)
- acne

The most common side effects of BIMZELX in people treated for psoriatic arthritis include:

- upper respiratory tract infections
- headache
- urinary tract infection
- oral thrush or infections in the mouth
- diarrhea

The most common side effects of BIMZELX in people treated for non-radiographic axial spondyloarthritis include:

- upper respiratory tract infections
- oral thrush or infections in the mouth

- headache
- cough
- joint pain
- tonsilitis
- urinary tract infection
- diarrhea
- feeling tired
- muscle aches
- liver enzyme increase

The most common side effects of BIMZELX in people treated for ankylosing spondylitis include:

- upper respiratory tract infections
- headache
- pain at injection site
- vaginal yeast infections
- oral thrush or infections in the mouth
- diarrhea
- rash

These are not all of the possible side effects of BIMZELX.

Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088.

How should I store BIMZELX?

- Store BIMZELX in the refrigerator between 36°F to 46°F (2°C to 8°C).
- BIMZELX may be stored at room temperature up to 77°F (25°C) for up to 30 days in the original carton. **Do not** place BIMZELX prefilled syringes or autoinjectors back in the refrigerator after they have been stored at room temperature.
- Write the date removed from the refrigerator in the space provided on the carton and throw away BIMZELX if it has been kept at room temperature and not been used within 30 days.
- Keep BIMZELX in the original carton until ready for use to protect from light.
- Do not freeze BIMZELX.
- Do not shake BIMZELX.
- Do not use BIMZELX past the expiration date printed on the carton.

Keep BIMZELX and all medicines out of the reach of children.

General information about the safe and effective use of BIMZELX.

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use BIMZELX for a condition for which it was not prescribed. Do not give BIMZELX to other people, even if they have the same symptoms that you have. It may harm them. You can ask your pharmacist or healthcare provider for information about BIMZELX that is written for health professionals.

What are the ingredients in BIMZELX?

Active ingredient: bimekizumab-bkzx

Inactive ingredients: glacial acetic acid, glycine, polysorbate 80, sodium acetate and Water for Injection, USP.

Manufactured by:
UCB, Inc.
1950 Lake Park Drive Smyrna, GA 30080
US License No. 1736

For more information, go to www.BIMZELX.com or call 1-844-599-2273

This Medication Guide has been approved by the U.S. Food and Drug Administration. Revised: November 2024

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761151Orig1s010

MULTIDISCIPLINE REVIEW(s)

NDA/BLA Multi-Disciplinary Review and Evaluation

Application Type	Efficacy Supplement
Application Number(s)	BLA 761151 S-010
Priority or Standard	Standard
Submit Date(s)	January 19, 2024
Received Date(s)	January 19, 2024
PDUFA Goal Date	November 19, 2024
Division/Office	Division of Dermatology and Dentistry (DDD) /Office of Immunology and Inflammation (OII)
Review Completion Date	November 18, 2024
Established/Proper Name	Bimekizumab-bkzx
(Proposed) Trade Name	BIMZELX
Pharmacologic Class	a humanized interleukin-17A and F antagonist
Code name	UCB4940 (CDP4940)
Applicant	UCB, Inc.
Dosage form	Injection
Applicant proposed Dosing Regimen	320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks thereafter.
Applicant Proposed Indication(s)/Population(s)	For the treatment of adult patients with moderate to severe hidradenitis suppurativa
Applicant Proposed SNOMED CT Indication Disease Term for each Proposed Indication	59393003 |Hidradenitis suppurativa (disorder)|
Recommendation on Regulatory Action	Approval
Recommended Indication(s)/Population(s) (if applicable)	BIMZELX is a humanized interleukin-17A and F antagonist indicated for the treatment of adults with moderate to severe hidradenitis suppurativa (HS).
Recommended SNOMED CT Indication Disease Term for each Indication (if applicable)	59393003 |Hidradenitis suppurativa (disorder)|
Recommended Dosing Regimen	320 mg (given as 2 subcutaneous injections of 160 mg each) at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks thereafter

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Reviewers of Multi-Disciplinary Review and Evaluation

Regulatory Project Manager	Strother Dixon
Office of Clinical Pharmacology Reviewer(s)	Selim Fakhruddin
Office of Clinical Pharmacology Team Leader(s)	Chinmay Shukla/Youwei Bi
Clinical Reviewer	Kevin Clark
Clinical Team Leader	Melinda McCord
Statistical Reviewer	Matthew Guerra
Cross-Disciplinary Team Leader	Melinda McCord
Office Director (or designated signatory authority)	Gordana Diglisic

Additional Reviewers of Application

OPQAIII	Xuhong Li/Samuel Mindaye
OPMA Facility	Wayne Seifert/Zhong Li
OMIR	Wayne Seifert
OPRO RBPM	Nowrin Kakon
DP	Shamir N. Kalaria
DHN	Eileen Navarro Almario/Paul H. Hayashi
DG	Arushi deFonseka/Tara Altepeter
DCN	Selena DeConti
DPMH/Maternal health	Wenjie Sun/Miriam Dinatale
DCOA	Yasmin Choudhry/Selena Daniels
PFSS	Monica Morell
DMPP	Susan Redwood/Barbara Fuller/LaShawn Griffiths
OPDP	Montherson Saint Juste
OSI	Roy Blay/Michelle Fedowicz/Jenn Sellers
OSE/DEPI	Zachary Pedretti
OSE/DMEPA	Madhuri Patel/ Yevgeniya Kogan /Murewa Oguntimein

OPQ=Office of Pharmaceutical Quality
OPDP=Office of Prescription Drug Promotion
OSI=Office of Scientific Investigations
OSE= Office of Surveillance and Epidemiology
DEPI= Division of EpidemiologyDMEPA=Division of Medication Error Prevention and Analysis
DRISK=Division of Risk Management
PFSS =Patient-Focused Statistical Scientists Reviewer

Signatures

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Pharmacology and Pharmacometrics Reviewer	Selim Fakhruddin, PhD	OTS/OCP/DIIP	Section: 6, 19.4	Select one: __X_ Authored ___ Approved
	Signature: Signed in DARRTS			
Clinical Pharmacology Team Leader	Chinmay Shukla, PhD	OTS/OCP/DIIP	Section: 6, 19.4	Select one: ___ Authored __X_ Approved
	Signature: Signed in DARRTS			
Pharmacometrics Team Leader	Youwei Bi, PhD	OTS/OCP/DPM	Section: 6, 19.4	Select one: ___ Authored __X_ Approved
	Signature:			
Clinical Reviewer	Jessica Nguyen, MD	OND/OII/DDD	Sections: 2, 3	Select one: _X_ Authored ___ Approved
	Signature: Signed in DARRTS			

DISCIPLINE	REVIEWER	OFFICE/DIVISION	SECTIONS AUTHORED/ APPROVED	AUTHORED/ APPROVED
Clinical Reviewer	Kevin Clark, MD	OND/OII/DDD	Sections: 1, 3.2, 4.1, 4.4, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.2	Select one: _X_ Authored ___ Approved
	Signature: Signed in DARRTS			
Clinical Team Leader	Melinda McCord, MD	OND/OII/DDD	Sections: 1, 2, 3, 4.1, 4.4, 7, 8.2, 8.4, 9, 10, 11, 12, 13, 19.2	Select one: ___ Authored _X_ Approved
	Signature: Signed in DARRTS			
Statistical Reviewer	Matthew Guerra, PhD	OTS/OB/DBIII	Sections: 8.1, 8.3	Select one: _X_ Authored _X_ Approved
	Signature: Signed in DARRTS			
Clinical Outcome Assessment (COA) Reviewer	Yasmin Choudhry, MD	ODES/DCOA	Sections: 8.1.2, 8.1.9	Select one: _X__ Authored ___ Approved
	Signature: Signed in DARRTS			
COA Team Leader/Deputy Division Director	Selena Daniels, PharmD, PhD	ODES/DCOA	Sections: 8.12, 8.1.9	Select one: _X__ Authored _X__ Approved
	Signature: Signed in DARRTS			
Associate Director for Therapeutic Review Signatory (Clinical)	Gordana Diglisic, MD	OND/OII/DDD	Sections: All	Select one: ___ Authored _X_ Approved
	Signature: Signed in DARRTS			

Glossary

AC	advisory committee
ADA	anti-drug antibody
ADME	absorption, distribution, metabolism, excretion
AE	adverse event
AN	number of abscesses plus number of inflammatory nodules
AR	adverse reaction
AT	aminotransferase
BKZ	bimekizumab
BLA	biologics license application
BPCA	Best Pharmaceuticals for Children Act
BRF	Benefit Risk Framework
BW	Body weight
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CDTL	Cross-Discipline Team Leader
CFR	Code of Federal Regulations
CMC	chemistry, manufacturing, and controls
COA	clinical outcome assessment
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	case report form
CRO	contract research organization
CRT	clinical review template
CSR	clinical study report
CSS	Controlled Substance Staff
DCOA	Division of Clinical Outcome Assessment
DHN	Division of Hepatology and Nutrition
DHOT	Division of Hematology Oncology Toxicology
DILI	Drug-induced Liver Injury
DLQI	Dermatology Life Quality Index
DMC	data monitoring committee
ECG	electrocardiogram
eCDF	empirical cumulative distribution function curves
eCTD	electronic common technical document
ETASU	elements to assure safe use
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Amendments Act of 2007
FDASIA	Food and Drug Administration Safety and Innovation Act
GCP	good clinical practice
GRMP	good review management practice

HiSCR50	Hidradenitis Suppurativa Clinical Response 50
HSSDD	HS Symptom Daily Diary
ICH	International Conference on Harmonisation
IMP	investigational medicinal product
IND	Investigational New Drug
ISE	integrated summary of effectiveness
ISS	integrated summary of safety
IRT	interactive response technology
ITT	intent to treat
MedDRA	Medical Dictionary for Regulatory Activities
mITT	modified intent to treat
NCI-CTCAE	National Cancer Institute-Common Terminology Criteria for Adverse Event
NDA	new drug application
NME	new molecular entity
OCS	Office of Computational Science
OPQ	Office of Pharmaceutical Quality
OSE	Office of Surveillance and Epidemiology
OSI	Office of Scientific Investigation
PBRER	Periodic Benefit-Risk Evaluation Report
PD	pharmacodynamics
PGI-C-SP	Patient Global Impression of Change of Severity in Skin Pain
PGI-S-SP	Patient Global Impression of Severity in Skin Pain
PI	prescribing information
PK	pharmacokinetics
PMC	postmarketing commitment
PMR	postmarketing requirement
PP	per protocol
PPI	patient package insert (also known as Patient Information)
PREA	Pediatric Research Equity Act
PRO	patient reported outcome
PsO	psoriasis
PSUR	Periodic Safety Update report
REMS	risk evaluation and mitigation strategy
SAE	serious adverse event
SAP	statistical analysis plan
SB	suicidal behavior
SC	subcutaneous
SGE	special government employee
SI	suicidal ideation
SI/B	suicidal ideation and behavior
SOC	standard of care
TEAE	treatment emergent adverse event

1 Executive Summary

1.1. Product Introduction

The Applicant, UCB, Inc., submitted a supplemental Biologics License Application for BLA 761151 (sBLA-010) to support the following new proposed indication for BIMXELX (bimekizumab-bkzx, hereafter referred to as bimekizumab or BKZ) injection:

> BIMZELX is indicated for the treatment of adult patients with moderate to severe hidradenitis suppurativa.

BKZ is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) that binds to Interleukin 17 A and F (IL-17A and IL-17F). IL-17 is a naturally occurring cytokine that is involved in inflammatory and immune responses. BKZ inhibits the release of proinflammatory cytokines and chemokines.

BIMZELX was approved in the United States on October 18, 2023, for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The approved dosage of BIMZELX for the treatment of moderate to severe plaque psoriasis in adult patients is 320 mg at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. For patients weighing ≥ 120 kg, consider a dosage of 320 mg every 4 weeks after Week 16.

BIMZELX was approved on September 20, 2024 for the following indications (BLA 761151 S006, S007 and S008):

- For the treatment of adult patients with active psoriatic arthritis.
- For the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation.
- For the treatment of adult patients with active ankylosing spondylitis.

The recommended dosage for each of these 3 indications is 160 mg SC every 4 weeks.

On October 11, 2024, the FDA approved the use of two new presentations: (a) a single-injection prefilled syringe (also referred to as SS [safety syringe]) and (b) a single-injection autoinjector (AI), both containing 2 mL of BIMZELX (BLA 761151 S009). BIMZELX is supplied in the following product presentations:

- Injection (1 mL): 160 mg/mL in a single-dose prefilled syringe or single-dose prefilled autoinjector.
- Injection (2 mL): 320 mg/2mL in a single-dose prefilled syringe or single-dose prefilled autoinjector.

The use of BIMZELX is associated with potential toxicities. The Warnings and Precautions section of the labeling describes the potential risks of suicidal ideation and behavior (SI/B), infections, tuberculosis, liver biochemical abnormalities, inflammatory bowel disease, and avoidance of live vaccines.

The proposed dosage of BIMZELX for the treatment of adult patients with moderate to severe hidradenitis suppurativa is 320 mg at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks thereafter.

1.2. Conclusions on the Substantial Evidence of Effectiveness

The Applicant submitted data from two adequate and well-controlled trials (HS0003 and HS0004) which provided substantial evidence of the effectiveness of BKZ for the treatment of moderate to severe HS. The trials assessed the change from Baseline to Week 16 compared to placebo for the primary efficacy endpoint. The primary efficacy endpoint was the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16, defined by at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess or draining tunnel count relative to baseline.

In both trials, a higher proportion of BKZ-treated subjects achieved HiSCR50 compared to placebo. In Trial HS0003, 48% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 at Week 16 compared to 29% of subjects receiving placebo (difference 18%, 95% confidence interval [CI] 65, 30%). In Trial HS0004, 52% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 compared to 32% of subjects receiving placebo (difference 20%, 95% CI 8%, 32%). The Applicant has demonstrated that bimekizumab is effective for its intended use in the target population and has met the evidentiary standard to support approval.

1.3. Benefit-Risk Assessment

Benefit-Risk Summary and Assessment

Bimekizumab (BKZ) is a humanized, full-length monoclonal antibody (mAb) of immunoglobulin G1 (IgG1) that binds to Interleukin 17 A and F (IL-17A and IL-17F). IL-17 is a naturally occurring cytokine that is involved in inflammatory and immune responses. BKZ inhibits the release of proinflammatory cytokines and chemokines. BKZ is marketed under the trade name BIMZELX and was approved in the United States on October 18, 2023 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy. The approved dosage of BIMZELX for the treatment of moderate to severe plaque psoriasis in adult patients is 320 mg at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. For patients weighing ≥ 120 kg, consider a dosage of 320 mg every 4 weeks after Week 16. BKZ was approved on September 20, 2024 for the treatment of adult patients with active psoriatic arthritis, active non-radiographic axial spondyloarthritis with objective signs of inflammation, and active ankylosing spondylitis. The recommended dosage of BKZ for each of these indications is 160 mg every 4 weeks.

The Applicant submitted a supplemental Biologics License Application (sBLA 761151 S-010) to support the use of bimekizumab in a new patient population. The proposed indication is for the treatment of adult patients with moderate to severe hidradenitis suppurativa. Hidradenitis suppurativa (HS) is a chronic, recurrent suppurative disease that manifests with inflamed skin lesions, with or without skin tunnels or scarring, and may be associated with pain, pruritis, malodor, drainage, and disfigurement. HS primarily affects intertriginous areas, such as the axillae, groin, and anogenital regions. The extent or severity of disease is often characterized by the Hurley staging system, which divides patients with HS into three groups: Stage I – abscess(es) without skin tunnels or scarring; Stage II – recurrent single or multiple widely separated abscesses with skin tunnels and scarring; and Stage III – multiple interconnected skin tunnels and abscesses across an entire area.

The only products currently approved in the United States for the treatment of moderate to severe HS are adalimumab and secukinumab. Adalimumab is a tumor necrosis factor blocker, which is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older. Secukinumab is an IL-17A blocker which is indicated for the treatment of adults with moderate to severe HS. Off-label treatment options for HS include a variety of products. Success with these off-label treatment options is variable and may be limited by side effect profiles, disease severity, concomitant medical conditions, and patient preference. Additional details regarding approved and off-label therapies are presented in the benefit-risk table below.

The Applicant submitted data from two adequate and well-controlled trials of identical design (HS0003 and HS0004) which provided substantial evidence of the effectiveness of BKZ for the treatment of moderate to severe HS. The trials evaluated 1014 adult subjects ages 18 years and

older with moderate to severe HS. The protocol-specified definition for moderate to severe HS was ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules) at both the Screening and Baseline visits, HS lesions in at least 2 distinct anatomic locations, 1 of which must be Hurley Stage II or III, and no more than 20 draining tunnels at Baseline. Subjects were randomized in a 2:2:2:1 ratio to the following treatment arms: BKZ 320 mg every 2 weeks (Q2W) from Week 0-48, BKZ 320 mg Q4W from Week 0-48, BKZ 320 mg Q2W from Week 0-16, then 320 mg Q4W from Week 16-48, and placebo.

The primary efficacy endpoint was the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16, defined by at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess or draining tunnel count relative to baseline. In both trials, a higher proportion of BKZ-treated subjects achieved HiSCR50 compared to placebo. In Trial HS0003, 48% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 at Week 16 compared to 29% of subjects receiving placebo (difference 18%, 95% confidence interval [CI] 65, 30%). In Trial HS0004, 52% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 compared to 32% of subjects receiving placebo (difference 20%, 95% CI 8%, 32%). Subjects who were responders tended to maintain response as no meaningful change in HiSCR50 response rate occurred through Week 48 in subjects treated with the proposed dosing regimen of BKZ 320 mg Q2W for 16 weeks, followed by BKZ 320 mg Q4W. Subjects treated with BKZ were also more likely to experience a reduction of between 2.4- and 4.8-points on the worst skin (lesion) pain score on a 0-10 numerical rating scale (NRS). Anchor-based analyses demonstrated that such a reduction is clinically meaningful.

The overall safety database was sufficient to characterize the safety of BKZ for the treatment of moderate to severe HS. Overall exposure in the phase 3 program for HS included 995 subjects exposed to BKZ. This includes 649 subjects with ≥12 months exposure and 496 with ≥24 months exposure. The primary analysis dataset (Pool S1) for the review of safety of BKZ for the treatment of moderate to severe HS included pooled data from the placebo-controlled Initial Treatment Period (Weeks 0-16) of phase 3 Trials HS0003 and HS0004. The review team evaluated long-term safety using Pool S3, which consists of data from the combined initial, maintenance, and open-label Periods of Trials HS0003, HS0004, and HS0005.

Based on the analysis of the submitted data, treatment with bimekizumab did not appear to increase the risk of mortality. In Pool S1, serious adverse events (SAEs) occurred in 2.6% of subjects treated with BKZ 320 mg Q2W, 2.5% of subjects treated with BKZ 320 mg Q4W, and 0 in subjects receiving placebo. The exposure-adjusted incidence rate (EAIR) for SAEs did not increase with longer exposure to BKZ as the EAIRs for SAEs were similar between Pool S1 and Pool S3. Treatment with BKZ was not associated with an increased risk of major adverse cardiovascular events (MACE), malignancy, or serious drug-related hypersensitivity reactions.

Treatment with BKZ is associated with a risk of suicidal ideation and behavior (SI/B), and this risk is conveyed in currently approved labeling for BKZ. Investigators assessed subjects for the development of SI/B using the Columbia Suicide Severity Rating Scale (C-SSRS) to monitor for

treatment-emergent SI/B during the HS program. In Pool S1, 1.9% of subjects receiving BKZ and 0.7% of subjects receiving placebo reported SI on the C-SSRS. Subjects without a prior history of SI/B treated with BKZ also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects receiving placebo (0.9% vs. 0%). In addition, there were 2 cases of SI that were adjudicated as suicide attempts. There were no completed suicides in the HS program. The risk of SI/B will continue to be communicated in Section 5.1 (Warnings and Precautions) of labeling. Data regarding SI/B in the HS program will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.

During the placebo-controlled period of the phase 3 trials, infections occurred more frequently in subjects treated with BKZ than subjects receiving placebo. When analyzed by treatment group, based on the proportions and EAIRs, infections were more common in the Q2W group than the Q4W group and were not increased with longer exposure to BKZ. The most commonly reported infections were comparable to those reported in subjects with plaque psoriasis. These included oral candidiasis, other candida infections (skin and genital), and tinea infections. Further details regarding infections are presented in the table below.

Elevated liver transaminases (>3xULN) occurred more frequently in subjects treated with BKZ than subjects receiving placebo. In Pool S1, such elevations occurred in 1.2% of subjects treated with BKZ and 0% receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BKZ. This information will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.

Inflammatory bowel disease (IBD) is a known risk of treatment with IL-17 inhibitors, including BKZ, and this risk is conveyed in Section 5.4 (Warnings and Precautions) of currently approved labeling for BKZ. In Pool S3, adjudicated cases of new onset of IBD (including ulcerative colitis (UC), Crohn's disease (CD) and IBD-undetermined) occurred in 5 subjects (0.39 per 100 patient-years [pt-yrs]). The majority of these cases were serious, and all resulted in discontinuation of BKZ. Additionally, flares of pre-existing IBD occurred in 2 subjects, which resulted in discontinuation of BKZ in both. This information will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.

In Pool S1, the most common adverse reactions (ARs) were Upper respiratory infections, Oral candidiasis, Injection site reactions, Other Candida infections, Pyrexia, Tinea infections, Fatigue, Folliculitis, Otitis externa, and Acne. These ARs are comparable to those identified during the development program for PsO and included in currently approved labeling for BKZ. As such, Section 6.1 of labeling for HS will include the statement "The safety profile observed in subjects with hidradenitis suppurativa treated with BIMZELX was comparable to the safety profile observed in subjects with plaque psoriasis treated with BIMZELX." Because of the small sample sizes for demographic subgroups, it was not possible to detect clinically meaningful imbalances in ARs between the subgroups.

Product labeling and patient labeling, including a Medication Guide, as well as routine pharmacovigilance are adequate to manage the risk of BIMZELX in the postmarketing milieu. A Risk Evaluation and Mitigation Strategy (REMS) is not needed. Postmarketing requirements (PMRs) under 505(o) will include recruitment of pregnant patients with HS into the prospective pregnancy registry and retrospective pregnancy cohort studies to be conducted under PMRs issued with the approval of BKZ for the treatment of moderate to severe plaque psoriasis in patients who are candidates for systemic therapy or phototherapy. Required pediatric assessments, under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c) will include a PK and safety trial in subjects 12 years to <18 years of age.

The available safety and efficacy data support the approval of BIMZELX (bimekizumab-bkzx) for the treatment of adults with moderate to severe HS. There are only 2 products currently approved for this indication. Neither provides a cure or universal response, and both are associated with serious potential risks. Because treatment may be complicated by inadequate response, loss of response, and adverse reactions, there is a need for additional therapeutic options.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Analysis of Condition	• Hidradenitis suppurativa (HS) is a chronic, recurrent suppurative disease that is clinically diagnosed based on characteristic inflamed skin lesions primarily affecting intertriginous areas. Clinical manifestations may include recurrent abscesses and inflamed nodules, draining skin tunnels (also known as sinus tracts or fistulae), and bands of scar, all of which may be associated with pain, pruritis, malodor, drainage, and disfigurement. • The exact prevalence in the United States, as well as worldwide, is not known and has ranged from 0.05% to 4.1%. The disease occurs in adolescents and adults, and rarely begins before puberty suggesting that hormones play a role in the pathophysiology of HS. In the United States, HS occurs with higher incidence in women and blacks. • Multiple complications associated with chronic, poorly controlled HS have been reported in the literature which include contractures, lymphatic obstruction, fistulae into the urethra, bladder, rectum, and peritoneum, infections, anemia, and depression, as well as suicide.	HS is a chronic disease that has a significant impact on how patients feel and function. HS is associated with comorbidities such as metabolic syndrome, hypertension, dyslipidemia, inflammatory bowel disease, thyroid disorder, arthropathies, polycystic ovarian syndrome, and psychiatric disorders. Moderate to severe HS has considerable negative effects on quality of life and emotional well-being.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Current Treatment Options	• There is no cure for HS. There are only 2 FDA-approved treatments for HS (adalimumab and secukinumab). Adalimumab is a tumor necrosis factor blocker, which is indicated for the treatment of moderate to severe hidradenitis suppurativa in patients 12 years of age and older. The labeling for adalimumab contains a boxed warning for malignancy, as well as serious infections, including active tuberculosis (TB) and reactivation of latent TB that frequently have frequently presented as disseminated or extrapulmonary disease, invasive fungal infections, and opportunistic infections. Section 5 (Warnings and Precautions) of labeling for adalimumab includes anaphylaxis, nervous system demyelinating diseases, cytopenias, Hepatitis B virus reactivation, and heart failure. Secukinumab is an IL-17A blocker which is indicated for the treatment of adults with moderate to severe HS. Section 5 (Warnings and Precautions) of labeling for secukinumab includes infections (including serious and fatal infections), anaphylaxis, inflammatory bowel disease, severe eczematous eruptions, and risk of hypersensitivity in latex-sensitive individuals. • There are a number of treatments used off-label to manage HS. These include topical antimicrobials (clindamycin), systemic antimicrobials (tetracycline, doxycycline, minocycline), colchicine, dapsone, rifampin, ertapenem), systemic retinoids (isotretinoin, acitretin), antiandrogenic agents (combined oral contraceptive, spironolactone, finasteride), metformin, cyclosporine, biological products other than adalimumab and secukinumab, botulinum toxin A injection, intralesional and systemic corticosteroids, incision and drainage of abscesses, surgical excision, skin grafting, and laser hair removal. •Systemic therapies and surgical interventions are considered for patients who have more severe and/or recalcitrant disease.	There is an unmet medical need for effective treatment of patients with HS. There are limited approved therapies, and existing therapies that are used off-label do not adequately manage the condition for many patients with moderate to severe HS.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Benefit	• Data from Trials HS0003 and HS0004 provided substantial evidence of the effectiveness of BKZ for the treatment of moderate to severe HS. The trials evaluated 1014 adult subjects ages 18 years and older with moderate to severe HS. The protocol-specified definition for moderate to severe HS was ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules) at both the Screening and Baseline visits, HS lesions in at least 2 distinct anatomic locations, 1 of which must be Hurley Stage II or III, and no more than 20 draining tunnels at Baseline. Subjects were randomized in a 2:2:2:1 ratio to the following treatment arms: BKZ 320 mg Q2W from Week 0-48, BKZ 320 mg Q4W from Week 0-48, BKZ 320 mg Q2W from Week 0-16, then 320 mg Q4W from Week 16-48, and placebo. • The primary efficacy endpoint, assessed at Week 16, was the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50), defined by at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess or draining tunnel count relative to baseline. In both trials, a higher proportion of BKZ-treated subjects achieved HiSCR50 compared to placebo. In Trial HS0003, 48% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 at Week 16 compared to 29% of subjects receiving placebo (difference 18%, 95% confidence interval [CI] 65, 30%). In Trial HS0004, 52% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 compared to 32% of subjects receiving placebo (difference 20%, 95% CI 8%, 32%). • Subjects who were responders tended to maintain response as no meaningful change in HiSCR50 response rate occurred through Week 48 in subjects treated with the proposed dosing regimen of BKZ 320 mg Q2W for 16 weeks, followed by BKZ 320 mg Q4W. • Subjects treated with BKZ were also more likely to experience a reduction of between 2.4- and 4.8-points or greater on the worst skin lesion pain score on a 0-10 NRS.	The data submitted by the Applicant met the evidentiary standard for provision of substantial evidence of effectiveness under the proposed conditions of use. The trials were adequate and well-controlled. The results are persuasive. Achievement of HiSCR50 constitutes clinically meaningful improvement in patients with moderate to severe HS. The data demonstrate that a patient with moderate to severe HS is likely to achieve SCR50 by Week 16 and to maintain this effect with continued treatment through Week 48. Anchor-based analyses demonstrated that a reduction of between 2.4- and 4.8-points or greater on the worst skin lesion pain NRS is clinically meaningful.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
Risk and Risk Management	• Overall exposure in the phase 3 program for HS included 995 subjects exposed to BKZ. This includes 649 subjects with ≥12 months exposure and 496 with ≥24 months exposure. The primary analysis dataset (Pool S1) for the review of safety of BKZ for the treatment of moderate to severe HS included pooled data from the placebo-controlled Initial Treatment Period (Weeks 0-16) of phase 3 Trials HS0003 and HS0004. The review team evaluated long-term safety using Pool S3, which consists of data from the combined initial, maintenance, and open-label Periods of Trials HS0003, HS0004, and HS0005. • In Pool S1, serious adverse events (SAEs) occurred in 2.6% of subjects treated with BKZ 320 mg Q2W, 2.5% of subjects treated with BKZ 320 mg Q4W, and 0 in subjects receiving placebo. There was no apparent increase in SAEs with longer exposure to BKZ. • Treatment with BKZ was associated with a risk of suicidal ideation and behavior (SI/B). In Pool S1, 1.9% of subjects receiving BKZ and 0.7% of subjects receiving placebo reported SI on the C-SSRS. Subjects without a prior history of SI/B treated with BKZ also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects receiving placebo (0.9% vs. 0%). In addition, there were 2 cases of SI that were adjudicated as suicide attempts. • Infections occurred more frequently in subjects treated with BKZ than subjects receiving placebo. In Pool S1, TEAEs from the SOC Infections and infestations occurred in 33% (EAIR 132.2/100 pt-yrs) of subjects in the combined BKZ group and 21% (EAIR 76.4/100 pt-yrs) in the placebo group. Serious infections occurred in 0.1% (EAIR 0.4/100 pt-yr) of subjects in the combined BKZ group and no subjects in the placebo group. In Pool S3, infections were reported in 68% (EAIR 104.7/100 pt-yrs) of subjects in the combined BKZ group. Serious infections occurred in 2.1% (1.7/100 pt-yrs) of subjects in the combined BKZ group. When analyzed by treatment group,	The overall safety database was sufficient to characterize the safety of BKZ for the treatment of moderate to severe HS. The data are sufficient to characterize the safety profile of BKZ in the target population. Product labeling will be updated with data from the HS program for SI/B, infections, liver biochemical abnormalities, and IBD. Prescription labeling, patient labeling (including Medication Guide), Instructions for Use, and routine pharmacovigilance, in conjunction with the post marketing requirements, are adequate to manage the risks of the product. The available data are insufficient to evaluate the risk of major birth defects, miscarriage, or adverse fetal or maternal outcomes associated with treatment with BKZ in the target population. As such, we will issue PMRs requiring the Applicant to recruit pregnant women with HS into the post-

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	based on the proportions and EAIRs, infections were more common in the Q2W group than the Q4W group and were not increased with longer exposure to BKZ. • The most commonly reported infections were comparable to those reported in subjects with plaque psoriasis. Oral candidiasis occurred in 7.8% of subjects (26.7 per 100 patient years) treated with BKZ 320 mg Q2W, 3.9% of subjects (12.9 per 100 patient years) treated with BKZ 320 mg Q4W, and 0 subjects receiving placebo. Other candida infections occurred in 3.6% of subjects (12.2 per 100 patient years) treated with BKZ 320 mg Q2W, 6.7% of subjects (22.6 per 100 patient years) treated with BIMZELX 320 mg Q4W, and 0 subjects receiving placebo. Tinea infections occurred in 3.1% of subjects (10.4 per 100 patient-years) treated with BIMZELX 320 mg Q2W, 2.5% of subjects (8.1 per 100 patient years) treated with BIMZELX 320 mg Q4W, and 0.7% (2.3 per 100 patient-years) receiving placebo. This information will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading. • Elevated liver transaminases (>3xULN) occurred more frequently subjects treated with BKZ than subjects receiving placebo. In Pool S1, such elevations occurred in 1.2% of subjects treated with BKZ and 0% receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BKZ. • Inflammatory bowel disease (IBD) is a known risk of treatment with IL-17 inhibitors, including BKZ, and this risk is conveyed in currently approved labeling for BKZ. In Pool S3, adjudicated cases of new onset of IBD (including ulcerative colitis (UC), Crohn's disease (CD) and IBD-undetermined) occurred in 5 subjects (0.39 per 100 patient-years). The majority of these cases were serious, and all resulted in discontinuation of BKZ. Additionally, flares of pre-existing IBD occurred in 2 subjects, which resulted in discontinuation of BKZ in	approval prospective and retrospective studies to be conducted to fulfill postmarketing requirements (PMRs) issued with the initial approval of BKZ for the treatment of moderate to severe PsO. We will also issue a PREA PMR requiring the Applicant to conduct a multicenter, open-label clinical trial to evaluate the PK and safety of bimekizumab in pediatric patients including those 12 years of age and older with moderate to severe HS. A Risk Evaluation and Mitigation Strategy (REMS) is not recommended. Precedent biologic products with comparable safety profiles have a similar approach to post-marketing risk management.

Dimension	Evidence and Uncertainties	Conclusions and Reasons
	both. • In Pool S1, the most common adverse reactions (ARs) were Upper respiratory infections, Oral candidiasis, Injection site reactions, Other Candida infections, Pyrexia, Tinea infections, Fatigue, Folliculitis, Otitis externa, and Acne. These ARs are comparable to those identified during the development program for PsO and included in currently approved labeling for BKZ. As such, Section 6.1 of labeling for HS will include the statement "The safety profile observed in subjects with hidradenitis suppurativa treated with BIMZELX was comparable to the safety profile observed in subjects with plaque psoriasis treated with BIMZELX." Because of the small sample sizes for demographic subgroups, it was not possible to detect clinically meaningful imbalances in ARs between the subgroups. • Treatment with BKZ was not associated with an increased risk of mortality, major adverse cardiovascular events (MACE), malignancy, or serious drug-related hypersensitivity reactions. • In the HS program, the Applicant reported a total of 10 pregnancies in 9 subjects in the development program for HS. Three pregnancies resulted in live birth of 4 heathy infants, with no congenital anomalies or major maternal complications, 3 pregnancies ended due to induced abortion, 2 pregnancies ended due to spontaneous abortion, 1 pregnancy was ongoing, and 1 pregnancy had an unknown outcome.	

1.4. Patient Experience Data

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

X	The patient experience data that were submitted as part of the application include:			Section of review where discussed, if applicable
	X	Clinical outcome assessment (COA) data, such as		
		X	Patient reported outcome (PRO)	Section 8.1.2
		☐	Observer reported outcome (ObsRO)	
		X	Clinician reported outcome (ClinRO)	Section 8.1.2
		☐	Performance outcome (PerfO)	
	X	Qualitative studies (e.g., individual patient/caregiver interviews, focus group interviews, expert interviews, Delphi Panel, etc.)		Section 8.1.9; Refer to DCOA review for full discussion on qualitative studies
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Natural history studies		
	☐	Patient preference studies (e.g., submitted studies or scientific publications)		
	☐	Other: (Please specify):		
☐	Patient experience data that were not submitted in the application, but were considered in this review:			
	☐	Input informed from participation in meetings with patient stakeholders		
	☐	Patient-focused drug development or other stakeholder meeting summary reports		
	☐	Observational survey studies designed to capture patient experience data		
	☐	Other: (Please specify):		
☐	Patient experience data was not submitted as part of this application.			

2 Therapeutic Context

2.1. Analysis of Condition

Hidradenitis suppurativa (HS) is a chronic, recurrent, inflammatory skin disease primarily affecting apocrine gland-bearing areas, including the axillae, inguinal and perianal areas, gluteal cleft, and inframammary folds.[1] However, lesions may develop at any site where there is skin-on-skin contact including the posterior neck, intermammary cleft, abdominal and flank folds, and medial thighs.[2] HS is clinically characterized by pruritic, painful, deep-seated nodules that often rupture and drain purulent malodorous or sanguineous material. Over time, the nodules can coalesce and lead to the formation of sinus tracts, or deep dermal 'inflamed' tunnels.[3] Other sequelae of active HS include "double-comedones;" post-inflammatory hyperpigmentation; atrophic, hypertrophic, and keloidal scarring and, in severe cases, contractures.[2]

Disease severity is most commonly graded using the Hurley Staging System.[2] The Hurley Staging System is a severity classification for HS that was developed in 1989 (Hurley, 1989). Stage I HS is the most common (68% of patients), while Stage II occurs in about 28% of patients and Stage III only occurs in about 4% of patients. The Hurley Staging System is described in Section 8.1.2. Study Endpoints.

The estimated prevalence of HS globally varies from 0.05% to 4.10%, depending on the methodology used to estimate the prevalence. Lower estimates are derived from registry studies and higher rates from prospective or self-reported studies.[3] In the United States, the prevalence of HS is estimated to be approximately 0.10%, with the highest occurrences noted among women, biracial groups and African Americans.[2] HS usually presents after puberty and in some, but not all, patients abates after menopause. The peak age of presentation is between 30 and 39 years of age.[2]

The pathogenesis of HS remains unclear. It is likely multifactorial, involving follicular occlusion and dilatation, subsequent follicular rupture with immune dysregulation leading to inflammatory response and cytokine activation. In chronic HS, profibrotic imbalance results in sinus tracts and scarring.[4] The immunopathogenesis is thought to involve a milieu of cytokines

[1] Goldberg SR, BE Strober, and MJ Payette, 2020, Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis, J Am Acad Dermatol, 82: 1045-1058.
[2] Jenkins T, J Isaac, A Edwards, and GA Okoye, 2023, Hidradenitis Suppurativa, Dermatol Clin, 41: 471–479.
[3] Saunte DML and GBE Jemec, 2017, Hidradenitis Suppurativa: Advances in Diagnosis and Treatment, JAMA, 318(20): 2019-2032.
[4] Cotton CH, SX Chen, SH Hussain, I Lara-Corrales, and AL Zaenglein, 2023, Hidradenitis Suppurativa in Pediatric Patients, Pediatrics, 151(5): 1-16.

including IL-1beta, TNF-alpha, IL-23, IL-17, and IL-10.[5] Other factors that may contribute to the development of HS include genetic predisposition, obesity, cigarette smoking, and friction shearing forces on the skin.[2]

Several 'proinflammatory' comorbid conditions have been associated with HS including: metabolic syndrome, hypertension, dyslipidemia, inflammatory bowel disease, thyroid disorder, arthropathies, and polycystic ovarian syndrome, and psychiatric disorders (depression, anxiety).[1]

2.2. Analysis of Current Treatment Options

Currently, there are only two FDA-approved therapies for HS: Humira (adalimumab) and Cosentyx (secukinumab). Adalimumab is a tumor necrosis factor blocker that was approved for the treatment of adults with chronic moderate to severe hidradenitis suppurativa on January 18, 2008. The recommended subcutaneous (SC) dosage of adalimumab for adults with HS is an initial dose of 160 mg, followed by 80 mg two weeks later, then 40 mg weekly or 80 mg every other week dosing two weeks later. The HS indication for adalimumab was expanded to adolescents 12 years and older who weigh greater than 30 kg on October 16, 2018. The labeling for Humira contains a boxed warning for serious infections, including active tuberculosis (TB) and reactivation of latent TB that frequently presented as disseminated or extrapulmonary disease, invasive fungal infections, and opportunistic infections. A boxed warning for malignancy is also included in labeling. Other labeled adverse reactions are anaphylaxis, nervous system demyelinating diseases, cytopenias, and heart failure.

Secukinumab is a human monoclonal IgG1κ antibody that selectively binds to the proinflammatory cytokine interleukin-17A (IL-17A) and blocks its interaction with the IL-17 receptor. This blockade inhibits the release of proinflammatory cytokines, chemokines, and mediators of tissue damage resulting from IL-17A mediated autoimmune and inflammatory diseases. Secukinumab was approved for the treatment of adults with chronic moderate to severe hidradenitis suppurativa on October 31, 2023. The recommended subcutaneous dosage of secukinumab for adults with HS is 300 mg administered by subcutaneous injection at Weeks 0, 1, 2, 3 and 4 and every 4 weeks thereafter. The labeling for secukinumab contains warnings and precautions for serious infections, including active tuberculosis (TB) and reactivation of latent TB, hypersensitivity reactions, inflammatory bowel disease, eczematous eruptions, and avoidance of live vaccines.

Current therapies for HS involve a multimodal approach including patient education about proper hygiene, smoking cessation, and weight loss; adequate pain management and wound

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[5] Scala E, S Cacciapuoti, N Garzorz-Stark, M Megna, C Marasca, P Seiringer, T Volz, K Eyerich, and G Fabbrocini, 2021, Hidradenitis Suppurativa: Where We Are and Where We Are Going, Cells ,10 (2094): 1-19.

care; and targeted therapy for acute flares and maintenance of disease based on disease severity.

Prior to the availability of FDA approved therapies, healthcare providers used multiple modalities off-label to treats their patients with HS with variable success. Disease severity guided the approach. Off-label treatment options for HS include topical antimicrobials (clindamycin), systemic antimicrobials (tetracycline, doxycycline, minocycline, colchicine, dapsone, rifampin, ertapenem), systemic retinoids (isotretinoin, acitretin), antiandrogenic agents (combined oral contraceptive, spironolactone, finasteride), metformin, cyclosporine, biological products other than adalimumab and secukinumab, botulinum toxin A injection, intralesional and systemic corticosteroids, incision and drainage of abscesses, surgical excision, grafting, and laser hair removal. [4]

Because of the limited number of FDA approved therapies and the cost burden, many healthcare providers still manage chronic HS with surgical interventions and the existing modalities used off-label. For mild HS or Hurley stage I disease, maintenance treatment options include topical antimicrobials, systemic retinoids, antiandrogens (OCP and spironolactone in women), and botulinum toxin injection/ laser hair removal. For treatment of acute flares, systemic antibiotics and intralesional corticosteroids can be used. For moderate to severe HS or Hurley stage II or III disease, maintenance therapy can include those used for mild HS, as well as additional antiandrogens (finasteride), metformin, cyclosporine, biologic agents, and surgical deroofing and radical surgical excision. Acute flares can be treated similar to mild HS with additional options that include systemic antibiotics and systemic corticosteroids.[4, 5] Success with these therapeutic modalities is variable and are limited by potential side effects, comorbid medical conditions, and patient preference.

HS is a debilitating medical condition with limited, FDA-approved treatment options. The psychosocial impacts on quality of life may be profound[6],[7]. The current product addresses this unmet need by expanding therapeutic options for this serious medical condition.

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[6] Weigelt MA et al. Psychosocial impact of hidradenitis suppurativa: a practical guide for clinicians. Journal of Dermatological Treatment. 2022.33(4): 1961-1868.

[7] Chernyshov PV et al. Quality of life measurement in hidradenitis suppurativa: position statement of the European Academy of Dermatology and Venereology task forces on Quality of Life and Patient-Oriented Outcomes and Acne, Rosacea and Hidradenitis Suppurativa. J Eur Acad Dermatol Venereol . 2019 Sep;33(9):1633-1643. doi: 10.1111/jdv.15519. Epub 2019 Apr 29

3 Regulatory Background

3.1. U.S. Regulatory Actions and Marketing History

BIMZELX (bimekizumab-bkzx) was approved on October 18, 2023 for the treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy. BIMZELX was subsequently approved on September 20, 2024 (BLA 761151 S006, S007 and S008) for the following indications:

- For the treatment of adult patients with active psoriatic arthritis.
- For the treatment of adult patients with active non-radiographic axial spondyloarthritis with objective signs of inflammation.
- For the treatment of adult patients with active ankylosing spondylitis.

On October 11, 2024, the FDA approved the use of two new presentations: (a) a single-injection prefilled syringe (also referred to as SS [safety syringe]) and (b) a single-injection autoinjector (AI), both containing 2 mL of BIMZELX (BLA 761151 S009).

3.2. Summary of Presubmission/Submission Regulatory Activity

The Applicant opened IND 134700 on June 9, 2017, with the submission of Protocol HS0001, entitled, "A Phase 2 Multicenter, Investigator-Blind, Subject-Blind, Placebo-Controlled Study of the Efficacy, Safety, and Pharmacokinetics of Bimekizumab in Subjects with Moderate to Severe Hidradenitis Suppurativa." The Agency sent a Study May Proceed letter to the Applicant on July 14, 2017. The letter included comments and recommendations regarding cardiovascular safety assessments, the potential confounding of treatment effect from concomitant antibiotic therapy, and neuropsychiatric exclusion criteria and safety assessments.

On February 28, 2018, following early termination of a clinical study evaluating bimekizumab for the treatment of ulcerative colitis (not conducted under an IND), the Agency advised the Applicant to:

- Modify the Informed Consent Form (ICF) to include new onset inflammatory bowel disease (IBD), or risk of worsening of IBD in subjects with a history of IBD.
- Re-consent subjects already enrolled in clinical trials for the indications of plaque psoriasis (PsO) and HS with the updated ICF.
- Modify the evaluation of safety during ongoing and planned trials for the indications of PsO and HS to include screening for signs and symptoms of IBD.
- Modify stopping criteria for ongoing and planned trials for the indications of PsO and HS to include onset or recurrence of symptoms of IBD

- Include IBD as an adverse event of special interest (AESI) in the analysis of adverse events from ongoing and planned trials for the indications of PsO and HS .

The Agency held an End-of Phase 2 (EoP2) meeting with the Applicant on July 17, 2019 to discuss the development program of bimekizumab for the treatment of HS. The Applicant proposed to conduct two phase 3 trials of identical design. The Applicant proposed to allow concomitant use of oral antibiotics (on stable regimen for at least 4 weeks prior to Baseline). Initially the Division was concerned that ongoing concomitant antibiotic therapy may confound the interpretation of safety and efficacy of the product. However, after discussion with the Medical Policy and Program Review Council (MPPRC), the Division agreed that it was acceptable to enroll subjects who are on a stable antibiotic regimen prior to the Baseline visit.

The Applicant also proposed to exclude subjects who received systemic nonbiologic or biologic therapies for HS with potential therapeutic impact for HS. The Agency recommended that this exclusion criterion be removed as phase 3 trials should represent real-world use of the product in the intended population. The Agency was also concerned that the proposed rescue therapy and lesion interventions may confound interpretation of the efficacy of the product and stated that any subject who receives systemic antibiotic rescue therapy should be considered a treatment failure. The Agency also advised that any lesion that received an intervention (i.e., analgesics, intralesional injections of triamcinolone, and/or incision and drainage) be counted as permanently present for the primary efficacy evaluation.

The EoP2 meeting also included discussions between the Agency and the Applicant regarding the efficacy endpoints for their phase 3 program. The Applicant proposed to evaluate skin pain using the Patient's Global Assessment (PGA) of skin pain, which was an 11-point numerical rating scale (NRS). The Applicant proposed a key secondary endpoint of the "proportion of subjects achieving at least a 30% reduction and at least a 1-unit reduction from Baseline on the PGA of Skin Pain" in subjects with an NRS of ≥3 at Baseline. The Agency stated there was insufficient evidence to support that a >30% reduction and ≥1 point reduction reflected a within-patient meaningful score change in the PGA of skin pain in the target population. The Agency recommended that the Applicant derive the meaningful within-patient change score for PGA of skin pain using anchor-based methods with phase 2 trial data. The Agency also stated that the proposed key secondary endpoint based on reduction in flares prior to Week 16 may not be clinically meaningful.

The Agency also requested the Applicant provide quantitative composition of their existing formulations and stated that the expectation that this formulation will be used in adolescents.

The Applicant submitted Protocols for HS0003 and HS0004 on November 11, 2019. In an advice letter dated January 21, 2020, the Agency recommended that adolescent subjects ages 12 years to less than 17 years of age be included in the Phase 3 trials. The Agency advised that alternatively, the Applicant may consider conducting a separate open-label pharmacokinetic (PK) and safety trial in adolescent subjects ages 12 years to 17 years. Such a trial could run in

parallel with the Phase 3 trials in adults, with dosing in adolescent subjects to be supported by adequate justification. The Agency noted the Applicant's proposal that enrollment of subjects currently using antibiotics will be capped at 30% of overall enrollment. Because the overall estimate of the treatment effect may be biased if such a cap does not coincide with the prevalence of the disease and if the treatment effect varies by antibiotic use, the Agency recommended enrolling all comers.

In the advice letter for the phase 3 protocols, the Agency also recommended that the Applicant evaluate the durability of response and effect of retreatment with their product (e.g., with a randomized withdrawal study design). In addition, the Agency reiterated comments from the EoP2 meeting that any subject who receives systemic antibiotic rescue therapy should be considered a treatment failure and that any lesion that received an intervention be counted as permanently present for the primary efficacy evaluation. Additionally, the Agency stated that subjects who experience flares represent treatment failures, therefore, the Applicant's proposed secondary endpoint regarding flares may not be clinically meaningful. Comments and recommendations from Biostatistics and the Division of Clinical Outcome Assessments (DCOA) were also provided.

The Applicant submitted Protocol HS0005 for an open-label extension trial on November 13, 2020. In an advice letter dated January 8, 2021, the Agency recommended the Applicant add a third arm for randomized withdrawal of treatment for HiSCR90 responders to evaluate durability of response. The Agency also stated that subjects who relapse, defined as loss of HiSCR50 response, may resume treatment (e.g., at their previous dose/regimen). In addition, the Agency recommended that the Applicant modify the protocol to include active assessment for local injection site reactions (e.g., pain, erythema, induration, swelling, etc.) at every visit and to specify in the protocol acceptable anatomic sites for administration of injections by subjects or caregivers. The Agency reiterated the previous recommendation that the Applicant count any lesion that received an intervention as permanently present for the evaluation of efficacy. The Agency also reiterated previous advice regarding that subjects who experience flares represent treatment failures, therefore the proposed secondary endpoint regarding flares may not be clinically meaningful.

The Agency held a Pre-sBLA meeting with the Applicant on January 12, 2023 to discuss the proposed content and format of the planned supplemental Biologics License Application (sBLA) for bimekizumab for the treatment of moderate to severe HS. The Agency advised that at the time of initial sBLA submission, the submission should include data through Week 52 for all subjects in their Phase 3 trials who continued to this timepoint to allow for evaluation of long-term safety of the product in the target population.

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

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

4.1. Office of Scientific Investigations (OSI)

The overall quality of the clinical information contained in this submission was adequate. The sites were selected for inspection by the Office of Scientific Investigations based on number of enrolled subjects, prior inspectional history, and site efficacy. The findings of the clinical inspection summary (review by Roy Blay, PhD dated August 19, 2024) are summarized in the table below.

Table 1: Site Inspection Results

Site Number, Name, and Address	Protocol ID	Number of Subjects	Classification
Site 40251 Evangelos Giamarellos-Bourboulis, M.D., Ph.D. 4th Department of Internal Medicine Attikon University Hospital 1 Rimini Str Athens, Attiki, Greece 12462	HS0003	40	NAI
Site 50151 Christopher Sayed, M.D. UNC Dermatology and Skin Cancer Center 410 Market Street Chapel Hill, NC 27516	HS0003	16	NAI
Site 40095 Wojciech Baran, M.D., Ph.D. Wromedica I. Bielicka, A. Strzalkowska S.C. Ul Mickiewicza 91 Wroclaw, Poland 51-685	HS0004	31	NAI
Site 40313 Kamelia Vekovska, M.D. Mc Medconsult Pleven -Dermatology, 18, Sv.Sv. Kiril I Metodiy Pleven, Bulgaria 5800	HS0004	31	NAI

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

The review team concluded that the conduct of the trials appears to be adequate, and that the data generated appear to be acceptable to support the use of this product for the proposed

indication. Refer to the Clinical Inspection Summary by Roy Blay, PhD, for further information regarding the findings of the Clinical Site Inspections.

4.2. Product Quality

There was no new chemistry, manufacturing, and controls (CMC) data submitted in this supplemental application. The drug product lots used in the clinical trials to support the new indication were manufactured and controlled using a process comparable to as described in the license. Furthermore, the same immunogenicity assays reported in the original BLA were used to evaluate the immunogenicity samples from the new trials.

The Applicant requested categorical exclusion from the requirements of preparing an environmental assessment under 21 CFR 25.31 (c). This is acceptable from an Office of Biologic Products (OBP) perspective. Refer to the Memorandum of Assessment by Xuhong Li dated June 25, 2024.

4.3. Clinical Microbiology

This section is not applicable.

4.4. Devices and Companion Diagnostic Issues

No new devices were evaluated in this sBLA. As such, this section is not applicable.

5 Nonclinical Pharmacology/Toxicology

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

6 Clinical Pharmacology

6.1. Executive Summary

The Applicant (UCB, Inc.) submitted an efficacy supplement (Supplement 10, SDN 165) under BLA761151 on January 19, 2024, seeking approval for a new indication of Bimzelx (Bimekizumab) to treat adult patients with moderate to severe hidradenitis suppurativa (HS). The proposed dosing regimen is 320 mg (administered as two 160 mg injections) subcutaneously (SC) at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks.

The clinical pharmacology section of this supplemental BLA is supported by efficacy, safety along with PK and immunogenicity data collected from 3 clinical trials: a phase 2 trial HS0001 and two identically designed pivotal phase 3 trials (HS0003 and HS0004) conducted in subjects with moderate to severe HS (refer to section 8.1.1 for detailed study design).

In addition, the Applicant conducted population pharmacokinetics (PopPK), dose/exposure-response and dose/exposure-safety analyses based on the data collected from the aforementioned 3 trials to support proposed dosing regimen.

The proposed dosage form and presentation to be used in patients with HS are the same as those approved for use in patients with psoriasis (PsO). The formulation (manufactured using processes 4 and 5) and device (bimekizumab-TN) used in the HS trials demonstrated bioequivalence (refer to study UP0033 which was reviewed and reported in section 6 of the unireview dated 5/11/2022) with those previously approved for commercial use (bimekizumab single-dose PFS [prefilled syringe] and AI [auto-injector], also known as bimekizumab-SS [safety syringe]-1mL and bimekizumab-AI-1mL, respectively).

Key Clinical Pharmacology Findings from HS studies:

- The population PK (PopPK) modeling for HS indicated that, for a 90 kg subject, apparent clearance (CL/F) was 31% higher and apparent volume of distribution (V/F) was 18% higher in subjects with HS. The t½ for a 90 kg individual was 20 days in subjects with HS. Consequently, the median steady state concentration at a dose of 320 mg Q4W was approximately 40% lower in HS subjects compared to the subjects with plaque psoriasis (PsO).
- PopPK model-based simulation suggested that bimekizumab exposures decreased with increased bodyweight, which is the typical characteristic of a biologic product.
- In PopPK analysis, only body weight, prior use of biologics, and disease severity (Hurley stage III) were found to be significant determinants of PK, although none of these covariates were concluded to be clinically relevant in terms of Hidradenitis Suppurativa Clinical Response (HiSCR) outcomes and did not warrant for bimekizumab dose modification in HS.
- No dose adjustments are needed based on patient covariates.

- Dose/exposure-response analysis for Hidradenitis Suppurativa Clinical Response 50%/75%/90%/100% (HiSCR50/75/90/100) endpoints showed no dose-response relationship for the tested dosing regimens (Induction/maintenance regimens: 320 mg Q4W/Q4W, Q2W/Q4W, Q2W/Q2W). Per E-R model-based simulation, the proposed dosing regimen (Q2W/Q4W) demonstrated ~3% higher median response rates at Week 16 than that of Q4W/Q4W regimen, while Week 48 response median rates are almost same for both regimens.
- During combined initiation treatment period (ITP) and maintenance treatment period (MTP) from Week 0 to 48, the rate of anti-drug antibody (ADA) was 57% (167/291) following 320 mg Q2W in ITP followed by 320 mg Q4W in MTP. In this dosing arm, 65% (108/167) of those who developed positive ADA, had neutralizing antibodies (NAb).
- Overall, formation of ADA, neutralizing antibodies (NAb), and ADA titers did not demonstrate clinically meaningful impact on PK, efficacy, and safety in any of the tested dosing arms.

6.1.1. Recommendations

Based on the review of this supplemental BLA, the Office of Clinical Pharmacology recommends the approval of proposed dosage regimen of bimekizumab for the treatment of adult patients with moderate to severe HS.

6.1.2. Post-marketing requirement/commitment (PMR/PMC)

None.

6.2. Summary of Clinical Pharmacology Assessment

6.2.1. Summary of Clinical Pharmacology and Pharmacokinetics

Table 2: Summary of Clinical Pharmacology Review Issues and Recommendations

Review Issue	Recommendations and Comments
Pharmacokinetics	• Bimekizumab exhibited dose-proportional PK for doses ranged between 80 mg and 320 mg in healthy subjects. The PK of bimekizumab was similar between healthy subjects and patients with PsO. However, the systemic exposure in subjects with HS was approximately 40% lower than PsO. • Pivotal HS clinical studies indicate that the PK of bimekizumab is approximately dose-proportional and consistent across the HS studies. Steady state was attained by Week 8 for all tested regimens (Table 3). Geometric mean concentrations of bimekizumab were lower in HS patients than those observed in other indications (e.g., PsO, psoriatic arthritis [PsA], axial spondyloarthritis [axSpA]).

	• PopPK model indicates that CL/F and V/F were 31% and 18% higher, respectively, in HS patients (for a 90 kg patient) compared to other indications. Consequently, the median steady state concentration at a dose of 320 mg Q4W was approximately 40% lower in HS compared to other indications. The model-estimated half-life was 19.7 days in HS patients. • Following 320 mg Q2W or Q4W through Week 48, median predicted accumulation ratios were 2.33 and 1.48, respectively. • PopPK model-based simulation implies that the exposures ($AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$) are 30 – 40% lower in HS patients weighing 142 kg (95th percentile) and 50-70% higher for a body weight of 62 kg (5th percentile) compared to a reference HS patient weighing 90 kg.
Dosing in patient subgroups (intrinsic and extrinsic factors)	• Though body weight, prior use of biologics, and disease severity (Hurley stage III) were significant covariates influencing bimekizumab PK, none of these are concluded to be clinically relevant in terms of HiSCR outcomes. No other covariates were found to have significant effects on bimekizumab PK in subjects with HS. Hence, no dose adjustment is needed based on any intrinsic and extrinsic patient covariates. For more information, refer to pharmacometrics review in Appendix 19.4.2.
PK Bridging	The drug substance of acetate-based formulation used in HS trials were produced using manufacturing processes P4 (HS0001) and P5 (pivotal phase 3 HS trials). The drug substance of approved formulation employed P5 manufacturing process. However, a different device (bimekizumab-TN) than the to-be-marketed presentations (PFS, AI) was used in the pivotal HS studies. In Trial HS0001, the formulation was supplied in the single-use vials. Because of the differences in formulation and device used in HS trials with the to be marketed (TBM) formulations and devices, a PK bridge between these formulations and devices was established in the study UP0033, which was reviewed and found to be adequate (see section 6.1).
Bioanalytical Assay	Bimekizumab concentrations in human serum were quantified using a validated electrochemiluminescence immunoassay (ECLIA) assay. The assay was well validated, and the calibration range is 0.25-20 µg/mL. See section 19.4.1 for more information.

6.2.2. General Dosing and Therapeutic Individualization

General Dosing

The Applicant proposed a bimekizumab dosing regimen of 320 mg (two 160 mg injections) administered by subcutaneous injection at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks. The proposed dosing regimen is supported by the overall PK, efficacy, and safety data derived from HS clinical studies and therefore acceptable. Refer to section 8.1 for efficacy results.

Therapeutic Individualization

Notwithstanding the body weight, prior use of biologics, and disease severity (hurley state III) were found to have significant effect on the PK of bimekizumab, these did not show clinical relevance in efficacy outcomes. Therefore, no therapeutic individualization based on any covariates is necessary.

Outstanding Issues

There are no outstanding issues that would preclude the approval of this BLA supplement from a clinical pharmacology perspective.

6.3. Comprehensive Clinical Pharmacology Review

6.3.1. General Pharmacology and Pharmacokinetic Characteristics

Bimekizumab is a humanized, full-length immunoglobulin (Ig) G1 monoclonal antibody that selectively bind and neutralize interleukin-17A (IL-17A), IL-17F, and IL-17AF proinflammatory cytokines upregulated in HS tissue. Therefore, inhibition of these cytokines provides a therapeutic effect in patients with HS.

The Applicant submitted the data and reports from three clinical studies (HS0001, HS0003, and HS0004) conducted in subjects with HS to support this supplemental BLA. The PK of bimekizumab was characterized in HS based on observed predose plasma concentrations and PopPK analysis.

Pharmacokinetics of bimekizumab in subjects with HS
The observed PK of bimekizumab was described based on predose trough concentrations derived in the HS clinical studies. Observed dose adjusted geometric mean trough concentrations were lower in HS subjects than that in other indications. Steady state was achieved by Week 8 for all tested dosing regimens. Similar to other indications, the plasma concentrations also increased in an approximately dose-proportional manner in HS subjects. At Week 48 (steady state), the overall geometric mean trough concentrations were 29 µg/mL, 11 µg/mL, and 11 µg/mL for Q2W/Q2W, Q2W/Q4W, and Q4W/Q4W regimens, indicating an approximate dose-proportional behavior of bimekizumab in HS. The observed PK variability in

terms of percent coefficient of variation (geometric %CV) ranged between 41% to 148% (Table 3).

Table 3: Geometric mean (geometric CV%) trough concentrations (in µg/mL) of bimekizumab observed in HS clinical studies.

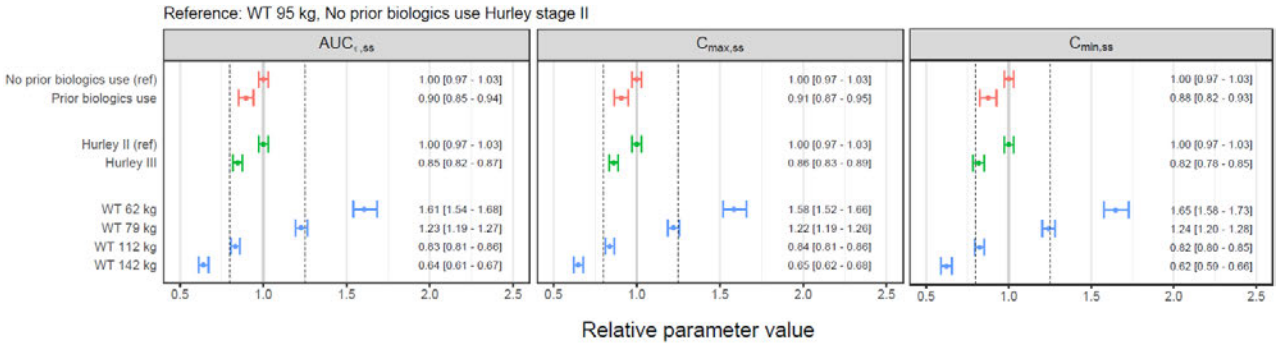
Study Regi-men	HS0001*		HS0003 Dose: 320 mg						HS0004 Dose: 320 mg					
			Q2W/Q2W		Q2W/Q4W		Q4W/Q4W		Q2W/Q2W		Q2W/Q4W		Q4W/Q4W	
Visits	n	GMean (GCV%)	n	GMean (GCV%)	n	GMean (GCV%)	n	GMean (GCV%)	n	GMean (GCV%)	n	GMean (GCV%)	n	GMean (GCV%)
W1 (Day 1)	46	-	136	16.3(50)	141	17.5(44)	135	15.6(65)	141	17.1(79)	137	17.5(42)	135	17.3(73)
W2	45	24.1(56)	136	12.3(51)	140	13.6(64)	135	12.8(48)	136	13.3(65)	138	14.0(41)	139	14.5(47)
W4	46	26.6(58)	132	18.7(75)	132	21.7 (51)	129	7.0(66)	132	22.6(48)	129	22.2(46)	132	8.5(53)
W8	43	30.2(55)	120	25.3(59)	122	28.5(56)	126	9.4(74)	126	30.4(60)	123	28.9(51)	125	12.0(66)
W12	42	25.3 (117)	119	26.6(65)	122	31.3(55)	115	9.7(72)	125	32.2(55)	124	31.7(55)	123	12.6(72)
W16	-	-	119	26.2(63)	117	32.6(56)	108	8.7(100)	116	32.8(59)	120	30.9(54)	121	12.0(99)
W18	-	-	110	27.5(62)	108	32.4(61)	106	17.6(53)	113	34.5(56)	112	30.2(86)	115	22.0(67)
W20	-	-	108	26.4(63)	107	18.1(85)	102	8.9(110)	108	33.8(60)	106	17.9(75)	110	12.3(107)
W24	-	-	101	27.6(62)	99	14.1(95)	97	9.6(83)	98	33.3(62)	99	13.9(77)	102	12.2(109)
W36	-	-	85	27.1(76)	85	11.5(88)	77	9.4(84)	104	34.9(58)	98	12.1(84)	98	13(117)
W48	-	-	80	28(66)	52	10.1 (138)	74	8.7(106)	101	30.9(76)	97	11.5(94)	96	13.9(94)

*Phase 2 study that evaluated 620 mg (LD) then 320 mg Q2W from W2 to W12. GMean: Geometric Mean; GCV%: Geometric coefficient of variation (CV) %. Source: adapted from PK table 7.1.1.1 of respective study and confirmed by the reviewer's analysis based on adpc.xpt dataset corresponding to each HS study.

Additionally, PopPK analysis was conducted to characterize the PK of bimekizumab in subjects with HS and evaluate the influences of different covariates on the PK. Per PopPK report, apparent clearance (CL/F) and volume of distribution (V/F) were 31% and 18% higher in HS participants with a body weight of 90 kg compared to other indications. This translates to a half-life of 19.7 days in a 90 kg HS subject. Consistent with higher clearance, the exposure of bimekizumab was decreased in HS. PopPK model-estimated median steady state concentrations were ~40% lower in subjects with HS compared to other indications, following 320 mg Q4W throughout the treatment period.

In PopPK model, body weight (BW), prior use of biologics, and disease severity (Hurley stage III) were identified as significant covariates influencing bimekizumab PK. However, the forest plots (Figure 1) illustrating the effects of covariates on the secondary PK parameters (e.g., $AUC_{\tau,ss}$, Cmax,ss, and Cmin,ss) suggest that except BW, other covariates did not impact the PK of bimekizumab. It is noted that BW had a greater influence on the PK exposures as they entirely fell outside of the 80% – 125% no effect boundary; specifically, for the lower (62 kg, 5th percentile) and higher (142 kg, 95th percentile) BW values.

Figure 1: Forest plots illustrating the effects of various covariates on the PK of bimekizumab compared to that of a reference subject with HS for 320 mg Q4W regimen.



Note: AUCτ,ss: area under the concentration-time curve during a dosing interval at steady state; Cmax,ss: maximum concentration during a dosing interval at steady state; Cmin,ss: minimum concentration during a dosing interval at steady state. Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CIs; these values are calculated based on 200 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference subject (for whom covariate characteristics are provided above the plot) are shown by the solid vertical lines with the associated 90% CIs reflecting uncertainty in the estimated PK parameters; the dashed vertical lines indicate the 80%-125% margins relative to the reference subject. For categorical covariates, the impact of each category is shown, compared to the reference group. For WT, the impact at the 5%, 25%, 75% and 95% percentiles is shown, compared to the median of the covariate. Source: Applicant's PopPK report.

Overall, PopPK model-based simulations indicated that the exposure of bimekizumab increased with decreasing body weight. Based on predicted AUCτ,ss, Cmax,ss, Cmin,ss values, the exposure of bimekizumab was 30 – 40% lower for a 142 kg (95th percentile) and 50 – 70% higher for a 62 kg (5th percentile of observed weight distribution) subject with HS, compared to a reference HS subject (having a BW of 95 kg , no prior biologics use, and Hurley state II). Refer to section 19.4.2 - Pharmacometrics review for further details.

However, the change in exposure with the change in body weight was not clinically meaningful in terms of efficacy outcomes based on all HiSCR endpoints. Hence, the dose adjustment for any of the covariates including body weight is not necessary.

6.3.2. Immunogenicity

The incidence rates of ADA and NAb (neutralizing antibody) in the pivotal HS studies are presented in the Table 4:

- In Phase 3 trials, over the treatment period of Week 0 – 48 (combined ITP and MTP), 44.6% - 53.8% and 53.6 - 69.9% subjects had positive ADA at 1 visit or more in the tested bimekizumab dosing regimens (320 mg Q2W/Q2W, Q2W/Q4W, Q4W/Q4W, Placebo/Q2W) of the pivotal HS studies. At baseline, however, the occurrence of positive ADA was low (0.7% to 7%) in both studies.
- At Week 0-48, treatment-emergent ADA (TE-ADA) was observed in 38.5% - 53.1% and 50.7% - 64.4% subjects in Studies HS0003 and HS0004, respectively.
- The incidences of ADA and NAb were comparable across dosing regimens as reported in Table 4.

- Following the proposed Q2W/Q4W dosing regimen, the average ADA positive incidence rate was 59% (171/291) in both HS trials. NAb was developed in 63% (108/171) of those who had positive ADA.
- Across all treatment groups, most ADA titer values were low (~100). There was no tendency for increasing or very high titer levels over time.
- The incidence rates of treatment-emergent ADA (anti-drug antibodies) were 44.1% (64/145) and 64.4% (94/146) in HS0003 and HS0004 trials, respectively, following 320 mg Q2W/Q4W.
- Overall, the ADA positivity occurred at early timepoints. For example, >50% of subjects in the bimekizumab treatment groups had their first ADA positivity by Week 8. Most of the ADA positivity (>90%) had occurred by Week 24 to Week 36, independent of dosing regimen.
- On the other hand, the ADA incidence in the phase 2 HS trial was lower (19.6% [9/46]).

Table 4: ADA and NAb incidence rates in the pivotal HS studies.

Immunogenicity Status	Study HS0003 [Dose: 320 mg]				Study HS0004 [Dose: 320 mg]			
	PBO/ Q2W N=65 n (%)	Q2W N=141 n (%)	Q2W/ Q4W N=145 n (%)	Q4W N=143 n (%)	PBO/ Q2W N=69 n (%)	Q2W N=144 n (%)	Q2W/Q4W N=146 n (%)	Q4W N=142 n (%)
ADA Positive Incidence								
ITP (Week 0 -16)	NA	50 (35.5)	46 (31.7)	57 (39.9)	NA	68 (47.2)	84 (57.5)	72 (50.7)
ITP+MTP (Week 0 – 48)	29 (44.6)	74 (52.5)	69 (47.6)	77 (53.8)	37 (53.6)	87 (60.4)	102 (69.9)	96 (67.6)
ADA positive up to SFU	29 (44.6)	74 (52.5)	69 (47.6)	77 (53.8)	37 (53.6)	87 (60.4)	102 (69.9)	96 (67.6)
TE ADA* (Week 0 – 48)	25 (38.5)	68 (48.2)	64 (44.1)	76 (53.1)	35 (50.7)	86 (59.7)	94 (64.4)	90 (63.4)
NAb status up to Week 48								
NAb Positive	12 (18.5)	41 (29.1)	46 (31.7)	53 (37.1)	16 (23.2)	48 (33.3)	62 (42.5)	56 (39.4)
IL-17AA NAb Positive Only	4 (18.5)	5 (3.5)	5 (3.4)	3 (2.1)	2 (2.9)	8 (5.6)	13 (8.9)	12 (8.5)
IL-17FF NAb Positive Only	1 (1.5)	6 (4.3)	3 (2.1)	6 (4.2)	2 (2.9)	10 (6.9)	13 (8.9)	8 (5.6)
Both IL-17AA and IL-17FF Positive	7 (10.8)	30 (21.3)	38 (26.2)	44 (30.8)	12 (17.4)	30 (20.8)	36 (24.7)	36 (25.4)
NAb Positive up to SFU	12 (18.5)	42 (29.8)	46 (31.7)	53 (37.1)	17 (24.6)	48 (33.3)	63 (43.2)	56 (39.4)

Source: m5.3.5.3-Applicant's integrated summary of immunogenicity report.

Impact of immunogenicity on PK

The plasma concentration of bimekizumab is slightly and consistently lower in ADA positive subjects than in ADA negative subjects. The PopPK analysis showed that clearance was increased by 8.3% in ADA positive subjects, supporting the lower exposure observed in all dosing regimens reported in Table 5. However, the magnitude of decrease of exposure in ADA positive subjects is not deemed to be clinically meaningful based on E-R analysis.

Table 5: Geometric mean concentrations of bimekizumab in HS phase 3 studies.

Study HS0003												
	Q2W, ADA+		Q2W, ADA-		Q2W/QW4, ADA+		Q2W/Q4W, ADA-		Q4W, ADA+		Q4W, ADA-	
Visits	n	GM (%CV)	n	GM (%CV)	n	GM (%CV)	n	GM (%CV)	n	GM (%CV)	n	GM (%CV)
W4	71	18.5 (53)	65	18.4 (97)	67	20.5 (55)	70	23.0 (47)	76	6.8 (76)	60	7.2 (53)
W8	67	23.0 (60)	62	28.3 (55)	62	26.1 (58)	68	30.9 (53)	74	9.0 (79)	59	9.9 (67)
W12	64	25.2 (55)	61	28.2 (75)	65	28.3 (61)	65	34.6 (47)	72	8.7 (82)	57	11.1 (57)
W16	66	24.6 (53)	60	28.0 (72)	64	29.1 (61)	65	36.7 (47)	69	8.0 (93)	54	9.6 (108)
W18	64	26.5 (50)	58	28.7 (74)	62	30.4 (64)	61	34.8 (57)	69	16.1 (56)	52	19.5 (46)
W20	65	24.9 (56)	58	28.1 (71)	60	15.3 (96)	62	21.4 (68)	67	7.7 (111)	51	10.6 (103)
W24	63	25.4 (56)	57	29.9 (67)	59	11.9 (104)	57	17.0 (79)	62	8.2 (98)	51	11.3 (61)
W36	50	23.3 (71)	51	30.9 (77)	56	9.1 (99)	54	14.5 (66)	51	8.4 (91)	40	10.7 (74)
W48	50	25.0 (59)	45	31.3 (71)	52	8.5 (103)	49	11.9 (170)	46	7.8 (87)	39	9.8 (127)
Study HS0004												
Visits	Q2W, ADA+		Q2W, ADA-		Q2W/QW4, ADA+		Q2W/Q4W, ADA-		Q4W, ADA+		Q4W, ADA-	
W4	81	21.8 (47)	53	23.9 (49)	95	21.0 (49)	41	25.3 (35)	94	8.4 (51)	44	8.7 (57)
W8	81	28.5 (63)	48	34.1 (53)	91	27.5 (54)	39	32.5 (41)	85	12.2 (59)	44	11.8 (81)
W12	81	30.5 (55)	48	35.5 (54)	94	30.1 (60)	38	36.3 (35)	86	11.6 (75)	43	14.9 (63)
W16	77	30.4 (56)	49	37.1 (60)	93	29.5 (60)	39	34.4 (38)	87	10.7 (112)	42	15.4 (66)
W18	77	31.7 (58)	45	40.0 (50)	84	27.4(102)	39	37.6 (35)	86	21.0 (63)	41	24.3 (62)
W20	72	30.5 (62)	47	39.6 (51)	81	16.2 (86)	38	22.3 (40)	84	11.6 (116)	41	14.0 (85)
W24	69	31.2 (61)	42	37.0 (63)	73	12.6 (87)	36	17.0 (48)	80	11.2 (122)	34	14.7 (73)
W36	74	32.8 (59)	40	39.1 (54)	73	11.3 (99)	34	14.1 (43)	77	12.1 (139)	38	15.1 (71)
W48	72	28.1 (83)	38	36.9 (57)	73	11.2 (80)	34	12.1 (125)	72	13.6 (104)	36	14.4 (75)

GM: Geometric mean; %CV: Percent coefficient of variation. Source: adapted from PK table 7.1.1.2 of the respective clinical study report.

Impact of immunogenicity on efficacy and safety

The response rates for the HiSCR50 endpoint in subjects with positive and negative ADA are compiled in Table 6 for bimekizumab treatment. The data indicates that there is no clear effect of ADA positivity on efficacy of bimekizumab. Despite the reduced response rate for the Q2W/Q2W regimen in ADA positive subjects, the trend is not consistent across trials, dosing regimens, or timepoints. For example, in Q4W/Q4W regimen, ADA positive subjects showed greater responses compared to ADA negative subjects. Similarly, no trend in efficacy was observed between NAb positive and negative subjects as well.

Table 6: Comparison of efficacy in terms of clinical endpoint, HiSCR50, between ADA positive and negative subjects at Week 16 and 48 for Studies HS0003 and HS0004.

Study	Visits	Q2W, ADA+	Q2W, ADA-	Q2W/Q4W, ADA+	Q2W/Q4W, ADA-	Q4W, ADA+	Q4W, ADA-
		RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)	RR (95% CI)
		N=46	N=73	N= 44	N=79	N=48	N=69

HS0003	W16	49.0 (34.4, 63.6)	59.9 (48.4, 71.4)	40.9 (NC, NC)	48.1 (NC, NC)	54.5 (40.1, 68.9)	36.5 (24.9, 48.0)
	W48	33.1 (19.3, 46.9)	49.2 (37.2, 61.2)	46.4 (31.1, 61.7)	38.5 (27.5, 49.5)	39.8 (25.4, 54.3)	31.3 (19.8, 42.7)
HS0004		N=58	N=65	N= 64	N=62	N=62	N=65
	W16	49.5 (36.6, 62.5)	49.7 (37.5, 61.9)	50.5 (38.2, 62.8)	57.9 (45.4, 70.4)	54.1 (41.6, 66.6)	51.6 (39.3, 64.0)
	W48	38.5 (25.7, 51.3)	53.2 (40.8, 65.7)	39.3 (27.1, 51.5)	45.5 (32.5, 58.5)	51.2 (38.4, 63.9)	49.4 (36.9, 61.9)

Source: Adapted from Table 6.4.1.2 of the respective clinical study report.

Overall, clinically meaningful response rates were observed for both HiSCR50 and HiSCR75 (data not shown) irrespective of ADA and NAb status. There was no indication of a reduced HiSCR50/75 response with increasing ADA titers at Week 16 or Week 48.

Based on the available data, the presence of ADA and NAb had no clinically meaningful impact on the safety profile of bimekizumab in HS and was not associated with serious or severe hypersensitivity events.

6.3.3. Clinical Pharmacology Questions

Does the clinical pharmacology program provide supportive evidence of effectiveness?

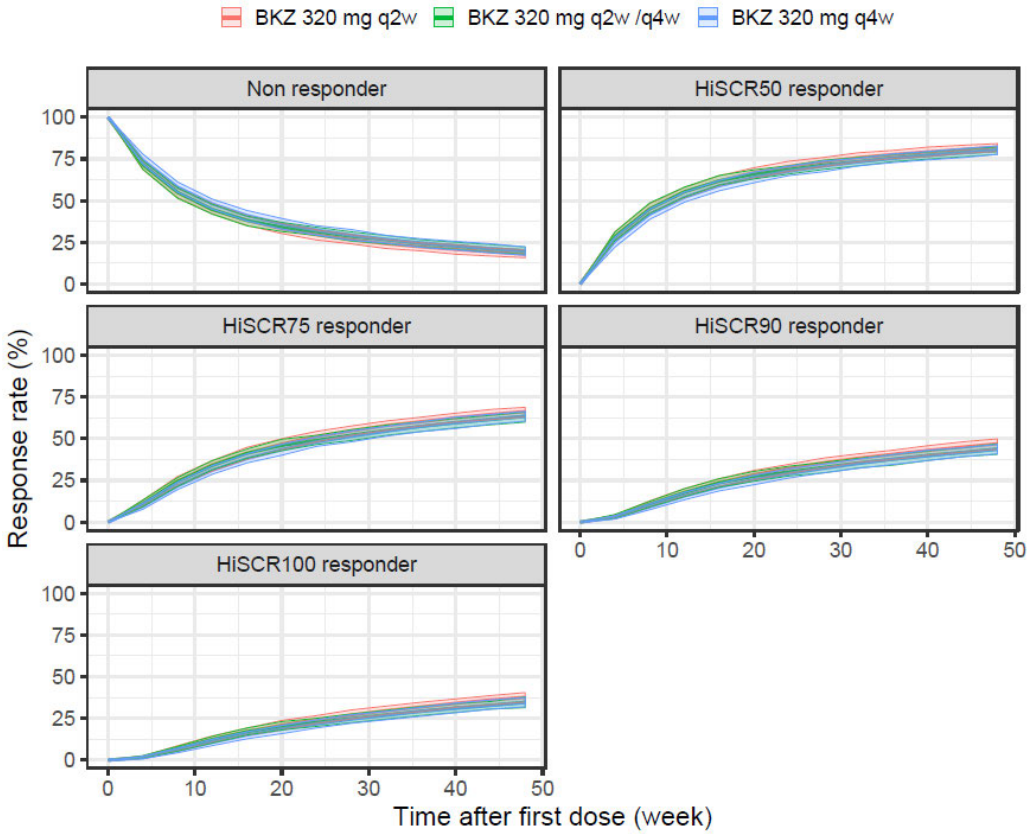
Yes. The efficacy of proposed dosing regimen of bimekizumab 320 mg Q2W/Q4W for the treatment of adults with moderate to severe HS was demonstrated in the pivotal phase 3 trials of HS subjects for the primary endpoint, HiSCR50. Efficacy results indicate that both HS trials demonstrated statistically significant and clinically meaningful improvements when comparing treatment with bimekizumab 320 mg Q2W to placebo at Week 16 as measured by HiSCR50 response rates. Alternatively, the Q4W regimen up to Week 16 showed statistically significant and clinically meaningful improvement in HiSCR50 response rates in only trial HS0004 when compared to placebo. Bimekizumab 320 mg Q2W dosing regimen in both trials also met the ranked secondary endpoint of HiSCR75 with a statistically significant difference in response rates at Week 16 compared to placebo. For the Q4W regimen, the difference in HiSCR75 response rate was statistically significant in only Trial HS0004.

The improvements in response were durable during maintenance treatment up to Week 48. The response rates were comparable at Week 48 between maintenance treatment with bimekizumab 320 mg Q4W or Q2W. Thus, the dosing regimen of Q2W during initial treatment and Q4W during maintenance treatment period is being proposed for the treatment of moderate to severe HS. See section 8.1 – statistical review for detailed data on efficacy outcomes.

To support the proposed dosing regimen, dose/exposure-response relationship was characterized based on the data derived from HS studies and using a proportional odds model. The probabilities of being non-responder, HiSCR50/75/90/100 responder were estimated for each dosing regimen. The dose/exposure-response curves illustrated in the Figure 2 imply that

there is a lack of dose-response over time for any of the HiSCR endpoints mentioned above. The predicted median and 95% prediction interval (PI) of response rates are generally overlapped and comparable across tested dosing regimens.

Figure 2: Predicted response rates versus time relationship for three dosing regimens (320 mg Q2W/Q2W, Q2W/Q2W, Q4W/Q4W) up to Week 48 with respect to different HiSCR endpoints.



Note: Predicted percentage of non-responder, HiSCR50 responder, HiSCR75 responder, HiSCR90 responder and HiSCR100 responder subjects versus nominal time since first dose (TSFD), colored by dosing regimen. The lines and the shaded areas represent the median and 95% prediction interval (PI) response rates, respectively.

Further simulations suggest that there is a ~3% greater response rate at Week 16 associated with Q2W over Q4W regimen for the primary endpoint of HiSCR50. However, the response rate at Week 48 was almost the same between Q2W/Q4W and Q4W/Q4W regimen. In the simulations, the median predicted proportion of HiSCR50 responders at Week 16 were 61.8% and 58.9% following dosing of 320 mg bimekizumab Q2W and Q4W, respectively. The corresponding proportions at Week 48 were 80% (Q2W/Q4W) and 80.2% (Q4W/Q4W). The response rates are also similar for other endpoints (HiSCR75/90/100). This suggests that the proposed dosing regimen does not have clear clinical benefit over the lower dosing regimen of Q4W/Q4W regimen. However, since the primary endpoint achieved significance in both phase 3 trials only for the Q2W/Q4W dosing regimen, this dose is acceptable from a clinical pharmacology perspective.

Simulation-based subgroup analysis indicates that nonsmokers had an approximately 10% higher response rate compared to smokers/previous smokers. Subjects with high baseline AN (number of abscesses and inflammatory nodules) counts had an approximately 5% - 10% lower response rates. No other covariates including body weight, prior use of biologics, disease severity, and ADA/NAb status were found to have influenced response rates.

No PD analyses (outside of the efficacy analyses, which included HiSCR responder rates) were conducted in HS trials.

E-R analyses for safety

Exploratory analysis suggests that plasma bimekizumab trough concentrations were not associated with clinically-relevant increases in incidences of treatment-emergent adverse effects (TEAEs) including infection/dermatitis/eczema in any treatment group. In Q2W/Q4W arm, the incidences of TEAEs were 86%, 91%, 91%, and 83% in the first, second, third, and fourth concentration quartiles, respectively. The corresponding incidences of infection TEAEs were 66%, 67%, 61% and 68%. Overall, no clear trend was observed for the incidences of TEAEs including infections, dermatitis, an eczema across different concentration quartiles of bimekizumab. See Section 8.2.4 for further details on safety assessment.

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

Yes. Despite dose/exposure-response relationship does not differentiate between the 320 mg Q2W/Q4W (proposed) and Q4W/Q4W regimen, the comprehensive evidence and overall benefit-risk assessment supports the proposed dosing regimen, hence reasonable for the general HS patient population.

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

No. A dose adjustment or management strategy for subpopulations based on intrinsic factors is not necessary.

Though extreme body weight values had potential impact on the bimekizumab exposures, these did not show clinically meaningful impact on the efficacy outcomes, hence an alternative dosing regimen is not necessary.

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

The Applicant did not conduct any drug interaction studies. The current approved label of bimekizumab indicates that the formation of CYP450 enzymes can be altered by increased

levels of certain cytokines (e.g., IL-1, IL-6, IL-10, TNFα, IFN) during chronic inflammation. Hence, treatment with bimekizumab may modulate serum levels of some cytokines.

The label recommends monitoring of therapeutic effect (e.g., for warfarin) or drug concentration (e.g., for cyclosporine) of CYP3A4 substrates (particularly with narrow therapeutic index) upon initiation or discontinuation of bimekizumab and considering dosage modification of the CYP450 substrate.

7 Sources of Clinical Data and Review Strategy

7.1. Table of Clinical Studies

Table 7: Listing of Clinical Trials Relevant to BLA 761151 S-010

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		Controlled Studies to Support Efficacy and Safety						
HS0003	04242446	Phase 3, randomized, DB, PBO-controlled	BKZ or PBO via SC injection/ BKZ 320mg Q2W from W0 to W48. BKZ 320mg Q4W from W0 to W48. BKZ 320mg Q2W to W16, continuing on BKZ 320mg Q4W from W16 to W48. PBO to W16, continuing on BKZ 320mg Q2W from W16 to W48	Primary efficacy: $HiSCR_{50}$ at Week 16, defined as ≥ 50% reduction in AN count with no increase from Baseline in abscess or draining tunnel count	48 weeks/ 20-week SFU for subjects not entering HS0005	505	Adults with moderate to severe HS (AN ≥5, HS lesions in 2 distinct anatomic areas, 1 of which must be Hurley Stage II or III, and draining tunnel count ≤20 at Baseline)	86; Australia, Belgium, Canada, Denmark, France, Germany, Greece, Israel, Italy, Netherlands, Norway, Spain, Switzerland, Turkey, and United States
HS0004	04242498	Phase 3, randomized, DB, PBO-controlled	BKZ or PBO via SC injection/ BKZ 320mg Q2W from W0 to W48. BKZ 320mg Q4W from W0 to W48. BKZ 320mg Q2W to W16, continuing on BKZ 320mg Q4W from W16 to W48.	Primary efficacy: $HiSCR_{50}$ at Week 16	48 weeks/ 20-week SFU for subjects not entering HS0005	509	Adults with moderate to severe HS (AN ≥5, HS lesions in 2 distinct anatomic areas, 1 of which must be Hurley Stage II or III, and draining	90; Australia, Bulgaria, Canada, Czech Republic, France, Germany, Hungary, Ireland, Israel, Italy, Japan, Poland, Spain, United Kingdom, and

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
			PBO to W16, continuing on BKZ 320mg Q2W from W16 to W48.				tunnel count ≤20 at Baseline)	United States
		Studies to Support Safety						
HS0005	04901195	Phase 3, OL, parallel group, extension (ongoing, clinical data cut on 11/15/2022)	BKZ 320mg Q2W or BKZ 320mg Q4W/SC injection	Primary (Safety): TEAEs Secondary (Safety): • TESAEs • TEAEs leading to study withdrawal	Up to 100 weeks	653	Adults with moderate to severe HS who completed Trials HS0003 or HS0004	Number of sites not provided: Australia, Belgium, Bulgaria, Canada, Czech Republic, France, Germany, Greece, Hungary, Ireland, Italy, Japan, Netherlands, Poland, Spain, Switzerland, Turkey, United Kingdom, and United States
HS0001	03248531	Phase 2, randomized, Investigator-blind, Subject-blind, PBO-controlled, Active	BKZ, ADA, or PBO via SC injection/ BKZ: 640mg at BL (LD) then 320mg Q2W from W2 to W10.	Primary efficacy: $HiSCR_{50}$ at Week 12	12 weeks	90	Adults with moderate to severe HS (AN **≥3**, HS lesions in 2 distinct anatomic	Number of sites not provided; Australia, Belgium, Denmark, Germany, Norway,

Trial Identity	NCT no.	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No. of patients enrolled	Study Population	No. of Centers and Countries
		reference arm (ADA)	ADA 160mg at BL (LD), 80mg at W2, then 40mg Q1W from W4 to W10. PBO at BL (LD), W2, then Q1W from W4 to W10.				areas, 1 of which must be Hurley Stage II or III, and draining tunnel count ≤20 at Baseline)	Russia, and United States

ADA=adalimumab; AN=abscess and inflammatory lesion count; BKZ=bimekizumab; BL=Baseline; DB=double-blind; EudraCT=European Union Drug Regulating Authorities Clinical Trials; HS=hidradenitis suppurativa; HiSCR=Hidradenitis Suppurativa Clinical Response; ITP=Initial Treatment Period; LD=loading dose; MTP=Maintenance Treatment Period; NCT number=ClinicalTrials.gov identifier; OL=open-label; PBO=placebo; PK=pharmacokinetics; ; Q1W=every 1 week; Q2W=every 2 weeks; Q4W=every 4 weeks; SC=subcutaneous; SFU=Safety Follow-Up; TEAEs=Treatment-emergent adverse events; TESAEs=Treatment-emergent serious adverse events; W=Week

7.2.Review Strategy

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

- Original submission: \\CDSESUB1\evsprod\BLA761151\0116\m5

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

8 Statistical and Clinical and Evaluation

8.1.Review of Relevant Individual Trials Used to Support Efficacy

8.1.1. Trial Design: HS0003 and HS0004

The Applicant conducted two identically designed, randomized, multicenter, double-blind, placebo-controlled, parallel-group, phase 3 trials (HS0003 and HS0004) to assess the safety and efficacy of bimekizumab for the treatment of moderate to severe HS. For enrollment, the protocols specified the following key inclusion criteria:

- Adult male or female who is at least 18 years of age
- A diagnosis of HS based on clinical history and physical examination for at least 6 months prior to the baseline visit
- HS lesions present in at least 2 distinct anatomic areas (e.g., left and right axilla), 1 of which must be at least Hurley Stage II or Hurley Stage III at both the screening and baseline visits
- Moderate to severe HS, defined as a total of ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules) at both the screening and baseline visits
- Subject must have had an inadequate response to a course of a systemic antibiotic for treatment of HS as assessed by the investigator through study participant interview and review of medical history. The protocol specifies that subjects who meet any of the following are NOT automatically excluded from the trial:
    - Demonstrated intolerance to (or became intolerant to) systemic antibiotics
    - Had a contraindication to systemic antibiotics
    - Responded to course(s) of systemic antibiotic(s) and subsequently exhibited recurrence after discontinuation of the antibiotic
- Subjects with a draining tunnel count of >20 at baseline will be excluded from the trials

Figure 33 presents the study design schematic for Trials HS0003 and HS0004. The trials consisted of a screening period (up to 5 weeks), a double-blind initial treatment period (16 weeks), a double-blind maintenance treatment period (32 weeks), and a safety follow-up period (20 weeks) for subjects who did not enter the subsequent extension study (HS0005) or withdraw prematurely from treatment.

Each trial was designed to enroll and randomize a total 490 subjects to one of the following treatment groups in a 2:2:2:1 ratio:

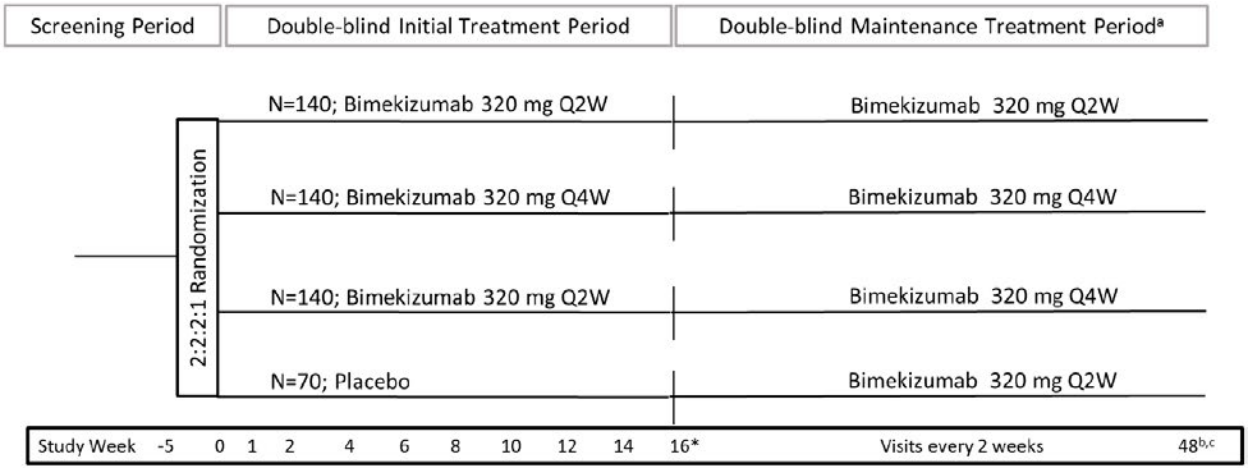
- Bimekizumab 320 mg Q2W from Weeks 0 to 48 (N=140)
- Bimekizumab 320 mg Q4W from Weeks 0 to 48 (N=140)
- Bimekizumab 320 mg Q2W up to Week 16, then 320 mg Q4W from Weeks 16 to 48 (N=140)

- Placebo up to Week 16, then bimekizumab 320 mg Q2W from Weeks 16 to 48 (N=70)

The protocol specified stratifying the randomization by Hurley Stage (II or III) and antibiotic use at baseline (Yes or No). All doses of investigational medicinal product (IMP) were administered by subcutaneous (SC) injection. Subjects were scheduled to have the following study visits: screening, baseline (Week 0), and Weeks 1, 2, 4, 6, 8, 10, 12, 14, 16, and then Q2W from Week 16 through Week 48. Subjects who complete the trials had the option of enrolling in an extension study (HS0005). Subjects who elected not to enroll in HS0005 at Week 48 were specified to have a safety follow-up visit 20 weeks after the final injection of IMP.

If a subject does not achieve a partial response (defined as a ≥25% reduction in the AN count from baseline) at any visit from Week 32 to 46, the protocol specified that the investigator should contact the medical monitor to discuss whether the subject should continue in the trial. Subjects who were discontinued from IMP were specified to be encouraged by the investigator to return for all scheduled visits through Week 48, and the safety follow-up visit (if the Week 48 visit is ≥20 weeks after the final dose of IMP, then the safety follow-up visit is not required).

Figure 3: Study Design Schematic for Trials HS0003 and HS0004



Source: page 13 of the clinical study protocol (Amendment 5) for Trial HS0003.
HiSCR50=a 50% reduction in the total abscess and inflammatory nodule count with no increase from Baseline in abscess or draining tunnel count; IMP=investigational medicinal product; Q2W=every 2 weeks; Q4W=every 4 weeks
*Week 16 = primary endpoint (HiSCR50 bimekizumab versus placebo)
[a] Study participants should discontinue from the study from Week 32 on if no partial response is achieved (partial response is defined as ≥25% improvement in abscess and inflammatory nodule count relative to Baseline [Week 0] lesion values)
[b] Study participants achieving an improvement of at least 25% in abscess and inflammatory nodule count continue in HS0005 (Extension Study).
[c] 20-week Safety Follow-up (from last IMP injection) for any study participant who discontinues from study prior to Week 48, or who does not continue in HS0005.

The protocol stated that there are differences in presentation between the bimekizumab and placebo treatments, thus the study sites will have blinded and "unblinded" personnel. Study drug injections was administered by "unblinded" dedicated study personnel according to the site-specific blinding plan. Study site pharmacists or other suitably qualified site personnel who

are responsible for preparation and administration of IMP treatments were specified to have access to treatment allocations for individual subjects via the interactive response technology (IRT). The unblinded pharmacy monitors from the Contract Research Organization (CRO), and the UCB Clinical Trial Supply representative will also have access to the treatment allocations and to the drug accountability records, if applicable. The protocol specified that the unblinded study site personnel will not be involved in the trials in any way other than assuring the IMP is taken from the correct kit and prepared according to the IMP-handling manual and administering the IMP to the subjects.

The protocol specified that study medication will be stopped if the subject has a confirmed coronavirus disease 2019 (COVID-19) test result or a suspected COVID-19 infection. Study medication resumed after the subject's recovery from COVID-19, based on the Investigator's clinical judgement.

Use of Rescue Medications, Analgesics, and Approach to Lesion Intervention:
The protocol specified that for subjects entering the trial in the antibiotic strata, they should be on a stable dose and regimen of doxycycline, minocycline, or an equivalent systemic tetracycline for 28 days prior to baseline. The dose and regimen should remain stable throughout trial participation, but at least through Week 16. The protocol specified that antibiotics taken on an as needed basis are not considered as a stable dose. After Week 16, the protocol specified that subjects may receive an antibiotic if required in the judgement of the investigator.

The protocol specified that any systemic antibiotic that is initiated (new antibiotic or change in the dose/type of current antibiotic) on or after baseline will be considered rescue medication for both the initial treatment period and maintenance treatment period (Weeks 0 to 48). In addition, the protocol specified that any analgesic that is initiated (new analgesic, new class of analgesic, increased dose of an analgesic stable since baseline, regardless of duration of treatment) after baseline will be considered rescue pain medication for the initial treatment period and maintenance treatment period (Weeks 0 to 48).

A total of 2 protocol-allowed interventions were specified to be permissible during the initial treatment period (from baseline to Week 16). The protocol specified that this does not include analgesic rescue treatment in the number of protocol-allowed interventions. An intervention can occur on maximally 2 different lesions at the same visit, or on the same lesion at 2 different study visits. The same lesion cannot be treated 2 times at the same visit. If a subject required more than 2 interventions within the first 16 weeks of the trial, then the subject was specified to be discontinued from the trial.

During the maintenance treatment period (Weeks 16 to 48), a maximum of 2 interventions every 4 weeks were specified to be permitted. The protocol specified that this does not include analgesic rescue treatment in the number of protocol-allowed interventions. An intervention can occur on 2 different lesions at the same visit or on the same lesion at 2 different study

visits. Within each 4-week period, the same type of intervention cannot be used 2 times on the same lesion. If a subject requires more than 2 interventions within a 4-week period or has 2 of the same interventions on the same lesion within that period, then the subject was specified to be discontinued from the trial.

The SAP stated that "if participants undergo lesion interventions as specified in the study protocol, the affected lesions will be counted by the Investigator as permanently present, thus accounting for potential bias due to the intervention."

8.1.2. Study Endpoints

The protocol-specified primary efficacy endpoint is the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16. HiSCR50 is defined as at least a 50% reduction in the total AN count with no increase from baseline in abscess or draining tunnel count.

The protocol and SAP list the following key secondary efficacy endpoints (multiplicity-controlled endpoints):

- Proportion of subjects achieving HiSCR75 at Week 16; HiSCR75 is defined as at least a 75% reduction in the total AN count with no increase from baseline in abscess or draining tunnel count
- Proportion of subjects who experience at least one flare by Week 16, with flare defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to baseline [ONLY Trial HS0004]
- Absolute change from baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 16
- Absolute change from baseline in the Worst HS Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HS Symptom Daily Diary (HSSDD)
- Proportion of subjects with a ≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16 among subjects with a baseline score ≥ 3

<u>Hurley Stage:</u>
The Hurley Stage is assigned to a given anatomic region. The overall worst Hurley Stage (i.e., the highest Hurley Stage across all anatomic regions) for a given subject at a given visit is then the subject-level Hurley Stage. The Hurley Stage is defined by the following criteria:

- Stage I: Abscess formation, single or multiple, without sinus tracts and cicatrization (scarring).
- Stage II: Recurrent abscesses with tract formation and cicatrization, single or multiple, widely separated lesions.
- Stage III: Diffuse or near-diffuse involvement, or multiple interconnected tracts and abscesses across the entire area.

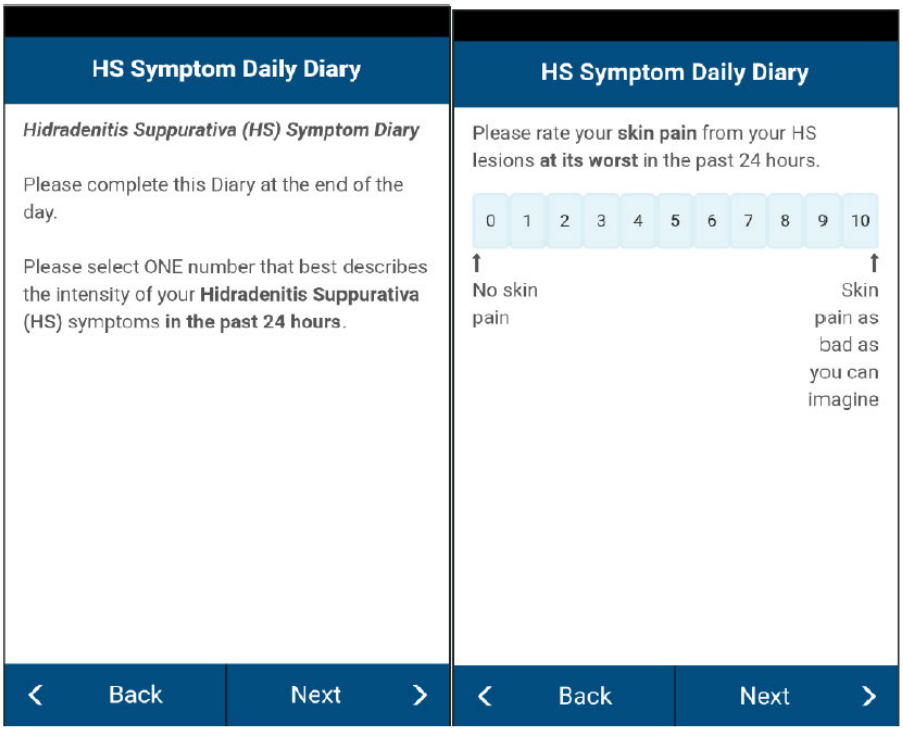
Dermatology Life Quality Index (DLQI):
The DLQI is a 10-item PRO instrument designed to assess the impacts of generic skin conditions. Each item is rated on a 4-point verbal ratings scale, ranging from 0 ("Not at all") to 3 ("Very much"). The recall period is the previous week. The DLQI was administered at Baseline, Weeks 4, 8, 12, 16, 20, 32, 36, 48 and EOT.

The DLQI generates a total score, which ranges from 0 to 30, with higher scores indicating a greater impact on quality of life (i.e., poor quality of life).

HS Symptom Daily Diary (HSSDD) Worst Skin Pain Item:
The HSSDD Worst Skin Pain item (Figure 4) is a single item within the HSSDD, a 5-item PRO instrument designed to assess HS signs/symptoms of HS. The Worst Skin Pain item is designed to assess skin pain intensity at its worst using an 11-point numeric rating scale (NRS) ranging from 0 ("No skin pain") to 10 ("Skin pain as bad as you can imagine"). The recall period is the previous 24 hours. The HSSDD Worst Skin Pain was administered electronically daily (at the end of the day) from Screening through Week 16.

The HSSDD Worst Skin Pain item generates a single item score that ranges from 0 to 10, with a higher score indicating greater skin pain intensity.

Figure 4: HSSDD Worst Skin Pain Item



The SAP stated:

- "Baseline will be computed as the average from the first 7 consecutive day period in which there are at least 4 non-missing entries. That is, first consider the first 7 consecutive days prior to the Baseline visit, but not including the Baseline visit day itself. If there are at least 4 non-missing values (not necessarily consecutive), then the Baseline average will be calculated. If there are less than 4 values, the 7 consecutive day period will move one day earlier. If there are at least 4 non-missing values (not necessarily consecutive) in that period, then the Baseline average will be calculated. This will continue until there are at least 4 non-missing values in a 7 consecutive day period in the 14 days prior to Baseline. If there is no period in which there are at least 4 non-missing entries, then the Baseline value will be set to missing."
- "Weekly averages will be derived for each of the items of the HSSDD for weeks matching the post-Baseline dosing weeks up to Week 16. A weekly average is the sum of the scored item over the course of the study week divided by the number of days on which the item was completed. The weekly averages will be relative to the respective visit date except for Baseline, which will be anchored to the first dose of study drug. A weekly average will only be calculated if at least 4 non-missing values (not necessarily consecutive) are available. Otherwise, the HSSDD weekly average for the given question will be set to missing."

8.1.3. Statistical Methodology

Analysis Sets:

The SAP specified the following analysis sets:

- Enrolled Set (ES): all subjects who have given informed consent.
- Randomized Set (RS): all randomized subjects.
- Safety Set (SS): all subjects who received at least 1 dose (full or partial) of IMP.
- Full Analysis Set (FAS): all subjects who received at least 1 dose (full or partial) of IMP and had a valid baseline measurement and a post-baseline measurement for abscess, inflammatory nodules, and draining tunnel counts.
- Active Medication Set (AMS): all subjects who have received at least 1 dose (full or partial) of bimekizumab.
- Maintenance Set (MS): all subjects who have received at least 1 dose (full or partial) of bimekizumab in the maintenance treatment period.
- Per-Protocol Set (PPS): all subjects in the FAS who had no important protocol deviations affecting the primary efficacy variable.

Estimands:

The SAP specified the following as the main estimand for the primary and binary secondary efficacy endpoints:

- Treatments: Bimekizumab 320 mg Q2W, bimekizumab 320 mg Q4W, and placebo.

- Population: Subjects meeting the protocol-specified inclusion/exclusion criteria.
- Endpoint: Binary outcome variable.
- Intercurrent Events (ICEs) and Strategy for Handling: The SAP specified receipt of systemic antibiotic rescue medication and discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16 as ICEs. The SAP specified using a composite variable strategy where subjects are considered non-responders starting at the start date of antibiotic rescue or at the last study treatment date + 17 days for discontinuation of study treatment due to an AE or lack of efficacy.
- Population-level Summary Measure: Odds ratio comparing bimekizumab to placebo adjusted for stratification factors used in the randomization. The SAP also specified calculating the difference in proportions and associated 95% confidence interval (CI).

For the continuous secondary efficacy endpoint, the SAP specified the following main estimand:

- Treatments: Bimekizumab 320 mg Q2W, bimekizumab 320 mg Q4W, and placebo.
- Population: Randomized Set (RS).
- Endpoint: Continuous outcome variable.
- Intercurrent Events and Strategy for Handling: The SAP specified receipt of systemic antibiotic rescue medication and discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16 as ICEs. The SAP specified using a hypothetical strategy, whereby all data at and after the ICE will be treated as missing.
- Population-level Summary Measure: mean changes from baseline and difference in mean changes from baseline between bimekizumab and placebo.

If subjects underwent lesion interventions as specified in the protocol, the affected lesions were counted by the Investigator as permanently present, thus accounting for potential bias due to the intervention. Therefore, lesion intervention was not specified as an ICE in the above estimands.

Analysis Methods:

The SAPs specified analyzing the primary and binary secondary efficacy endpoints using logistic regression. The model was specified to include fixed effects of treatment, Hurley stage at baseline, and baseline antibiotic use. The odds ratio and its 97.5% and 95% confidence intervals (CIs) were specified to be calculated from the logistic regression model. In addition to calculating the odds ratio, associated CIs, and p-values for the pairwise comparisons of bimekizumab and placebo, the SAP specified calculating the difference in proportions and 95% CI for each difference based on the logistic regression model. This review presents the differences in proportions instead of the odds ratios as the difference is easier to interpret and is the population-level summary measure of greater interest.

The SAP specified analyzing the continuous secondary efficacy endpoints using analysis of covariance (ANCOVA). The model was specified to include fixed effects of treatment, Hurley Stage at baseline, baseline antibiotic use, and baseline value as a covariate. The least square

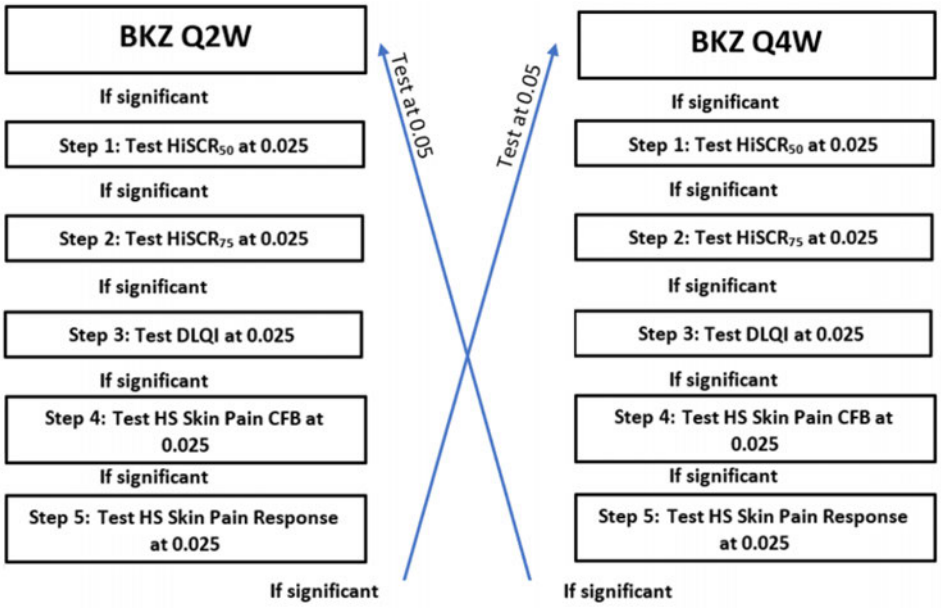
(LS) means for each treatment group was calculated based on the ANCOVA model. In addition, for the comparison between placebo and bimekizumab, the difference between the LS means and its 97.5% and 95% CIs were calculated. This review only presents the 95% CIs.

The primary method for handling missing data specified in the SAP was the multiple imputation approach (MI). For each treatment group separately, intermittent missing data was specified to be first imputed 100 times using the Markov-Chain Monte Carlo (MCMC) method, followed by the regression method for monotone missing data. Hurley Stage at baseline, baseline antibiotic use, and baseline value, and each post-baseline visit (in chronological order) was specified to be included in the imputation model. For HiSCR response (e.g., HiSCR50 and HiSCR75), the SAP specified imputing the lesion counts and then determining the response status based on the imputed lesion counts.

Multiplicity Adjustment Plan:

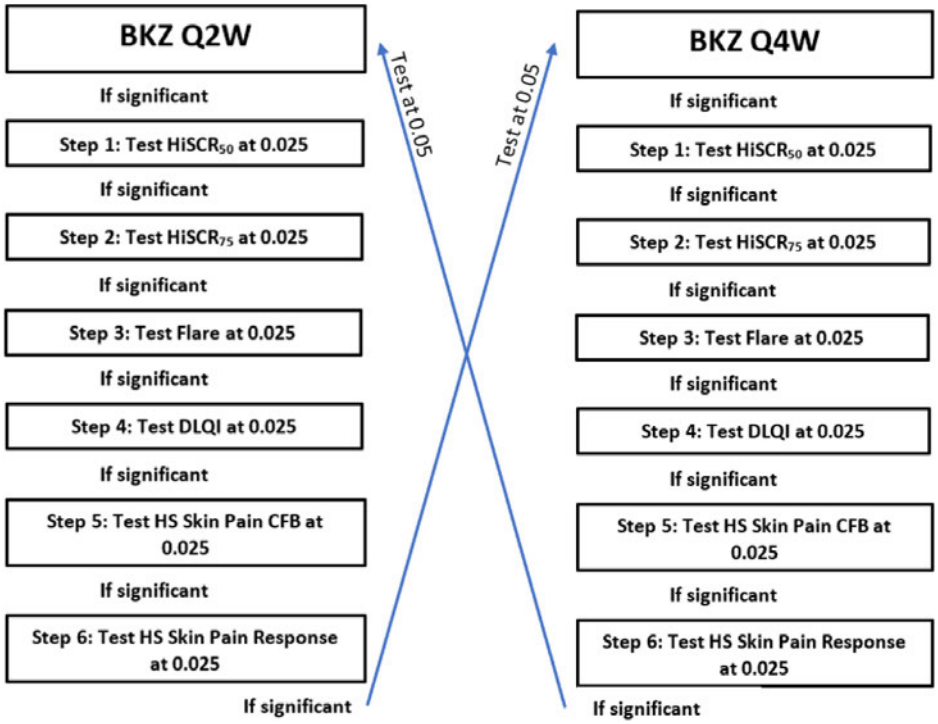
The SAP specified using a closed testing procedure under a parallel gatekeeping framework to control the Type I error rate at 0.05, see Figure 5 for Trial HS0003 and Figure 66 for Trial HS0004. Under this framework, each bimekizumab dose (i.e., 320 mg Q2W and 320 mg Q4W) was compared to placebo in the first instance at a familywise error rate of 0.025 (two-sided). Simultaneously within each dose, closed testing for the primary and secondary efficacy endpoints was performed. If the last step (i.e., Step 5 for Trial HS0003 and Step 6 for Trial HS0004) was significant at 0.025 for a given dose, then the steps for the other dose was repeated using a significance level of 0.05.

Figure 5: Close Testing Procedure for Trial HS0003



Source: page 43 of the SAP (Amendment 3) for Trial HS0003.

Figure 6: Close Testing Procedure for Trial HS0004



Source: page 44 of the SAP (Amendment 2) for Trial HS0004.

Sensitivity and Supplementary Analyses:

For the primary efficacy endpoint, the SAP specified the following sensitivity analyses for the handling of missing data:

- Non-Responder Imputation (NRI): missing data imputed as non-responders.
- MI-MCMC / Reference-Based Imputation: intermittent missing data is imputed based on the MCMC method, and monotone missing data are imputed using an imputation model based on placebo (reference) data.
- Tipping Point Analysis: The stated objective of the tipping point analyses is to evaluate the sensitivity of results to departures from the missing at random assumption and to identify the point at which departures cause results to "tip" from statistically significant to statistically non-significant. The SAP specified first evaluating the worst-case scenario (i.e., all missing data for subjects to bimekizumab [where missing values include observations after the intercurrent event date and any other missing values] are imputed as non-responders, while all missing values for placebo-randomized subjects are imputed as responders). If this analysis based on the worst-case scenario results in a p-value that is not significant (e.g., greater than 0.025), then additional tipping point analyses will be performed to identify the point at which results switch or "tip" from significant to non-significant. In the tipping point analysis, a shift parameter or delta adjustment is applied to missing, and subsequently imported primary endpoint values (where missing values include observations after the intercurrent event and any other

missing values). The delta adjustments result in subjects randomized to bimekizumab with missing data having a lower probability of response compared to subjects randomized to placebo with missing data.

- Observed Case: missing data is not imputed. Only subjects with available data who had not discontinued IMP at the given timepoint were considered. Subjects with missing data or who had prematurely discontinued IMP were treated as missing.

The SAP specified conducting a supplementary analysis where the specified ICEs (i.e., antibiotic rescue medication and discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) are handled using a treatment policy strategy.

8.1.4. Subject Disposition, Demographics, and Baseline Disease Characteristics

Trial HS0003 enrolled and randomized a total of 505 subjects from 80 investigational sites. Trial HS0004 enrolled and randomized a total of 509 subjects from 87 investigational sites. Table 8 presents the subject disposition for the initial treatment period (Weeks 0 to 16). A total of 4 subjects in Trial HS0003 and 3 subjects in Trial HS0004 were randomized but did not receive their randomized treatment. The trial discontinuation rate during the initial treatment period was generally comparable across the treatment groups in Trial HS0003. In Trial HS0004, the trial discontinuation rate was slightly higher the bimekizumab Q2W group than the other two groups. Overall, the trial discontinuation rate was slightly higher in Trial HS0003 compared to Trial HS0004 (i.e., 10% vs. 8%).

Table 8: Subject Disposition for Initial Treatment Period (Weeks 0 to 16)

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W	**Q4W**	**Placebo**	**Q2W**	**Q4W**	**Placebo**
Randomized	289	144	72	291	144	74
Treated	286	143	72	290	142	74
Discontinued from trial, n (%)[1]	27 (9)	16 (11)	7 (10)	28 (10)	9 (6)	5 (7)
Adverse events	7 (2)	5 (3)	1 (1)	9 (3)	1 (1)	1 (1)
Lack of efficacy	0	0	0	1 (<1)	0	0
Protocol violation	2 (1)	2 (1)	0	1 (<1)	0	1 (1)
Lost to follow-up	2 (1)	3 (2)	1 (1)	3 (1)	0	1 (1)
Consent withdrawn by subject (not due to AE)	14 (5)	6 (4)	4 (6)	12 (4)	8 (6)	2 (3)
Other	2 (1)	0	1 (1)	2 (1)	0	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] The percentages were calculated based on the number of subjects that were randomized.

Table 9 and Table 10 present the subject disposition for the maintenance treatment period (Weeks 16 to 48) for Trials HS0003 and HS0004, respectively. The trial discontinuation rate during the maintenance treatment period was higher in Trial HS0003 compared to Trial HS0004 (26% vs. 16%).

Table 9: Subject Disposition for Maintenance Treatment Period (Weeks 16 to 48) for Trial HS0003 (MS[1])

	Bimekizumab 320 mg Q2W/Q2W (N=129)	**Bimekizumab 320 mg Q2W/Q4W (N=129)**	**Bimekizumab 320 mg Q4W/Q4W (N=125)**	**Placebo/ Bimekizumab 320 mg Q2W (N=65)**
Discontinued from trial, n (%)	31 (24)	25 (19)	38 (30)	21 (32)
Adverse events	6 (5)	5 (4)	7 (6)	9 (14)
Lack of efficacy	3 (2)	3 (2)	7 (6)	1 (2)
Lost to follow-up	3 (2)	3 (2)	5 (4)	2 (3)
Protocol violation	2 (2)	1 (1)	2 (2)	1 (2)
Consent withdrawn by subject (not due to AE)	14 (11)	11 (9)	12 (10)	7 (11)
Other	3 (2)	2 (2)	5 (4)	1 (2)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Maintenance Set (MS): all subjects who received at least 1 dose (full or partial) of bimekizumab in the maintenance treatment period.

Table 10: Subject Disposition for Maintenance Treatment Period (Weeks 16 to 48) for Trial HS0004 (MS[1])

	Bimekizumab 320 mg Q2W/Q2W (N=131)	**Bimekizumab 320 mg Q2W/Q4W (N=130)**	**Bimekizumab 320 mg Q4W/Q4W (N=133)**	**Placebo/ Bimekizumab 320 mg Q2W (N=69)**
Discontinued from trial, n (%)	21 (16)	23 (18)	24 (18)	8 (12)
Adverse events	4 (3)	6 (5)	7 (5)	0
Lack of efficacy	2 (2)	2 (2)	4 (3)	0
Lost to follow-up	2 (2)	1 (1)	3 (2)	2 (3)
Protocol violation	1 (1)	2 (2)	0	0
Consent withdrawn by subject (not due to AE)	11 (8)	10 (8)	9 (7)	6 (9)
Other	1 (1)	2 (2)	1 (1)	0

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Maintenance Set (MS): all subjects who received at least 1 dose (full or partial) of bimekizumab in the maintenance treatment period.

For both trials, Table 11 presents the demographics and Table 12 presents the baseline disease characteristics. The demographics and baseline disease characteristics were generally balanced across the treatment arms within each trial and were comparable across trials. Trial HS0003 had a higher proportion of subjects from the United States than Trial HS0004.

Table 11: Demographics (RS[1])

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
Age (years)						
Mean (SD)	36.9 (12.4)	36.3 (11.2)	36.4 (12.4)	36.9 (12.3)	35.2 (11.9)	38.1 (13.2)
Median	36.0	35.0	33.5	35.0	33.0	37.0
Min, Max	18.0, 72.0	18.0, 78.0	18.0, 65.0	18.0, 71.0	18.0, 75.0	20.0, 69.0
Categories, n (%)						
< 65	283 (98)	143 (99)	71 (99)	287 (99)	142 (99)	70 (95)
≥ 65	6 (2)	1 (1)	1 (1)	4 (1)	2 (1)	4 (5)
Sex, n (%)						
Female	176 (61)	98 (68)	44 (61)	150 (52)	77 (53)	31 (42)
Male	113 (39)	46 (32)	28 (39)	141 (48)	67 (47)	43 (58)
Race, n (%)						
White	233 (81)	105 (73)	55 (76)	232 (80)	119 (83)	64 (86)
Black or African American	41 (14)	21 (15)	8 (11)	22 (8)	13 (9)	5 (7)
Asian	2 (1)	3 (2)	3 (4)	22 (8)	7 (5)	5 (7)
Other	2 (1)	1 (1)	0	1 (<1)	1 (1)	0
Missing	11 (4)	14 (10)	6 (8)	14 (5)	4 (3)	0
Ethnicity, n (%)						
Hispanic or Latino	20 (7)	13 (9)	4 (6)	15 (5)	10 (7)	5 (7)
Not Hispanic or Latino	268 (93)	131 (91)	67 (93)	274 (94)	134 (93)	69 (93)
Missing	1 (<1)	0	1 (1)	2 (1)	0	0
Weight (kg)						
n	286	144	72	291	143	74
Mean (SD)	97.2 (25.4)	102.7 (24.7)	94.6 (24.8)	95.4 (24.2)	95.3 (22.0)	100.3 (23.6)
Median	95.4	103.6	88.2	91.9	94.7	95.5
Min, Max	48.0, 189.0	54.3, 195.9	51.5, 172.4	51.8, 183.3	56.4, 146.5	64.0, 158.0
Categories, n (%)						
< 100	166 (57)	66 (46)	47 (65)	189 (65)	84 (58)	40 (54)
≥ 100	120 (42)	78 (54)	25 (35)	102 (35)	59 (41)	34 (46)
Missing	3 (1)	0	0	0	1 (1)	0
Country, n (%)						
United States	115 (40)	66 (46)	25 (35)	62 (21)	34 (24)	17 (23)
Outside United States	174 (60)	78 (54)	47 (65)	229 (79)	110 (76)	57 (77)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Randomized Set (RS) population: all randomized subjects.

Table 12: Baseline Disease Characteristics (RS[1])

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
Duration of Disease (years)						
Mean (SD)	8.5 (7.6)	8.8 (8.5)	11.5 (9.9)	7.4 (7.4)	5.8 (5.4)	8.0 (8.6)
Median	5.7	5.6	8.7	4.9	4.2	4.8
Min, Max	0.5, 40.7	0.5, 38.5	0.5, 46.9	0.5, 41.3	0.5, 30.0	0.5, 51.3
Prior Biologic Use for HS, n (%)						
No	213 (74)	113 (78)	53 (74)	250 (86)	128 (89)	64 (86)
Yes	76 (26)	31 (22)	19 (26)	41 (14)	16 (11)	10 (14)
Hurley Stage at Baseline (Stratification), n (%)						
II	159 (55)	80 (56)	40 (56)	187 (64)	92 (64)	47 (64)
III	130 (45)	64 (44)	32 (44)	104 (36)	52 (36)	27 (36)
Antibiotic Use at Baseline (Stratification), n (%)						
No	263 (91)	131 (91)	66 (92)	264 (91)	131 (91)	67 (91)
Yes	26 (9)	13 (9)	6 (8)	27 (9)	13 (9)	7 (9)
Total AN Count at Baseline						
Mean (SD)	15.3 (13.5)	17.8 (25.3)	15.0 (11.9)	16.7 (15.5)	17.6 (15.4)	13.9 (7.8)
Median	10.0	12.0	10.0	11.0	12.0	11.5
Min, Max	4.0, 89.0	2.0, 272.0	5.0, 68.0	1.0, 154.0	5.0, 88.0	5.0, 41.0
Total Draining Tunnels at Baseline						
Mean (SD)	4.0 (4.9)	3.8 (4.9)	3.2 (4.0)	3.6 (4.0)	2.8 (3.1)	3.5 (3.7)
Median	2.0	2.0	1.5	2.0	2.0	2.5
Min, Max	0.0, 20.0	0.0, 20.0	0.0, 15.0	0.0, 20.0	0.0, 19.0	0.0, 19.0
Worst HS Skin Pain at Baseline						
n	234	117	55	248	133	61
Mean (SD)	5.5 (2.5)	5.9 (2.6)	6.0 (2.5)	5.3 (2.4)	5.3 (2.5)	5.0 (2.4)
Median	5.7	6.3	6.2	5.3	5.5	5.4
Min, Max	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 10.0	0.0, 8.3

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Randomized Set (RS) population: all randomized subjects.

8.1.5. Intercurrent Events and Lesion Intervention

Table 13 summarizes the number and percentage of subjects with intercurrent events (ICEs) for the initial treatment period (Weeks 0 to 16). Table 14 and Table 15 summarize the ICEs for the entire treatment period (Weeks 0 to 48) for Trials HS0003 and HS0004, respectively. For these three tables, if a subject has more than one ICE, then the tables list the ICE that occurred first. During the initial treatment period, the percentage of subjects that received systemic antibiotic rescue was higher in the placebo group compared to the bimekizumab groups in Trial HS0003; however, in Trial HS0004, the percentage was higher in bimekizumab groups compared to the placebo group. Overall, the percentage of subjects that received systemic antibiotic rescue was higher in Trial HS0003 than in Trial HS0004.

Table 13: Intercurrent Events (ICEs) for the Initial Treatment Period [Weeks 0 to 16] (RS[1])

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
All ICEs, n (%)	52 (18)	28 (19)	16 (22)	53 (18)	19 (13)	7 (9)
Discontinued due to AE	5 (2)	6 (4)	1 (1)	8 (3)	1 (1)	1 (1)
Discontinued due to lack of efficacy	0	0	0	0	0	0
Systemic antibiotic rescue	47 (16)	22 (15)	15 (21)	45 (15)	18 (13)	6 (8)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Randomized Set (RS) population: all randomized subjects.

Table 14: Intercurrent Events (ICEs) for the Entire Treatment Period (Weeks 0 to 48) for Trial HS0003 (RS[1])

	Bimekizumab 320 mg Q2W/Q2W (N=143)	Bimekizumab 320 mg Q2W/Q4W (N=146)	Bimekizumab 320 mg Q4W/Q4W (N=144)	Placebo/ Bimekizumab 320 mg Q2W (N=72)
All ICEs, n (%)	62 (43)	65 (45)	71 (49)	38 (53)
Discontinued due to AE	2 (1)	8 (5)	10 (7)	1 (1)
Discontinued due to lack of efficacy	0	0	2 (1)	1 (1)
Systemic antibiotic rescue	60 (42)	57 (39)	59 (41)	36 (50)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Randomized Set (RS) population: all randomized subjects.

Table 15: Intercurrent Events (ICEs) for the Entire Treatment Period (Weeks 0 to 48) for Trial HS0004 (RS[1])

	Bimekizumab 320 mg Q2W/Q2W (N=145)	Bimekizumab 320 mg Q2W/Q4W (N=146)	Bimekizumab 320 mg Q4W/Q4W (N=144)	Placebo/ Bimekizumab 320 mg Q2W (N=74)
All ICEs, n (%)	56 (39)	63 (43)	51 (35)	18 (24)
Discontinued due to AE	7 (5)	7 (5)	4 (3)	1 (1)
Discontinued due to lack of efficacy	1 (1)	1 (1)	3 (2)	0
Systemic antibiotic rescue	48 (33)	55 (38)	44 (31)	17 (23)

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt
[1] Randomized Set (RS) population: all randomized subjects.

Table 16 summarizes the number and percentage of subjects that received lesion interventions as well as the number of lesion interventions for the initial treatment period (Weeks 0 to 16). Table 17 and Table 18 summarizes the lesion interventions for the maintenance treatment period (Weeks 16 to 48) for Trials HS0003 and HS0004, respectively. In both trials, the percentage of subjects that received lesion interventions was relatively small (i.e., approximately 4% in both trials) for the initial treatment period. For both treatment periods, the overall percentage of subjects that received lesion interventions was slightly higher in Trial HS0003 than in Trial HS0004.

Table 16: Lesion Intervention for the Initial Treatment Period [Weeks 0 to 16] (RS[1])

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
Subjects with ≥1 lesion intervention, n (%)	9 (3)	6 (4)	4 (6)	6 (2)	10 (7)	4 (5)
1 lesion intervention	8 (3)	5 (3)	2 (3)	5 (2)	7 (5)	0
2 lesion interventions	0	1 (1)	2 (3)	1 (<1)	3 (2)	3 (4)
3 lesion interventions	1 (<1)	0	0	0	0	1 (1)

Source: Applicant's Table 6.3.35.1 in clinical study reports for Trials HS0003 and HS0004.
[1] Randomized Set (RS) population: all randomized subjects.

Table 17: Lesion Intervention for the Maintenance Treatment Period (Weeks 16 to 48) for Trial HS0003 (RS[1])

	Bimekizumab 320 mg Q2W/Q2W (N=129)	Bimekizumab 320 mg Q2W/Q4W (N=129)	Bimekizumab 320 mg Q4W/Q4W (N=125)	Placebo/ Bimekizumab 320 mg Q2W (N=65)
Subjects with ≥1 lesion intervention, n (%)	10 (8)	14 (11)	14 (11)	9 (14)
1 lesion intervention	5 (4)	13 (10)	10 (8)	4 (6)
2 lesion interventions	1 (1)	1 (1)	1 (1)	2 (3)
3 lesion interventions	1 (1)	0	3 (2)	1 (2)
>3 lesion interventions	3 (2)	0	0	2 (3)

Source: Applicant's Table 6.3.35.2 in clinical study reports for Trials HS0003 and HS0004.
[1] Randomized Set (RS) population: all randomized subjects.

Table 18: Lesion Intervention for the Maintenance Treatment Period (Weeks 16 to 48) for Trial HS0004 (RS[1])

	Bimekizumab 320 mg Q2W/Q2W (N=131)	Bimekizumab 320 mg Q2W/Q4W (N=130)	Bimekizumab 320 mg Q4W/Q4W (N=133)	Placebo/ Bimekizumab 320 mg Q2W (N=69)
Subjects with ≥1 lesion intervention, n (%)	7 (5)	11 (8)	10 (8)	4 (6)
1 lesion intervention	4 (3)	8 (6)	7 (5)	2 (3)
2 lesion interventions	2 (2)	3 (2)	1 (1)	1 (1)
3 lesion interventions	1 (1)	0	2 (2)	1 (1)
>3 lesion interventions	0	0	0	0

Source: Applicant's Table 6.3.35.2 in clinical study reports for Trials HS0003 and HS0004.
[1] Randomized Set (RS) population: all randomized subjects.

As noted in Sections 8.1.1 and 8.1.3, the SAP specified that if subjects underwent lesion interventions as specified in the protocol, the affected lesions were counted by the Investigator as permanently present. During the filing review, the statistical reviewer identified at least one instance where a lesion that received lesion intervention was not counted as permanently present. In the Filing Communication Letter dated April 2, 2024, the following potential review issue was conveyed to the Applicant:

> "The statistical analysis plans (SAPs) and clinical study report for the Phase 3 trials (HS0003 and HS0004) state that 'if participants undergo lesion interventions as specified in the study protocol, the affected lesions will be counted by the Investigator as permanently present, thus accounting for potential bias due to the intervention.' Submit detailed information on the process (e.g., capturing, documentation, and tracking) for lesion intervention as it is not clear how these lesions were counted as permanently present. In addition, we have found at least one instance where a lesion that received lesion intervention was not counted as permanently present. Subject (b) (6) had an abscess receive lesion intervention (i.e., 'INCISION & DRAINAGE' according to ADHSLIT.xpt) at Week 2; however, the abscess count at Week 16 is 0 for this subject. Therefore, it is not clear whether lesions that received intervention were counted as permanently present. Clarification is needed."

On April 26, 2024, the Applicant submitted their response to the potential review issue in the Filing Communication Letter. In their response, the Applicant stated the following:

- "A total of 1014 study participants were randomized across the 2 studies. The total number of Baseline lesions (AN) across both the HS0003 and HS0004 studies was 16,484. There were 53 lesions occurring in 39 participants across the 2 studies that required intervention through Week 16, representing 0.3% of all lesions present at Baseline (53/16,484)."
- "While interventions were recorded at the lesion level, the actual lesion counts were recorded as a total based on body region. Therefore, it is not clear from the data whether a specific lesion with intervention has been counted as present at all visits following the intervention. For example, in the case of participant (b) (6) it is apparent that an intervened lesion was not counted as present at subsequent visits by the investigator. There are 35 lesions occurring in 28 participants across the 2 studies where there was an intervention, but later there were counts of 0 recorded. This represents 0.2% of all lesions present at Baseline (35/16,484)."

The Applicant conducted the following two *post hoc* sensitivity analyses:

- *Post Hoc* Analysis #1: 1 lesion was added to the lesion count from the time point of intervention for any abscess or inflammatory nodule that required intervention. This approach assumed that all intervened lesions were not subsequently considered present by the investigator.
- *Post Hoc* Analysis #2: 1 lesion was added to the lesion count whenever the subject had a 0 following the timepoint of intervention of the abscess or inflammatory nodule. This

approach corrects for confirmed cases of a lesion not being counted as present following an intervention.

Table 20 in Section 8.1.6 presents the results of the Applicant's *post hoc* sensitivity analyses for the handling lesion interventions.

8.1.6. Results for the Primary Efficacy Endpoint

Table 19 presents the results for the primary efficacy endpoint at Week 16 for Trials HS0003 and HS0004. In both trials, bimekizumab Q2W was statistically superior to placebo (p-values ≤ 0.006). Bimekizumab Q4W was statistically superior to placebo (p-value = 0.003) in Trial HS0004; however, per the multiplicity testing procedure, statistical superiority of bimekizumab Q4W over placebo cannot be claimed for Trial HS0003 as the p-value of 0.030 was not less than 0.025 and one of the secondary efficacy endpoints for bimekizumab Q2W was not statistically significant (see Table 21 in Section 8.1.7).

Table 19: Results for the Primary Efficacy Endpoint at Week 16 (RS[1])

	Trial HS0003			**Trial HS0004**		
	Bimekizumab 320 mg			**Bimekizumab 320 mg**		
	Q2W (N=289)	**Q4W (N=144)**	**Placebo (N=72)**	**Q2W (N=291)**	**Q4W (N=144)**	**Placebo (N=74)**
HiSCR50 at Week 16	48%	45%	29%	52%	54%	32%
Difference from placebo (95% CI)[2]	18% (6%, 30%)	15% (2%, 29%)		20% (8%, 32%)	21% (8%, 35%)	
P-value[2]	0.006	0.030		0.004	0.003	
Significant per MTP[3]	Yes	No		Yes	Yes	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
[2] Difference, 95% CI, and p-value were based on logistic regression with treatment, Hurley Stage at baseline, and baseline antibiotic use were used as fixed effects.
[3] Multiplicity Testing Procedure (MTP): a closed testing procedure under a parallel gatekeeping framework was used, see Figure 5 and Figure 6.

Table 70 in Appendix 19.6.5 presents the number and percentage of subjects with missing data for the primary efficacy endpoint at Week 16. Approximately 12% and 8% of the subjects had missing data in Trials HS0003 and HS0004, respectively. Table 71 in Appendix 19.6.5 presents the results for the primary efficacy endpoint at Week 16 by the various prespecified imputation methods for handling missing data. In both trials, the results were generally similar across various imputation methods.

The results (not shown) of the Applicant's supplementary analysis using the treatment policy strategy to handle the ICEs were supportive of the main estimand (i.e., using a composite variable strategy to handle the ICEs) and had larger treatment effects than the main estimand for the primary efficacy endpoint for both dose regimens of bimekizumab in both trials (Trial HS0003: Q2W [23% vs. 18%] and Q4W [22% vs. 15%]; Trial HS0004: Q2W [27% vs. 20%] and Q4W [25% vs. 21%]).

Table 20 presents the Applicant's post hoc sensitivity analyses for handling lesion intervention. The results for both analyses are similar to those of the main analysis in Table 19. For Trial HS0003, the treatment effects were 1-2% larger in the *post hoc* analyses than in the main analysis. However, for Trial HS0004, the treatment effects were 1% smaller in the *post hoc* analyses than in the main analysis. Overall, the results of the *post hoc* analyses are supportive of the main analysis.

Table 20: Applicant's *Post Hoc* Sensitivity Analyses for Handling Lesion Interventions (RS[1])

	Trial HS0003			**Trial HS0004**		
	Bimekizumab 320 mg			**Bimekizumab 320 mg**		
	Q2W (N=289)	**Q4W (N=144)**	**Placebo (N=72)**	**Q2W (N=291)**	**Q4W (N=144)**	**Placebo (N=74)**
***Post Hoc* Analysis #1[2]**						
HiSCR50 at Week 16	45%	42%	24%	50%	51%	31%
Difference from placebo (95% CI)[4]	20% (9%, 32%)	17% (4%, 31%)		19% (7%, 31%)	20% (7%, 34%)	
P-value[4]	0.002	0.014		0.004	0.005	
***Post Hoc* Analysis #2[3]**						
HiSCR50 at Week 16	45%	42%	26%	50%	51%	31%
Difference from placebo (95% CI)[4]	19% (7%, 31%)	17% (4%, 30%)		19% (7%, 31%)	20% (7%, 34%)	
P-value[4]	0.004	0.018		0.004	0.005	

Source: Applicant's HS0003 Posthoc Table 6.1.1.2.1, HS0003 Posthoc Table 6.1.1.2.1a, HS0004 Posthoc Table 6.1.1.2.2, and HS0004 Posthoc 6.1.1.2.2a; submitted on April 26, 2024.

[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).

[2] *Post Hoc* Analysis #1: 1 lesion was added to the lesion count from the time point of intervention for any abscess or inflammatory nodule that required intervention.

[3] *Post Hoc* Analysis #2: 1 lesion was added to the lesion count whenever the subject had a 0 following the timepoint of intervention of the abscess or inflammatory nodule.

[4] Difference, 95% CI, and p-value were based on logistic regression with treatment, Hurley Stage at baseline, and baseline antibiotic use were used as fixed effects.

8.1.7. Results for the Secondary Efficacy Endpoints

Table 21 presents the results for the secondary efficacy endpoints in both trials. In Trial HS0003, bimekizumab Q2W was statistically superior to placebo for all of the secondary endpoints except for the last endpoint (i.e., ≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16), and statistical superiority of bimekizumab Q4W over placebo cannot be claimed for any of the secondary efficacy endpoints per the multiplicity testing strategy. In Trial HS0004, both bimekizumab Q2W and bimekizumab Q4W were statistically superior to placebo on the 1st secondary endpoint (i.e., HiSCR75 at Week 16); however, both dose regimens of bimekizumab were not statistically superior to placebo (p-values ≥ 0.497) on the 2nd secondary endpoint (i.e., at least 1 flare by Week 16). Consequently, per the multiplicity testing procedure, statistical significance of the remaining secondary endpoints cannot be claimed in Trial HS0004.

Table 21: Results of the Secondary Efficacy Endpoints (RS[1])

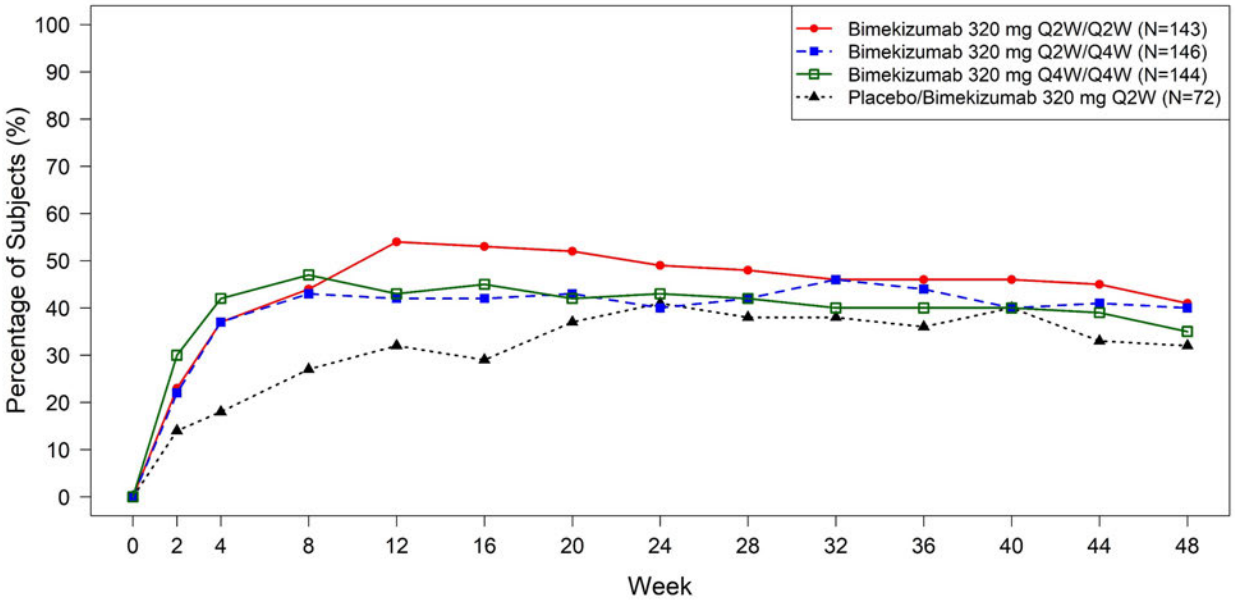
	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
HiSCR75 at Week 16	33%	24%	19%	36%	33%	16%
Difference from placebo (95% CI)[2]	15% (4%, 27%)	6% (-6%, 19%)		20% (10%, 31%)	18% (6%, 30%)	
P-value[2]	0.021	0.350		0.002	0.007	
Significant per MTP[4]	Yes	No		Yes	Yes	
At least 1 flare by Week 16	29%	36%	48%	29%	24%	28%
Difference from placebo (95% CI)[2]	Not a Multiplicity-Controlled Secondary Efficacy Endpoint in Trial HS0003			1% (-10%, 12%)	-4% (-16%, 8%)	
P-value[2]				0.868	0.497	
Significant per MTP[4]				No	No	
Change from baseline in DLQI at Week 16						
LS Mean[3]	-5.2	-5.1	-2.5	-4.7	-4.8	-2.4
Difference from placebo (95% CI)[3]	-2.7 (-4.2, -1.2)	-2.6 (-4.2, -0.9)		-2.3 (-3.5, -1.1)	-2.4 (-3.7, -1.1)	
P-value[3]	<0.001	0.002		<0.001	<0.001	
Significant per MTP[4]	Yes	No		No	No	
Change from baseline in Worst HS Skin Pain score at Week 16						
LS Mean[3]	-2.2	-1.5	-1.0	-1.6	-1.2	-0.3
Difference from placebo (95% CI)[3]	-1.2 (-2.1, -0.3)	-0.6 (-1.5, 0.4)		-1.3 (-1.9, -0.6)	-0.9 (-1.6, -0.2)	
P-value[3]	0.002	0.201		<0.001	0.010	
Significant per MTP[4]	Yes	No		No	No	
	N=190	**N=103**	**N=46**	**N=209**	**N=108**	**N=49**
≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16[5]	32%	22%	15%	32%	29%	11%
Difference from placebo (95% CI)[2]	19% (3%, 34%)	8% (-8%, 24%)		20% (7%, 32%)	17% (3%, 30%)	
P-value[2]	0.041	0.367		0.010	0.028	
Significant per MTP[4]	No	No		No	No	

Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADFA.xpt, ADDLQI.xpt, ADHSSDD.xpt
[1] Randomized Set (RS) population: all randomized subjects. Missing data was imputed using multiple imputation (MI).
[2] Difference, 95% CI, and p-value were based on logistic regression with treatment, Hurley Stage at baseline, baseline antibiotic use, and analgesic use (only Worst HS Skin Pain endpoint) were used as fixed effects.
[3] LS means, difference, 95% CI, and p-value were based on ANCOVA with fixed effects of treatment, Hurley Stage at baseline, baseline antibiotic use, and analgesic use (only Worst HS Skin Pain endpoint) and baseline value as a covariate.
[4] Multiplicity Testing Procedure (MTP): a closed testing procedure under a parallel gatekeeping framework was used, see Figure 5 and Figure 6.
[5] Analysis based on subjects with a baseline Worst HS Skin Pain score ≥ 3.

8.1.8. Efficacy Over Time

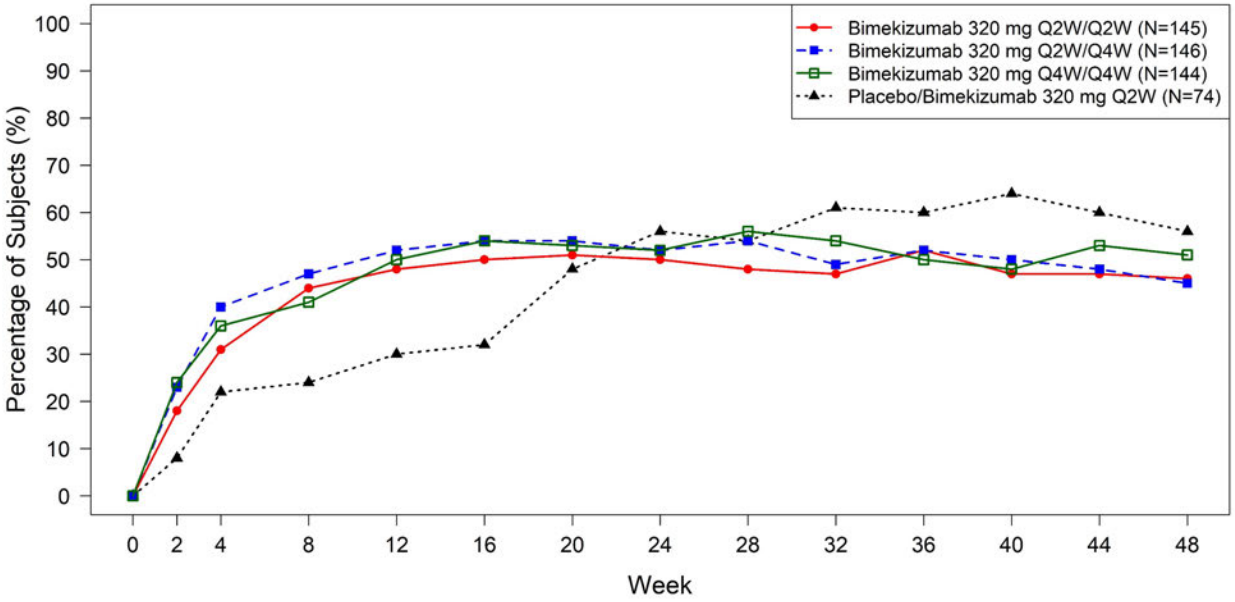
Figure 7 and Figure 8 present the results of HiSCR50 over time (Weeks 0 to 48) for Trials HS0003 and HS0004, respectively. Figure 9 and Figure 10 present the results of HiSCR75 over time (Weeks 0 to 48) for Trials HS0003 and HS0004, respectively.

Figure 7: Results of HiSCR50 Over Time for Trial HS0003 (RS[1])



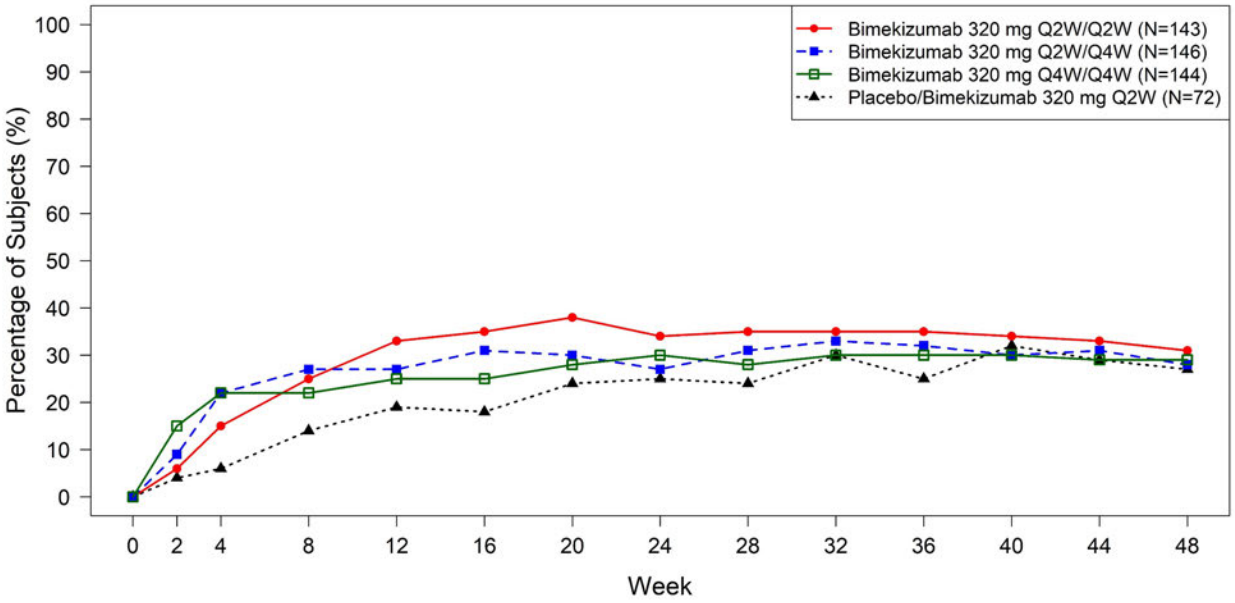
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).

Figure 8: Results of HiSCR50 Over Time for Trial HS0004 (RS[1])



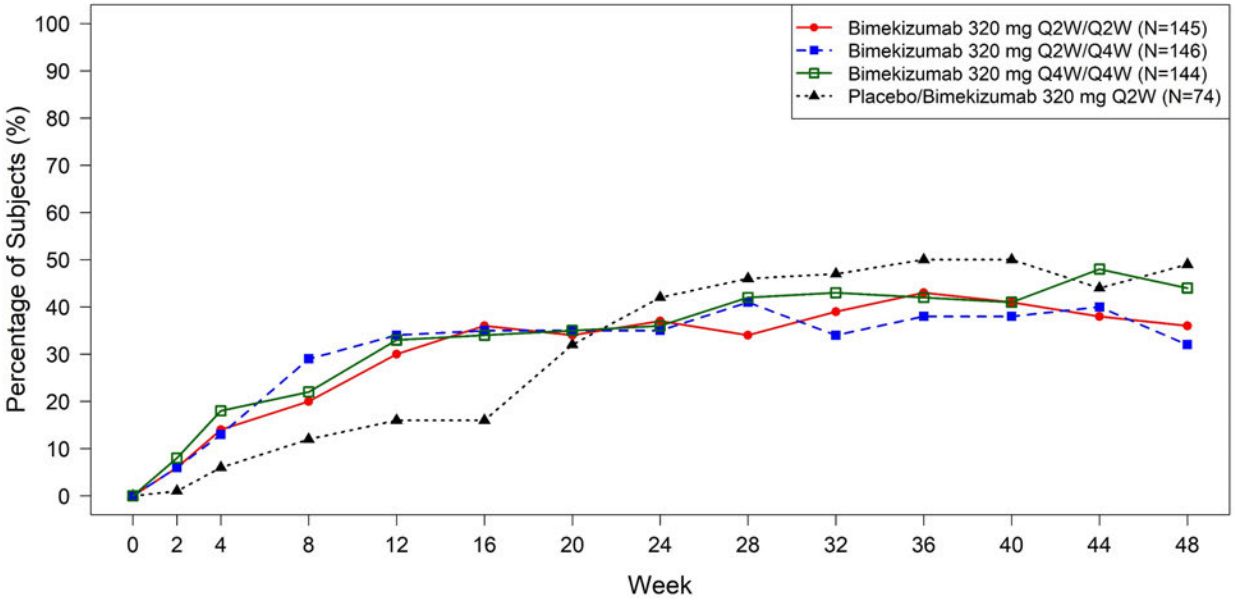
Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).

Figure 9: Results of HiSCR75 Over Time for Trial HS0003 (RS[1])



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).

Figure 10: Results of HiSCR75 Over Time for Trial HS0004 (RS[1])



Source: Statistical Reviewer's Analysis (same as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).

8.1.9. Findings in Special/Subgroup Populations

Table 22 and Table 23 present the results of the primary efficacy endpoint (i.e., HiSCR50) at Week 16 by age, sex, race, ethnicity, weight, smoking status, country, Hurley stage at baseline, antibiotic use at baseline, and prior biologic therapy for Trials HS0003 and HS0004, respectively. There were generally no substantial differences in treatment effect was across these subgroups. However, the sample size for some of the subgroups (e.g., age ≥ 65 years) were relatively small; therefore, it would be difficult to detect any difference in efficacy between these subgroups and their complements.

Table 22: Results of the Primary Efficacy Endpoint at Week 16 by Age, Sex, Race, Ethnicity, Weight, Smoking Status, Country, Hurley Stage at Baseline, Antibiotic Use at Baseline, and Prior Biologic Therapy for Trial HS0003 (RS[1])

	Bimekizumab			Difference	
Subgroup (N_{BQ2W}, N_{BQ4W}, N_P)[2]	**320 mg Q2W (N=289)**	**320 mg Q4W (N=144)**	**Placebo (N=72)**	**Q2W vs. Placebo (95% CI)**	**Q4W vs. Placebo (95% CI)**
Age (years)					
< 65 (283, 143, 71)	48%	45%	28%	20% (7%, 32%)	17% (3%, 30%)
≥ 65 (6, 1, 1)	50%	100%	100%	-50% (-90%, -10%)	0% (NC)
Sex					
Female (176, 98, 44)	50%	44%	35%	15% (-1%, 31%)	9% (-8%, 27%)
Male (113, 46, 28)	45%	48%	20%	25% (7%, 43%)	28% (6%, 49%)
Race					
White (233, 105, 55)	48%	42%	26%	22% (8%, 35%)	16% (1%, 31%)
Non-White (56, 39, 17)	48%	53%	39%	9% (-18%, 36%)	15% (-15%, 44%)
Ethnicity					
Hispanic or Latino (20, 13, 4)	45%	69%	0%	45% (21%, 69%)	69% (42%, 96%)
Not Hispanic or Latino / Missing (269, 131, 68)	48%	43%	31%	17% (4%, 30%)	12% (-2%, 26%)
Weight (kg)					
< 100 (166, 66, 47)	49%	41%	30%	20% (4%, 35%)	12% (-6%, 30%)
≥ 100 (120, 78, 25)	45%	48%	28%	18% (-3%, 38%)	21% (-1%, 43%)
Missing (3, 0, 0)	52%	-	-	-	-
Smoking Status					
Never (111, 62, 27)	49%	55%	30%	19% (0%, 39%)	25% (4%, 47%)
Current (127, 53, 37)	47%	38%	28%	19% (2%, 37%)	10% (-10%, 30%)
Former (43, 28, 7)	50%	37%	23%	28% (-9%, 65%)	14% (-24%, 53%)
Missing (8, 1, 1)	24%	44%	100%	-76% (NC)	-56% (NC)
Country					
United States (115, 66, 25)	46%	49%	31%	14% (-7%, 35%)	18% (-5%, 41%)
Outside United States (174, 78, 47)	49%	42%	28%	21% (6%, 36%)	14% (-3%, 31%)
Hurley Stage at Baseline (Derived)[3]					
II (149, 71, 34)	53%	43%	30%	23% (5%, 41%)	13% (-7%, 33%)
III (140, 73, 38)	42%	47%	28%	14% (-3%, 31%)	19% (3%, 38%)
Antibiotic Use at Baseline (Derived)[4]					
No (262, 136, 67)	48%	46%	30%	19% (6%, 31%)	16% (2%, 30%)
Yes (27, 8, 5)	43%	38%	20%	23% (-17%, 63%)	18% (-31%, 66%)

Subgroup (N_{BQ2W}, N_{BQ4W}, N_P)[2]	Bimekizumab 320 mg Q2W (N=289)	Bimekizumab 320 mg Q4W (N=144)	Placebo (N=72)	Difference Q2W vs. Placebo (95% CI)	Difference Q4W vs. Placebo (95% CI)
Prior Biologic Therapy					
No (213, 113, 53)	51%	46%	36%	15% (0%, 30%)	10% (-6%, 27%)
Yes (76, 31, 19)	39%	42%	11%	28% (10%, 46%)	31% (8%, 54%)

Source: Statistical Reviewer's Analysis (similar as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
[2] N_{BQ2W}: subgroup sample size for bimekizumab 320 mg Q2W; N_{BQ4W}: subgroup sample size for bimekizumab 320 mg Q4W; N_P: subgroup sample size for placebo.
[3] Derived Hurley Stage for each subject was the worst overall Hurley Stage derived from the Hurley Stages recorded across all anatomical regions.
[4] Derived antibiotic use at baseline was defined as eCRF record of a stable dose and regimen of systemic tetracycline use for at least 28 days prior to baseline; otherwise, derived antibiotic use at baseline was defined as "No".
NC: Not Calculable.

Table 23: Results of the Primary Efficacy Endpoint at Week 16 by Age, Sex, Race, Ethnicity, Weight, Smoking Status, Country, Hurley Stage at Baseline, Antibiotic Use at Baseline, and Prior Biologic Therapy for Trial HS0004 (RS[1])

Subgroup (N_{BQ2W}, N_{BQ4W}, N_P)[2]	Bimekizumab 320 mg Q2W (N=291)	Bimekizumab 320 mg Q4W (N=144)	Placebo (N=74)	Difference Q2W vs. Placebo (95% CI)	Difference Q4W vs. Placebo (95% CI)
Age (years)					
< 65 (287, 142, 70)	52%	53%	34%	18% (5%, 30%)	19% (5%, 33%)
≥ 65 (4, 2, 4)	75%	100%	0%	75% (33%, 100%)	100% (NC)
Sex					
Female (150, 77, 31)	51%	54%	34%	17% (-2%, 36%)	20% (-1%, 40%)
Male (141, 67, 43)	53%	53%	31%	22% (6%, 38%)	22% (4%, 41%)
Race					
White (232, 119, 64)	54%	52%	35%	19% (6%, 33%)	18% (3%, 33%)
Non-White (59, 25, 10)	43%	59%	17%	27% (-2%, 55%)	42% (11%, 74%)
Ethnicity					
Hispanic or Latino (15, 10, 5)	43%	53%	20%	23% (-20%, 67%)	33% (-15%, 80%)
Not Hispanic or Latino / Missing (276, 134, 69)	52%	54%	33%	19% (6%, 32%)	20% (6%, 35%)
Weight (kg)					
< 100 (189, 84, 40)	56%	57%	36%	20% (4%, 37%)	21% (3%, 39%)
≥ 100 (102, 59, 34)	45%	50%	28%	16% (-2%, 34%)	21% (1%, 42%)
Missing (0, 1, 0)	-	29%	-	-	-
Smoking Status					
Never (106, 57, 26)	58%	66%	33%	25% (4%, 46%)	32% (10%, 55%)
Current (134, 73, 38)	47%	44%	35%	12% (-5%, 30%)	9% (-10%, 29%)
Former (49, 14, 10)	51%	53%	20%	31% (3%, 60%)	33% (-4%, 69%)
Missing (2, 0, 0)	68%	-	-	-	-
Country					
United States (62, 34, 17)	43%	58%	22%	22% (-2%, 46%)	36% (10%, 62%)
Outside United States (229, 110, 57)	54%	52%	35%	19% (5%, 33%)	17% (1%, 33%)
Hurley Stage at Baseline (Derived)[3]					
II (177, 89, 45)	58%	55%	29%	29% (14%, 45%)	26% (9%, 44%)

Subgroup (N_{BQ2W}, N_{BQ4W}, N_P)[2]	Bimekizumab 320 mg Q2W (N=291)	Bimekizumab 320 mg Q4W (N=144)	Placebo (N=74)	Difference Q2W vs. Placebo (95% CI)	Difference Q4W vs. Placebo (95% CI)
III (114, 55, 29)	42%	51%	38%	4% (-15%, 24%)	13% (-9%, 35%)
Antibiotic Use at Baseline (Derived)[4]					
No (261, 134, 68)	52%	54%	35%	17% (3%, 30%)	19% (4%, 33%)
Yes (30, 10, 6)	55%	50%	0%	55% (36%, 73%)	50% (16%, 84%)
Prior Biologic Therapy					
No (250, 128, 64)	51%	53%	30%	22% (9%, 35%)	24% (9%, 38%)
Yes (41, 16, 10)	57%	56%	50%	7% (-27%, 42%)	6% (-33%, 46%)

Source: Statistical Reviewer's Analysis (similar as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects. Subjects with an ICE (i.e., antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. Missing data was imputed using multiple imputation (MI).
[2] N_{BQ2W}: subgroup sample size for bimekizumab 320 mg Q2W; N_{BQ4W}: subgroup sample size for bimekizumab 320 mg Q4W; N_P: subgroup sample size for placebo.
[3] Derived Hurley Stage for each subject was the worst overall Hurley Stage derived from the Hurley Stages recorded across all anatomical regions.
[4] Derived antibiotic use at baseline was defined as eCRF record of a stable dose and regimen of systemic tetracycline use for at least 28 days prior to baseline; otherwise, derived antibiotic use at baseline was defined as "No".
NC: Not Calculable.

8.1.10. Additional Efficacy Considerations

Review of COAs for Evaluation of Clinical Benefit

The Applicant submitted an evidence dossier for the HSSDD Worst Skin Pain item. The HSSDD Worst Skin Pain item was reviewed for content validity, other measurement properties, and score interpretability (i.e., meaningful score change).

Content Validity

The Applicant completed the following instrument development activities to evaluate the content validity of the HSSDD Worst Skin Pain item:

- Literature review and PRO Gap Analysis
- Expert input (interviews with key opinion leaders)
- Item generation
- Patient input (cognitive interviews and usability testing)

The review team evaluated the data generated from these instrument development activities.

Based on the evidence submitted the HSSDD Worst HS Skin Pain item assesses an important aspect of HS (i.e., pain intensity). The HSSDD Worst HS Skin Pain item appears to be well-understood; however, patients did not use the term "skin pain" when characterizing their HS experience.

Refer to the full COA review by Yasmin Choudhry, M.D. from the Division of Clinical Outcome Assessment (DCOA) for detailed results of the content validity of these COAs.

Other Measurement Properties (Reliability, Construct validity, Responsiveness)

The Applicant evaluated other measurement properties of the HSSDD Worst Skin Pain item using pooled blinded data from Studies HS0003 and HS0004. The other measurement properties of the HSSDD Worst Skin Pain item were generally within acceptable and within reasonable range.

Refer to the full review by Yasmin Choudhry, M.D., from DCOA, dated October 11, 2024 for a detailed discussion of the other measurement properties of these COAs.

Score Interpretability of skin pain

Background
The Agency recommends the use of anchor-based methods to establish meaningful within-patient change in COA-based endpoint scores, although other methods (e.g., qualitative evidence) can be used (April 2023[8]). The Applicant conducted anchor-based analyses supplemented with empirical cumulative distribution function (eCDF) curves to evaluate clinically meaningful within-patient change in HSSDD worst skin pain item from baseline to Week 16 using the Patient Global Impression of Severity in Skin Pain (PGI-S-SP) and Patient Global Impression of Change of Severity in Skin Pain (PGI-C-SP) as anchor measures (Appendix B of the DCOA Review dated October 11, 2024) and data collected from their phase 3 trials (HS0003 and HS0004). The Applicant identified a range of clinically meaningful within-patient change thresholds from baseline to Week 16 of a 3- to 4- point decrease, which corresponds to the mean and median decrease in the HSSDD Worst Skin Pain item for subjects who reported a 2-category improvement on the PGI-S-SP measure and the mean decrease in the HSSDD Worst Skin Pain for patients who reported "much better" on the PGI-C-SP measure.

Refer to Appendix 19.6.4 for a review of the Applicant's strategy to establish meaningful within-patient change in COA-based endpoint scores.

Conclusion
From a COA perspective, the HSSDD Worst HS Skin Pain score could potentially support labeling claims, if supported by the study design and statistical analysis. Given that the results for the HSSDD Worst HS Skin Pain-based endpoints were not statistically significant, a descriptive claim could be an alternative option. However, the term "skin pain" should be further defined.

[8] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-incorporating-clinical-outcome-assessments-endpoints-regulatory

Anchor-based analyses to assess meaningful within-patient change in the HSSDD Worst Skin Pain score between Baseline and Week 16 indicates patients consider a reduction of between 2.4 and 4.8 points to be meaningful. The observed treatment effect on the HSSDD Worst Skin Pain endpoint substantiated a clinically meaningful within-patient improvement in patients receiving bimekizumab compared to placebo.

8.2.Review of Safety

8.2.1. Safety Review Approach

The primary review of the safety of bimekizumab for the treatment of moderate to severe hidradenitis suppurativa (HS) focused on pooled data from phase 3 trials HS0003 and HS0004. Long-term safety data was provided by the ongoing phase 3, open-label, long term extension Trial HS0005. Supportive safety data was provided by phase 2 Trial HS0001.

The phase 3 trials were conducted in adult subjects with moderate to severe HS, defined as HS lesions in at least 2 distinct anatomic areas, 1 of which must have been Hurley Stage II or III, and a total of 5 or more inflammatory lesions (AN, defined as abscesses plus inflammatory nodules) at the Screening and Baseline Visits. Subjects were also required to have a history of inadequate response to a course of a systemic antibiotics for treatment of HS. Subjects in Trial HS0001 were required to have moderate to severe HS, defined as having HS lesions present in at least 2 distinct anatomic areas, 1 of which must have been at least Hurley Stage II or III; and an AN count ≥3 at the Baseline Visit. Refer to Section 8.1.2 Study Endpoints for a description of the Hurley Staging system. Subjects were also required to have a history of inadequate response to a course of a systemic antibiotics for treatment of HS.

As previously discussed, (Section 8.1.1), Trials HS0003 and HS0004 were phase 3, randomized, double-blind, placebo-controlled, multicenter trials of identical design. Subjects were randomized 2:2:2:1 to the following treatment arms:

- Bimekizumab (BKZ) 320 mg every 2 weeks (Q2W) for the 16-week double-blind Initial Treatment Period, followed by BKZ 320 mg Q2W in the 32-week (Weeks 16-48) double-blind Maintenance Treatment Period (Q2W/Q2W)
- BKZ 320 mg Q4W in the Initial Treatment Period, followed by BKZ 320 mg Q4W in the Maintenance Treatment Period (Q4W/Q4W)
- BKZ 320 mg Q2W in the Initial Treatment Period, followed by BKZ 320 mg Q4W in the Maintenance Treatment Period (Q2W/Q4W)
- Placebo in the Initial Treatment Period, followed by BKZ 320 mg Q2W in the Maintenance Treatment Period (PBO/Q2W)

Trial HS0005 is an ongoing open-label, parallel-group, multicenter, extension trial. Trial HS0005 included subjects who completed Trials HS0003 or HS0004 and achieved a 25% or greater improvement in AN count. Treatment assignment in HS0005 was based on achievement of a

90% or greater reduction in total AN count relative to feeder trial baseline (HiSCR90). Subjects who achieved HiSCR90 response in the feeder trials were treated with BKZ 320 mg Q4W. Subjects who did not achieve HiSCR90 response were treated with BKZ 320 mg Q2W. Subjects in the Q4W arm who did not sustain an average improvement in AN count of ≥90% from feeder trial baseline over any 8-week consecutive period, or if a subject had ≤75% improvement in AN count from feeder trial baseline at any single visit, could be increased to BKZ 320 mg Q2W at the investigator's discretion. No further dosage adjustments were permitted for such subjects in the open-label extension (OLE) period.

The analysis of the safety of BKZ for the treatment of HS was performed using the following pools of safety data:

- Pool S1: The primary analysis dataset for the review of safety included pooled data from the placebo-controlled Initial Treatment Period (Weeks 0-16) of phase 3 Trials HS0003 and HS0004.
- Pool S2: This is comprised of data from the Initial and Maintenance Treatment Periods (Baseline to Week 48) of Trials HS0003 and HS0004 and supported the analysis of safety through Week 48 as well as the comparative safety of the dosing regimens. The review team conducted separate safety analyses for Weeks 0-48 and Weeks 16-48.
- Pool S3: This is comprised of data from phase 2 Trial HS0001, phase 3 Trials HS0003 and HS0004, and the ongoing open-label extension Trial HS0005 through the data cutoff (November 15, 2022). Because Trial HS0001 evaluated different dosing regimens and had different entry criteria, safety data from this trial was analyzed separately. The review team focused on data from Trials HS0003, HS0004, and HS0005 for Pool S3.

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

8.2.2. Review of the Safety Database

Overall Exposure

As described in the previous section, the primary analysis dataset (Pool S1) for the review of safety of bimekizumab (BKZ) for the treatment of moderate to severe HS included pooled data from the placebo-controlled Initial Treatment Period (Weeks 0-16) of phase 3 Trials HS0003 and

HS0004. The safety population for Pool S1 included 576 subjects treated with BKZ 320 mg Q2W, 285 subjects treated with BKZ 320 mg Q4W, and 146 subjects treated with placebo. Pool S2 consisted of data from the Initial and Maintenance Treatment Periods (Baseline to Week 48) of Trials HS0003 and HS0004 and supported the analysis of safety through Week 48 as well as the comparative safety of the dosing regimens.

The safety population for Pool S2 consisted of 285 subjects treated with BKZ 320 mg Q2W/Q2W, 291 subjects treated with BKZ 320 mg Q2W/Q4W, 285 subjects treated with BKZ 320 mg Q4W/Q4W, and 134 subjects treated with placebo/BKZ 320 mg Q2W. Pool S3 consisted of data from phase 2 Trial HS0001, phase 3 Trials HS0003 and HS0004, and the ongoing open-label extension Trial HS0005 through the data cutoff (November 17, 2023 for the 120-day safety update). Because Trial HS0001 evaluated different dosing regimens and had different entry criteria, safety data from this trial was analyzed separately and the review team focused on data from Trials HS0003, HS0004, and HS0005 for Pool S3. As of the 120-day safety update, the safety population for Pool S3 consisted of 833 subjects treated with BKZ 320 mg Q2W and 685 subjects treated with BKZ 320 mg Q4W. Safety data from these populations were analyzed according to the treatment that subjects received.

The Applicant provided an overall summary of exposure in the 120-day Safety Update. During the phase 3 trials in subjects with moderate to severe HS, a total of 995 subjects were exposed to bimekizumab, including 649 subjects with ≥12 months exposure and 496 with ≥24 months exposure. The overall exposure to bimekizumab in the phase 3 trials for HS was 1668.3 patient-years.

Relevant characteristics of the safety population:

In Pool S1, the majority of subjects were white (79.7%) and female (56.7%). The mean age was 36.6 years (range 18 years to 78 years) and a total of 18 (1.8%) subjects were 65 years of age and older. The demographic characteristics were comparable across treatment groups. Refer to Section 8.1.4 for summary demographic information for Pool S1.

The most common concomitant conditions reported in medical histories of subjects in the phase 3 population included hypertension (19.8%), obesity (36%), and depression (14.0%).

Adequacy of the safety database:

The total subject exposure to bimekizumab 320 mg Q2W or Q4W for the treatment of moderate to severe HS provides adequate data for the evaluation of safety. The demographics of the study population are sufficiently representative of the target population. The total exposures for up to 1 year are sufficient to characterize the safety of the product over longer treatment periods.

8.2.3. Adequacy of Applicant's Clinical Safety Assessments

Issues Regarding Data Integrity and Submission Quality

Overall, the quality of the data submitted is adequate to characterize the safety and efficacy of bimekizumab for the treatment of HS. We evaluated data quality and fitness in conjunction with the Office of Computational Science (OCS) Clinical Services and OCS Specialized Analysis Support Teams. We discovered no significant deficiencies that would impede a thorough analysis of the data presented by the Applicant.

Categorization of Adverse Events

The Applicant defined an adverse event (AE) as "any untoward medical occurrence in a patient or clinical study participant, temporally associated with the use of study medication, whether or not considered related to the study medication." The Applicant defined a treatment-emergent adverse event (TEAE) as "those AEs that had a start date on or following the first dose of study treatment through the final dose of study treatment + 140 days (covering the 20-week Safety Follow-up [SFU] Period). If it was not possible (due to partial dates) to determine whether or not an AE was treatment-emergent, then it was assumed to be a TEAE." TEAEs form the primary basis for the review of safety. The Applicant classified TEAEs based on the Medical Dictionary for Regulatory Activities (MedDRA) Version 19.0.

AEs were collected as spontaneous reports by the subjects or as observed by the Investigator at each visit and recorded in the electronic Case Report form (eCRF). Investigators were instructed to report any AE that was experienced by a subject during all phases of study participation and to follow the AE until it had resolved, had stable sequelae, the Investigator determined that it was no longer clinically significant, or the subject was lost to follow up. Investigators also recorded their assessment of relationship of the AE to study drug. The severity of AEs was characterized by investigators using the following categories:

- Mild: An event that is easily tolerated by the participant, causing minimal discomfort and not interfering with everyday activities.
- Moderate: An event that causes sufficient discomfort and interferes with normal everyday activities.
- Severe: An event that prevents normal everyday activities. An AE that is assessed as severe should not be confused with a SAE. Severe is a category utilized for rating the intensity of an event; and both AEs and SAEs can be assessed as severe.

The investigators used the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE) as a supportive standardization instrument to evaluate AEs and SAEs. The Applicant classified the severity of abnormal laboratory values using CTCAE Version 4.03.

The Applicant defined a serious AE (SAE) as any AE that results in any of the following outcomes:

- Death
- Life threatening

  (Life threatening did not include a reaction that might have caused death had it occurred in a more severe form.)
- Significant or persistent disability/incapacity
- Congenital anomaly/birth defect (including that occurring in a fetus)
- Important medical event that, based upon appropriate medical judgment, may have jeopardized the patient or study participant and may have required medical or surgical intervention to prevent 1 of the other outcomes listed in the definition of serious AE (Important medical events may have included, but have not been limited to, potential Hy's Law, allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that did not result in inpatient hospitalization, or the development of drug dependency or drug abuse.)
- Initial inpatient hospitalization or prolongation of hospitalization

Confirmed active tuberculosis (TB) was also to be reported as an SAE. If an SAE was reported, the investigator was required to inform the Applicant within 24 hours of receipt of this information by the site.

If an Investigator was notified that a subject had become pregnant after the first intake of any investigational medicinal product (IMP), the Investigator immediately notified the Applicant by providing the completed Pregnancy Report and Outcome form. The subject was withdrawn from the study as soon as pregnancy was known (by positive pregnancy test), and the following were completed:

- The subject returned for an early discontinuation visit.
- The subject immediately stopped the intake of the IMP.
- A safety follow-up (SFU) Visit was scheduled 20 weeks after the subject has discontinued her IMP.

Investigators followed the progression of the pregnancy and the eventual outcome, including following the health of the infant (if applicable) for up to 12 months after the date of delivery. The Applicant considered abnormal pregnancy outcomes (e.g., spontaneous abortion, fetal death, stillbirth, congenital anomalies, ectopic pregnancy) to be SAEs.

The Applicant also designated adverse events of special interest (AESI), which are listed in Section 8.2.1 of this review and discussed in more detail in Section 8.2.5 of this review.

Routine Clinical Tests

The Applicant's safety assessments included clinical evaluation of AEs, SAEs, vital signs, physical examinations, clinical laboratory evaluation (chemistry, hematology, and urinalysis), and ECGs. Safety assessments also included pregnancy testing at Screening and periodically throughout the trials. Investigators assessed subjects for the development of suicidal ideation and behavior using the Columbia Suicide Severity Rating Scale (C-SSRS) in all trials, the Hospital Anxiety and Depression Scale (HADS) during the phase 2 trial, and the Patients' Health Questionnaire 9 (PHQ-9) during the phase 3 trials. Subjects were tested at Screening for tuberculosis (TB) and were reassessed periodically using a TB risk assessment questionnaire. The schedules of safety assessments were identical in phase 3 Trials HS0003 and HS0004.

8.2.4. Safety Results

Deaths

The Applicant reported 2 deaths in the initial sBLA submission. There were no additional deaths reported in the 120-Day Safety Update. The Applicant considered neither of the deaths to be related to treatment with BKZ. Brief narratives for these subjects are provided below:

- A 45-year-old (y/o) black male (Subject (b) (6) with a history of multiple risk factors for cardiovascular disease who was enrolled in Trial HS0003 and received BKZ 320 mg Q2W/Q2W, developed an SAE of moderate "acute-on-chronic" cardiac failure on Day 89, 3 days following his most recent dose of BKZ. Pertinent past medical history included history of (h/o) smoking for 20 years (average of 2 cigars per day), cardiac catheterization, hypertension, diabetes mellitus (treated with metformin and liraglutide injection), myocardial infarction, pacemaker, cardiac ventricular thrombosis, left ventricular hypertrophy, congestive cardiac failure, and ischemic cardiomyopathy. The healthcare provider attributed cardiac failure to dietary indiscretion with recent increase of fluid and salt intake as well as noncompliance with medications. The subject was hospitalized, responded well to treatment, and was discharged after 2 days. This SAE of cardiac failure was moderate in severity and resolved. The SAE was considered not related to treatment with BKZ. The subject remained in the trial and continued treatment with BKZ.

  Subsequently, the subject suffered a fatal event of "Cardiac failure congestive with sudden cardiac death" on Day 254, 14 days following his most recent dose of BKZ. He was found unresponsive at home and pronounced dead by paramedics. He had reportedly been noncompliant with diuretic therapy. No autopsy was performed. This case was an adjudicated MACE. Given the subject's extensive cardiac comorbidities which were present prior to enrollment, I concur that the death was unlikely related to treatment with BKZ.

- A 43 y/o white male (Subject (b) (6) with a history of multiple subcutaneous fistulas in the gluteal area, para-sacral abscess and chronic osteomyelitis of coccyx who

received BKZ 320 mg Q4W/Q4W developed a possible central nervous system (CNS) infection and died on Day 385. After the subject completed Trial HS0003, he enrolled in Trial HS0005 and received BKZ 320 mg Q2W. The subject developed sepsis with CNS infection and multiorgan failure that required mechanical ventilation and pressor therapy. He subsequently developed brain death. The SAEs of CNS infection and death occurred approximately 385 days after his first dose of BKZ in Trial HS0003, 50 days after the first dose in Trial HS0005 and 7 days following his most recent dose of BKZ. An autopsy was not performed. The immediate causes of death per the death certificate were "brain death, cytotoxic cerebral edema, septic encephalopathy, multiple organ dysfunction syndrome, soft tissue infection-osteomyelitis, and septic shock".

The Applicant reported confounding comorbidities of worsening of HS (chronic HS lesions including multiple subcutaneous fistulas in the gluteal area), parasacral abscess, chronic osteomyelitis of coccyx, and tobacco smoking (20 cigarettes/day for 16 years). The event was severe in intensity. The investigator and the Applicant considered the fatal event not related to treatment with BKZ. However, given the potential for immunosuppression for BKZ, I cannot exclude a possible relationship of this fatal event to treatment with BKZ.

Serious Adverse Events

Pool S1

In Pool S1, which is comprised of the 16-week placebo controlled Initial Treatment Periods of Trials HS0003 and HS0004, serious adverse events (SAEs) in each treatment group were reported by:

- BKZ 320 mg Q2W: 15/576 (2.6%; exposure-adjusted incidence rate [EAIR] 8.7/100 patient-years [pt-yrs])
- BKZ 320 mg Q4W: 7/285 (2.5%; EAIR 8.1/100 pt-yrs)
- Placebo: 0

The only SAE preferred term reported in more than 1 subject during this period was hidradenitis, which was reported in 3/576 (0.5%) of subjects in the BKZ 320 mg Q2W group. SAEs were reported most frequently in the system-organ classes (SOCs) of Skin and subcutaneous disorders, gastrointestinal disorders, and hepatobiliary disorders. For the SOC of Skin and subcutaneous disorders, SAEs were reported in 4/576 (0.7%) of subjects in the BKZ 320 mg Q2W group and 0 subjects in the BKZ 320 mg Q4W group. For the SOCs of gastrointestinal disorders and hepatobiliary disorders, SAEs were reported in 2/576 (0.3%) of subjects in the BKZ 320 mg Q2W group and in 1/285 (0.4%) of subjects in the BKZ 320 mg Q4W group. SAEs reported in Pool S1 by SOC and PT are presented in the table below.

Table 24: Serious AEs by SOC and PT

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any SAE	15 (2.6)	7 (2.5)	0 (0.0)
Skin and subcutaneous tissue disorders	4 (0.7)	0 (0.0)	0 (0.0)
Hidradenitis	3 (0.5)	0 (0.0)	0 (0.0)
Pain of skin	1 (0.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorders	2 (0.3)	1 (0.4)	0 (0.0)
Colitis ulcerative	1 (0.2)	0 (0.0)	0 (0.0)
Irritable bowel syndrome	1 (0.2)	0 (0.0)	0 (0.0)
Small intestinal obstruction	0 (0.0)	1 (0.4)	0 (0.0)
Hepatobiliary disorders	2 (0.3)	1 (0.4)	0 (0.0)
Cholelithiasis	1 (0.2)	1 (0.4)	0 (0.0)
Drug-induced liver injury	1 (0.2)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	1 (0.4)	0 (0.0)
Cardiac disorders	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac failure acute	1 (0.2)	0 (0.0)	0 (0.0)
Infections and infestations	1 (0.2)	0 (0.0)	0 (0.0)
Cellulitis	1 (0.2)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.2)	1 (0.4)	0 (0.0)
Meniscus injury	1 (0.2)	0 (0.0)	0 (0.0)
Fibula fracture	0 (0.0)	1 (0.4)	0 (0.0)
Tibia fracture	0 (0.0)	1 (0.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.2)	0 (0.0)	0 (0.0)
Rhabdomyolysis	1 (0.2)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.2)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.2)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	0 (0.0)	0 (0.0)
Pregnancy on contraceptive	1 (0.2)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	1 (0.2)	0 (0.0)	0 (0.0)
Menorrhagia	1 (0.2)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	1 (0.4)	0 (0.0)
Iron deficiency anaemia	0 (0.0)	1 (0.4)	0 (0.0)
Eye disorders	0 (0.0)	1 (0.4)	0 (0.0)
Keratitis	0 (0.0)	1 (0.4)	0 (0.0)
Psychiatric disorders	0 (0.0)	1 (0.4)	0 (0.0)
Suicidal ideation	0 (0.0)	1 (0.4)	0 (0.0)
Surgical and medical procedures	0 (0.0)	1 (0.4)	0 (0.0)
Abortion induced	0 (0.0)	1 (0.4)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S1" and TRT01A = "BKZ 320mg Q2W" (BKZ 320mg Q2W); TRT01A = "BKZ 320mg Q4W" and POOL = "S1" (BKZ 320mg Q4W); TRT01A = "Placebo" and POOL = "S1" (Placebo); TRTEMFL = "Y" and ANL01FL = "Y" and AESER = "Y" (Adverse Events).

The narrative for the subject who experienced an SAE of rhabdomyolysis is presented below. Additional selected narratives for subjects who experienced SAEs in Pool S1 are presented in the relevant subsections of Section 8.2.5 of this review.

- A 45 y/o Asian male (Subject (b) (6) with a h/o familial Mediterranean Fever (FMF), confirmed by genetic analysis, treated with colchicine was randomized to BKZ 320 mg Q2W. He had also begun treatment with doxycycline for HS approximately 1 month prior to randomization. On Day 76, and 6 days after his most recent dose of BKZ, the subject experienced an SAE of rhabdomyolysis requiring hospitalization. In the days prior to the event, he also had diarrhea and excessive sweating due to hot and humid weather which led to dehydration. The SAE of rhabdomyolysis was severe in intensity. Action taken with BKZ was drug interrupted. He later resumed treatment, completed Trial HS0004, and entered OLE Trial HS0005 without recurrence of rhabdomyolysis. The investigator and the Applicant considered the SAE not related to treatment with BKZ. The investigator considered the SAE of rhabdomyolysis to be related to treatment with colchicine and doxycycline with dehydration and recent alcohol consumption as a contributing factor. Treatment with colchicine, dehydration, and alcohol consumption are known to be risk factors for rhabdomyolysis[9]. As such, I concur with the investigator's conclusion.

Pool S2
Pool S2 is comprised of the combined Initial and Maintenance Treatment Periods of Trials HS0003 and HS0004 (Weeks 0-48). In Pool S2, the proportion of subjects who experienced SAEs by treatment group was as follows:

- BKZ 320 mg Q2W/Q2W: 23/285, 8.1%, EAIR 9.9/100 pt-yrs
- Placebo/BKZ 320 mg Q2W: 8/134, 6.0%, EAIR 10.0/100 pt-yrs
- BKZ 320 mg Q2W/Q4W: 13/291, 4.5%, EAIR 5.3/100 pt-yrs
- BKZ 320 mg Q4W/Q4W: 20/285, 7.0%, EAIR 8.6/100 pt-yrs

Overall, the EAIRs for SAEs were similar between Pool S1 and Pool S2. The EAIRs of SAEs in Pool S2 do not demonstrate a dose-response for SAEs. SAEs were reported most commonly in the SOCs of Infections and infestations, Skin and subcutaneous disorders, and Gastrointestinal disorders. SAE PTs reported by more than one subject in any treatment group were as follows:

- Cellulitis: 2/285 (0.7%), BKZ 320 mg Q2W/Q2W, none in other groups
- Hidradenitis:

[9] Bhai S, Dimachkie MM, 2024, Rhabdomyolysis: Epidemiology and Etiology, UpToDate.com, accessed 6/20/2024, most recent update 4/25/2024.

  - BKZ 320 mg Q2W/Q2W: 4/285 (1.4%)
  - Placebo/ BKZ 320 mg Q2W: 1/134 (0.7%)
  - BKZ 320 mg Q2W/Q4W: 2/291 (0.7%)
  - BKZ 320 mg Q4W/Q4W: 4/285 (1.4%)
- Suicidal ideation:
  - BKZ 320 mg Q2W/Q2W: 1/285 (0.4%)
  - Placebo/ BKZ 320 mg Q2W: 1/134 (0.7%)
  - BKZ 320 mg Q2W/Q4W: 0
  - BKZ 320 mg Q4W/Q4W: 2/285 (0.7%)

SAEs in Pool S2 by SOC are presented in the table below:

Table 25: Serious TEAEs by SOC, Pool S2

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any SAE	23 (8.1)	8 (6.0)	13 (4.5)	20 (7.0)
Infections and infestations	7 (2.5)	2 (1.5)	4 (1.4)	3 (1.1)
Skin and subcutaneous tissue disorders	6 (2.1)	1 (0.7)	3 (1.0)	5 (1.8)
Gastrointestinal disorders	3 (1.1)	2 (1.5)	1 (0.3)	2 (0.7)
Hepatobiliary disorders	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)
Vascular disorders	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)
Cardiac disorders	1 (0.4)	1 (0.7)	1 (0.3)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.7)	1 (0.3)	2 (0.7)
Musculoskeletal and connective tissue disorders	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (0.4)	1 (0.7)	1 (0.3)	2 (0.7)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.4)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S2" and TRTI1A = "BKZ 320mg Q2W/Q2W" (BKZ 320mg Q2W/Q2W); POOL = "S2" and TRTI1A = "Placebo/BKZ 320mg Q2W" (Placebo/BKZ 320mg Q2W); POOL = "S2" and TRTI1A = "BKZ 320mg Q2W/Q4W" (BKZ 320mg Q2W/Q4W); TRTI1A = "BKZ 320mg Q4W/Q4W" and POOL = "S2" (BKZ 320mg Q4W/Q4W); TRTEMFL = "Y" and ANL02FL = "Y" and AESER = "Y" (Adverse Events).

Selected narratives for subjects who experienced SAEs in Pool S2 are presented in the relevant subsections of Section 8.2.5 of this review. A table of SAEs by SOC and PT for Pool S2 is

presented in Appendix 19.6.1 of this review.

Pool S3

The safety analyses for Pool S3 focused on data from the Initial and Maintenance Periods of phase 3 Trials HS0003 and HS0004, and the ongoing open-label extension Trial HS0005 through the data cutoff for the initial BLA submission (November 15, 2022). In Pool S3, SAEs were reported as follows:

- BKZ 320 mg Q2W: 57/823 (6.9%; EAIR 8.0/100 pt-yrs)
- BKZ 320 mg Q4W: 39/650 (6.0%; EAIR 7.2/100 pt-yrs)

Pool S3 includes additional exposure in the OLE Trial HS0005. The additional exposure did not result in an increase in the EAIR for SAEs, nor a dose-response for the Q2W compared to the Q4W groups. As in Pool S2, SAEs were reported most commonly in the SOCs of Infections and infestations, Skin and subcutaneous disorders, and Gastrointestinal disorders. Most SAE PTs were reported for one subject in any treatment group. SAE PTs reported by more than one subject in any treatment group were as follows:

- Cellulitis: 2/823 (0.2%) in BKZ 320 mg Q2W, 1/650 (0.2%) in BKZ 320 mg Q4W
- Hidradenitis: 9/823 (1.1%) in BKZ 320 mg Q2W, 5/650 (0.8%) in BKZ 320 mg Q4W
- Meniscus injury: 2/823 (0.2%) in BKZ 320 mg Q2W, 0 in BKZ 320 mg Q4W
- Nephrolithiasis: 2/823 (0.2%) in BKZ 320 mg Q2W, 2/650 (0.3%) in BKZ 320 mg Q4W
- Suicidal Ideation: 2/823 (0.2%) in BKZ 320 mg Q2W, 3/650 (0.5%) in BKZ 320 mg Q4W
- Depression: 0 in BKZ 320 mg Q2W, 2/650 (0.3%) in BKZ 320 mg Q4W

SAEs in Pool S3 by SOC are presented in the table below:

Table 26: SAEs by SOC, Pool S3

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any SAE	57 (6.9)	39 (6.0)
Infections and infestations	13 (1.6)	9 (1.4)
Skin and subcutaneous tissue disorders	12 (1.5)	6 (0.9)
Gastrointestinal disorders	7 (0.9)	3 (0.5)
Injury, poisoning and procedural complications	5 (0.6)	3 (0.5)
Musculoskeletal and connective tissue disorders	4 (0.5)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.5)	2 (0.3)
Nervous system disorders	4 (0.5)	1 (0.2)
Renal and urinary disorders	4 (0.5)	2 (0.3)
Cardiac disorders	2 (0.2)	1 (0.2)
Hepatobiliary disorders	2 (0.2)	3 (0.5)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any SAE	57 (6.9)	39 (6.0)
Psychiatric disorders	2 (0.2)	4 (0.6)
Reproductive system and breast disorders	2 (0.2)	0 (0.0)
Vascular disorders	2 (0.2)	2 (0.3)
Congenital, familial and genetic disorders	1 (0.1)	0 (0.0)
General disorders and administration site conditions	1 (0.1)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	2 (0.3)
Blood and lymphatic system disorders	0 (0.0)	1 (0.2)
Ear and labyrinth disorders	0 (0.0)	1 (0.2)
Eye disorders	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	0 (0.0)	1 (0.2)
Surgical and medical procedures	0 (0.0)	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S3" and TRTNEW = "Phase 3 BKZ 320mg Q2W" (BKZ 320mg Q2W); POOL = "S3" and TRTNEW = "Phase 3 BKZ 320mg Q4W" (BKZ 320mg Q4W); TRTEMFL = "Y" and ANL03FL = "Y" and AESER = "Y" (Adverse Events).

Selected narratives for subjects who experienced SAEs in Pool S3 are presented in the relevant subsections of Section 8.2.5 of this review. A table of SAEs by SOC and PT for Pool S3 is presented in Appendix 19.6.1 of this review.

Overall, our analysis of SAEs was consistent with the established safety profile of BKZ and did not identify any new safety signals.

Dropouts and/or Discontinuations Due to Adverse Effects

Pool S1
In Pool S1, discontinuations because of AEs occurred in:

- BKZ 320 mg Q2W: 22/576 (3.8%; EAIR 12.8/100 pt-yrs) of subjects
- BKZ 320 mg Q4W: 9/285 (3.2%; EAIR 10.5/100 pt-yrs) of subjects
- Placebo : 1/146 (0.7%; EAIR 2.2/100 pt-yrs) of subjects

The only PTs for AEs leading to discontinuation reported in more than 1 subject in any treatment group were:

- Hidradenitis: 3/576 (0.5%) in subjects treated with BKZ 320 mg Q2W and 1/285 (0.4%) subject treated with BKZ 320 mg Q4W
- Psychiatric evaluation abnormal: 2/576 (0.3%) in subjects treated with BKZ 320 mg Q2W and 1/285 (0.4%) subject treated with BKZ 320 mg Q4W
- Diarrhea: 2/576 (0.3%) in subjects treated with BKZ 320 mg Q2W

- Oral candidiasis: 2/576 (0.3%) in subjects treated with BKZ 320 mg Q2W

The most common SOCs in which AEs leading to discontinuation occurred were Gastrointestinal Disorders, Skin and subcutaneous disorders, and Infections and infestations. AEs leading to discontinuation in Pool S1 are presented in the table below:

Table 27: AEs leading to Discontinuation by SOC and PT, Pool S1

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	22 (3.8)	9 (3.2)	1 (0.7)
Gastrointestinal disorders	6 (1.0)	2 (0.7)	1 (0.7)
Diarrhoea	2 (0.3)	0 (0.0)	0 (0.0)
Abdominal discomfort	1 (0.2)	0 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.2)	0 (0.0)	0 (0.0)
Gastrooesophageal reflux disease	1 (0.2)	0 (0.0)	0 (0.0)
Salivary gland mass	1 (0.2)	0 (0.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	1 (0.4)	0 (0.0)
Colitis microscopic	0 (0.0)	1 (0.4)	0 (0.0)
Nausea	0 (0.0)	0 (0.0)	1 (0.7)
Skin and subcutaneous tissue disorders	6 (1.0)	1 (0.4)	0 (0.0)
Hidradenitis	3 (0.5)	1 (0.4)	0 (0.0)
Night sweats	1 (0.2)	0 (0.0)	0 (0.0)
Pain of skin	1 (0.2)	0 (0.0)	0 (0.0)
Psoriasis	1 (0.2)	0 (0.0)	0 (0.0)
Infections and infestations	5 (0.9)	2 (0.7)	0 (0.0)
Oral candidiasis	2 (0.3)	0 (0.0)	0 (0.0)
Folliculitis	1 (0.2)	0 (0.0)	0 (0.0)
Genital candidiasis	1 (0.2)	0 (0.0)	0 (0.0)
Nasopharyngitis	1 (0.2)	1 (0.4)	0 (0.0)
Esophageal candidiasis	1 (0.2)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	1 (0.4)	0 (0.0)
Vulvovaginal candidiasis	0 (0.0)	1 (0.4)	0 (0.0)
Investigations	2 (0.3)	2 (0.7)	0 (0.0)
Psychiatric evaluation abnormal	2 (0.3)	1 (0.4)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	1 (0.4)	0 (0.0)
Aspartate aminotransferase increased	0 (0.0)	1 (0.4)	0 (0.0)
General disorders and administration site conditions	1 (0.2)	0 (0.0)	1 (0.7)
Injection site erythema	1 (0.2)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	1 (0.7)
Hepatobiliary disorders	1 (0.2)	0 (0.0)	0 (0.0)
Drug-induced liver injury	1 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (0.2)	0 (0.0)	0 (0.0)
Arthralgia	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	22 (3.8)	9 (3.2)	1 (0.7)
Neoplasms benign, malignant, and unspecified (incl cysts and polyps)	1 (0.2)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.2)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.2)	0 (0.0)	0 (0.0)
Migraine	1 (0.2)	0 (0.0)	0 (0.0)
Pregnancy, puerperium, and perinatal conditions	1 (0.2)	0 (0.0)	0 (0.0)
Pregnancy on contraceptive	1 (0.2)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (0.2)	3 (1.1)	0 (0.0)
Adjustment disorder	1 (0.2)	0 (0.0)	0 (0.0)
Alcohol abuse	0 (0.0)	1 (0.4)	0 (0.0)
Depression	0 (0.0)	1 (0.4)	0 (0.0)
Suicidal ideation	0 (0.0)	1 (0.4)	0 (0.0)
Reproductive system and breast disorders	1 (0.2)	0 (0.0)	0 (0.0)
Vulvovaginal pruritus	1 (0.2)	0 (0.0)	0 (0.0)
Vascular disorders	1 (0.2)	0 (0.0)	0 (0.0)
Hot flush	1 (0.2)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: TRT01A = "BKZ 320mg Q2W" and POOL = "S1" (BKZ 320mg Q2W); TRT01A = "BKZ 320mg Q4W" and POOL = "S1" (BKZ 320mg Q4W); TRT01A = "Placebo" and POOL = "S1" (Placebo); TRTEMFL = "Y" and ANL01FL = "Y" and AEDROP = "Y" (Adverse Events).

Selected narratives for subjects who experienced AEs leading to discontinuation in Pool S1 are presented in the relevant subsections of Section 8.2.5 of this review.

Pool S2

In Pool S2, from Weeks 0-48, the overall proportion of subjects who experienced AEs leading to discontinuation were higher than those reported from Week 0-16 in Pool S1. However, the EAIRs for AEs leading to discontinuation were similar to or less than the EAIRs for the BKZ groups from Week 0-16. AEs leading to discontinuation by treatment group for Week 0-48 in Pool S2 are as follows:

- BKZ 320 mg Q2W/Q2W: 17/285 (6.0%), EAIR 7.2/100 pt-yrs
- Placebo/BKZ 320 mg Q2W: 9/134 (6.7%), EAIR 11.3/100 pt-yrs
- BKZ 320 mg Q2W/Q4W: 20/291 (6.9%), EAIR 8.3/100 pt-yrs
- BKZ 320 mg Q4W/Q4W: 21/285 (7.4%), EAIR 9.0/100 pt-yrs

AEs leading to discontinuation in Pool S2 most commonly occurred in the SOCs of Gastrointestinal disorders, Skin and subcutaneous disorders, and Infections and infestations. Selected narratives for subjects who experienced AEs leading to discontinuation in Pool S2 are presented in the relevant subsections of Section 8.2.5 of this review. A table of AEs leading to

discontinuation for Pool S2 is presented in Appendix 19.6.1 of this review.

Pool S3
In Pool S3, the proportion of subjects with AEs leading to discontinuation were similar to or less than those reported for Pool S2. The EAIRs for these AEs were less than those reported for Pool S2. AEs leading to discontinuation from Week 0 until the data cutoff in Trial HS0005 were reported as follows:

- BKZ 320 mg Q2W: 53/823 (6.4%); EAIR 7.3/100 pt-yrs
- BKZ 320 mg Q4W: 35/650 (5.4%); EAIR 6.5/100 pt-yrs

Selected narratives for subjects with AEs leading to discontinuation in Pool S3 are presented in the relevant subsections of Section 8.2.5 of this review. A table of AEs leading to discontinuation for Pool S3 is presented in Appendix 19.6.1 of this review.

Significant Adverse Events

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

Treatment Emergent Adverse Events and Adverse Reactions

The primary analysis pool for treatment-emergent adverse events (TEAEs) and adverse reactions (ARs) for labeling is Pool S1. In Pool S1, treatment-emergent AEs (TEAEs) occurred in:

- BKZ 320 mg Q2W: 379/576 (65.8%); EAIR 399.9/100 pt-yrs
- BKZ 320 mg Q4W: 167/285 (58.6%); EAIR 332.6/100 pt-yrs
- Placebo: 90/146 (61.6); EAIR 343.0/100 pt-yrs

The SOCs for which TEAEs were most frequently reported were Infections and infestations, Skin and subcutaneous disorders, Gastrointestinal disorders, and General disorders and administration site conditions. A table of all TEAEs by SOC and PT for Pool S1 is presented in Appendix 19.6.1 of this review. TEAEs occurring in ≥1% in any BKZ Group and more frequently than placebo are presented in the table below.

Table 28: TEAEs by SOC and PT Occurring in **≥1%** in any BKZ Group and More Frequently than Placebo

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Infections and infestations	193 (33.5)	91 (31.9)	30 (20.5)
Oral candidiasis	41 (7.1)	7 (2.5)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Nasopharyngitis	23 (4.0)	10 (3.5)	3 (2.1)
Corona virus infection	20 (3.5)	5 (1.8)	2 (1.4)
Folliculitis	16 (2.8)	8 (2.8)	0 (0.0)
Vulvovaginal mycotic infection	10 (1.7)	5 (1.8)	0 (0.0)
Otitis externa	9 (1.6)	2 (0.7)	1 (0.7)
Upper respiratory tract infection	9 (1.6)	0 (0.0)	1 (0.7)
Pharyngitis	7 (1.2)	5 (1.8)	1 (0.7)
Tinea pedis	7 (1.2)	2 (0.7)	0 (0.0)
Vulvovaginal candidiasis	6 (1.0)	11 (3.9)	0 (0.0)
Sinusitis	5 (0.9)	3 (1.1)	1 (0.7)
Tonsillitis	5 (0.9)	4 (1.4)	0 (0.0)
Hordeolum	4 (0.7)	3 (1.1)	1 (0.7)
Fungal skin infection	3 (0.5)	4 (1.4)	1 (0.7)
Skin candida	3 (0.5)	3 (1.1)	0 (0.0)
Skin and subcutaneous tissue disorders	148 (25.7)	67 (23.5)	26 (17.8)
Eczema	14 (2.4)	5 (1.8)	2 (1.4)
Pruritus	13 (2.3)	6 (2.1)	1 (0.7)
Dermatitis contact	12 (2.1)	4 (1.4)	0 (0.0)
Seborrhoeic dermatitis	11 (1.9)	7 (2.5)	0 (0.0)
Acne	9 (1.6)	3 (1.1)	0 (0.0)
Urticaria	8 (1.4)	1 (0.4)	0 (0.0)
Dry skin	5 (0.9)	3 (1.1)	0 (0.0)
Intertrigo	5 (0.9)	8 (2.8)	2 (1.4)
Psoriasis	5 (0.9)	3 (1.1)	0 (0.0)
Dermatitis	4 (0.7)	4 (1.4)	0 (0.0)
Gastrointestinal disorders	102 (17.7)	39 (13.7)	20 (13.7)
Diarrhoea	36 (6.3)	17 (6.0)	7 (4.8)
Abdominal pain	13 (2.3)	4 (1.4)	2 (1.4)
Constipation	10 (1.7)	1 (0.4)	0 (0.0)
Nausea	10 (1.7)	8 (2.8)	3 (2.1)
Abdominal pain upper	9 (1.6)	1 (0.4)	2 (1.4)
Dyspepsia	6 (1.0)	1 (0.4)	0 (0.0)
Vomiting	5 (0.9)	3 (1.1)	1 (0.7)
Food poisoning	2 (0.3)	3 (1.1)	1 (0.7)
Haemorrhoids	2 (0.3)	3 (1.1)	1 (0.7)
General disorders and administration site conditions	90 (15.6)	38 (13.3)	13 (8.9)
Pyrexia	19 (3.3)	8 (2.8)	2 (1.4)
Fatigue	16 (2.8)	8 (2.8)	3 (2.1)
Injection site reaction	14 (2.4)	1 (0.4)	0 (0.0)
Asthenia	10 (1.7)	5 (1.8)	2 (1.4)
Injection site pain	9 (1.6)	8 (2.8)	1 (0.7)
Injection site erythema	7 (1.2)	1 (0.4)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Chills	4 (0.7)	4 (1.4)	1 (0.7)
Nervous system disorders	54 (9.4)	25 (8.8)	13 (8.9)
Investigations	43 (7.5)	23 (8.1)	16 (11.0)
Psychiatric evaluation abnormal	7 (1.2)	7 (2.5)	2 (1.4)
Musculoskeletal and connective tissue disorders	38 (6.6)	15 (5.3)	15 (10.3)
Myalgia	7 (1.2)	2 (0.7)	1 (0.7)
Musculoskeletal pain	2 (0.3)	3 (1.1)	0 (0.0)
Muscle spasms	0 (0.0)	3 (1.1)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	31 (5.4)	19 (6.7)	5 (3.4)
Oropharyngeal pain	15 (2.6)	4 (1.4)	2 (1.4)
Cough	6 (1.0)	5 (1.8)	1 (0.7)
Nasal congestion	1 (0.2)	4 (1.4)	0 (0.0)
Psychiatric disorders	23 (4.0)	16 (5.6)	4 (2.7)
Anxiety	6 (1.0)	3 (1.1)	1 (0.7)
Depression	6 (1.0)	5 (1.8)	1 (0.7)
Eye disorders	19 (3.3)	7 (2.5)	2 (1.4)
Blepharitis	4 (0.7)	3 (1.1)	1 (0.7)
Reproductive system and breast disorders	16 (2.8)	7 (2.5)	2 (1.4)
Ear and labyrinth disorders	13 (2.3)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.2)	3 (1.1)	0 (0.0)
Hepatobiliary disorders	6 (1.0)	1 (0.4)	0 (0.0)
Cardiac disorders	5 (0.9)	6 (2.1)	1 (0.7)
Tachycardia	1 (0.2)	4 (1.4)	1 (0.7)
Immune system disorders	3 (0.5)	0 (0.0)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S1" and TRT01A = "BKZ 320mg Q2W" (BKZ 320mg Q2W); TRT01A = "BKZ 320mg Q4W" and POOL = "S1" (BKZ 320mg Q4W); TRT01A = "Placebo" and POOL = "S1" (Placebo); TRTEMFL = "Y" and ANL01FL = "Y" (Adverse Events).
Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks

TEAEs related to AESIs are discussed in more detail in subsections of Section 8.5 of this review.

The TEAEs identified by the review team as adverse reactions (ARs) and reported as single PTs in Pool S1 are presented in the table below.

Table 29: ARs Defined by Single Preferred Terms, Pool S1

AR	BKZ 320 mg Q2W (N=576) n (%) EAIR	BKZ 320 mg Q4W (N=285) n (%) EAIR	Placebo (N=146) n (%) EAIR
Pyrexia	19 (3.3) 11.0	8 (2.8) 9.4	2 (1.4) 4.5
Fatigue	16 (2.8) 9.3	8 (2.8) 9.4	3 (2.1) 6.8
Folliculitis	16 (2.8) 9.3	8 (2.8) 9.3	0
Otitis Externa	9 (1.6) 5.2	2 (0.7) 2.3	1 (0.7) 2.2

Acne	9 (1.6) 5.2	3 (1.1) 3.5	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
Source: Reviewer's Table, data from OCS Specialized Analysis Service

To better evaluate the overall frequency of occurrence, the review team pooled preferred terms (PTs) for TEAEs for clinically similar events. The review team then identified imbalances in TEAEs occurring in ≥1% of subjects treated with BKZ and more frequently than placebo as potential ARs. These TEAEs are presented in the table below.

Table 30: Pooled Terms for Adverse Reactions, Pool S1

Pooled Term	BKZ 320 mg Q2W (N=576) n (%) EAIR	BKZ 320 mg Q4W (N=285) n (%) EAIR	Placebo (N=146) n (%) EAIR
Upper respiratory infections [a]	59 (10.2) 35.7	23 (8.1) 27.7	9 (6.2) 35.7
Oral candidiasis [b]	45 (7.8) 26.7	11 (3.9) 12.9	0
Injection site reactions [c]	37 (6.4) 22.2	13 (4.6) 15.4	2 (1.4) 4.5
Other Candida infections [d]	21 (3.6) 12.2	19 (6.7) 22.6	0
Tinea infections [e]	18 (3.1) 10.4	7 (2.5) 8.1	1 (0.7) 2.3
Herpes simplex infections [f]	3 (0.5) 1.7	2 (0.7) 2.3	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
[a] Upper Respiratory Infections - Includes high level term Upper respiratory tract infections plus the preferred terms Pharyngitis streptococcal, Pharyngitis bacterial, Influenza, and Viral upper respiratory tract infection.
[b] Oral Candidiasis - Includes the preferred terms Oral candidiasis, Esophageal candidiasis, Oropharyngeal candidiasis, and Oral fungal infection.
[c] Injection site reactions- Includes preferred terms Injection site pain, Injection site reaction, Injection site erythema, Injection site swelling, Injection site pruritus, Injection site bruising, Injection site urticaria, Injection site rash, Injection site discoloration, and Injection site hemorrhage
[d] Other Candida Infections - Includes preferred terms Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Skin candida, Genital candidiasis, Anal fungal infection, and Genital infection fungal.
[e] Tinea infections- Includes Tinea pedis, Body tinea, Dermatophytosis, Tinea capitis, Tinea cruris, Tinea manuum, Tinea versicolor, and Fungal skin infection.
[f] Herpes Simplex Infections - Includes preferred terms Oral herpes and Genital herpes
Source: Reviewer's table, data from Applicant

The following table is currently included in Section 6.1 (Adverse Reactions, Clinical Trials Experience) of approved labeling for BKZ (Adverse Reactions identified in the PsO development program):

Table 1: Adverse Reactions Occurring in ≥1% of Subjects with Plaque Psoriasis in the BIMZELX 320 mg Q4W Group and More Frequently than in the Placebo Group in Trials Ps-1 and Ps-2

	BIMZELX N=670 n (%)	**Placebo N=169 n (%)**
URI[a]	102 (15)	24 (14)
Oral Candidiasis[b]	61 (9)	0 (0)

	BIMZELX N=670 n (%)	**Placebo N=169 n (%)**
Headache	22 (3)	0 (0)
Injection Site Reactions[c]	19 (3)	2 (1)
Tinea Infections[d]	18 (3)	1 (1)
Gastroenteritis[e]	12 (2)	0 (0)
Herpes Simplex Infections[f]	9 (1)	0 (0)
Acne	8 (1)	0 (0)
Folliculitis	8 (1)	0 (0)
Other Candida Infections[g]	7 (1)	1 (1)
Fatigue	7 (1)	0 (0)

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

Adverse reactions that occurred in < 1% but > 0.1% of subjects in the BIMZELX group and at a higher rate than in the placebo group through Week 16 were **neutropenia, eczema, otitis externa, otitis media, and pyrexia**.

The pooled terms for ARs in Pool S1 are the same as those currently included in labeling for BKZ. The review team also noted imbalances for ARs of folliculitis, acne, fatigue, pyrexia, otitis externa, and otitis media (<1% of subjects in either BKZ group) which are also included in current labeling. In Pool S1, there were no imbalances for TEAEs of gastroenteritis or headache. Overall, TEAE PTs reported in Pool S1 were consistent with the established safety profile of BKZ. The review team identified no new safety signals or new ARs.

In Section 6.1 of labeling, under Hidradenitis Suppurativa Clinical Trials, the Applicant proposes to include the following statement: "The safety profile observed in subjects with hidradenitis suppurativa treated with BIMZELX was overall similar to the safety profile seen in subjects with plaque psoriasis." The Applicant also proposes to include data from the HS program in Section 6.1, Hidradenitis Suppurativa Clinical Trials, Specific Adverse Reactions, for subheadings of Suicidal Ideation and behavior, Infections, Inflammatory Bowel Disease, and Liver Biochemical Abnormalities. The review team concurs with the Applicant's proposal.

Specific labeling recommendations for Suicidal Ideation and behavior, Infections, Inflammatory Bowel Disease, and Liver Biochemical Abnormalities are presented in relevant subsections of

Section 8.2.5 of this review.

Long-Term Safety

Pool S2
Through Week 48 (Pool S2), overall TEAEs by treatment group were as follows:

- BKZ 320 mg Q2W/Q2W: 248/285 (87.0%); EAIR 297.5/100 pt-yrs
- Placebo/BKZ 320 mg Q2W: 102/134 (76.1%); EAIR 262.4/100 pt-yrs
- BKZ 320 mg Q2W/Q4W: 252/291 (86.6%); EAIR 325.5/100 pt-yrs
- BKZ 320 mg Q4W/Q4W: 235/285 (82.5%); EAIR 253.9/100 pt-yrs

Although the proportion of subjects reporting TEAEs in each treatment group were higher in Pool S2, the EAIRs for overall TEAEs were lower than those observed in Pool S1. As such, when adjusted for exposure, the rate of TEAEs did not increase with increased duration of exposure to BKZ. The SOCs in which TEAEs were most frequently reported in Pool S2 were the same as Pool S1.

Pool S3
In Pool S3, overall TEAEs by treatment group were as follows:

- BKZ 320 mg Q2W: 674/823 (81.9%); EAIR 281.3/100 pt-yrs
- BKZ 320 mg Q4W: 534/650 (82.2%); EAIR 266.2/100 pt-yrs

As in Pool S2, EAIRs for overall TEAEs were lower than those reported for Pool S1. As such, when adjusted for exposure, the rate of TEAEs did not increase with increased duration of exposure to BKZ. The SOCs in which TEAEs were most frequently reported in Pool S3 was the same as Pools S1 and S2. The review team identified no new safety signals or ARs in Pools S2 and S3.

Laboratory Findings

During the development program for HS, the evaluation of systemic safety included assessment of clinical laboratory data: hematology, serum chemistry, and urinalysis. Liver biochemistries and leukopenia, including neutropenia, will be discussed in Sections 8.2.5.3 and 8.2.5.7, respectively, of this review. Excluding these parameters, the Applicant reported no clinically meaningful changes from baseline in laboratory values.

The review team evaluated TEAEs related to laboratory abnormalities. These TEAEs, other than elevated liver enzymes and leukopenia/neutropenia, are discussed below. In Pool S1, TEAE PTs reported in >1 subject in any BKZ group and more frequently than placebo included the following:

- Blood cholesterol increased: BKZ 320 mg Q2W 2/576 (0.3%), BKZ 320 mg Q4W 1/285 (0.4%) and placebo 0
- Blood urea increased: BKZ 320 mg Q2W 2/576 (0.3%), BKZ 320 mg Q4W and placebo 0
- Blood uric acid increased: BKZ 320 mg Q2W 2/576 (0.3%), BKZ 320 mg Q4W and placebo 0
- Blood urine present: BKZ 320 mg Q2W 0, BKZ 320 mg Q4W 2/285 (0.7%), and placebo 0

All TEAEs were mild in severity except for 1 TEAE of blood urea increased (BKZ 320 mg Q2W) and 1 TEAE of Blood urine present (BKZ 320 mg Q4W), which were of moderate severity. None of these TEAEs were serious or led to discontinuation.

In Pool S2, no TEAEs regarding laboratory abnormalities, other than elevated liver enzymes and leukopenia/neutropenia, were serious or led to discontinuation.

Overall, the review team discovered no safety signal for laboratory abnormalities other than elevated liver enzymes and leukopenia/neutropenia, which are discussed elsewhere in this review.

Vital Signs

The Applicant's evaluation of safety included periodic assessment of vital signs. In Pool S1, the Applicant reported no clinically meaningful changes in mean vital signs (pulse rate, systolic BP, and diastolic BP) across treatment groups. The proportion of subjects with any post-baseline increase in systolic blood pressure >180 mm Hg and increase of ≥ 20 mmHg from baseline was 2/576 (0.3%) in the BKZ 320 mg Q2W group, 1/285 (0.4%) in the BKZ 320 mg Q4W group, and none in the placebo group. This increase in systolic blood pressure was not accompanied by an imbalance in elevations of diastolic blood pressure > 105 mmHg and increase of ≥ 15 mmHg from baseline compared with placebo. Such increases in diastolic blood pressure were reported in 8/576 (1.4%) in the BKZ 320 mg Q2W group, 1/285 (0.4%) in the BKZ 320 mg Q4W group, and 2/146 (1.4%) in the placebo group. In addition, there was no imbalance in TEAEs of Hypertension, which were reported in 5/576 (0.9%) in the BKZ 320 mg Q2W group, 0 in the BKZ 320 mg Q4W group, and 2/146 (1.4%) in the placebo group. As such, the review team did not consider the reported changes in blood pressure to be clinically meaningful.

The only TEAE PT for which an imbalance was noted in the BKZ groups compared to placebo was Pyrexia. Pyrexia was reported in 19/576 (3.3%) of subjects in the BKZ 320 mg Q2W group, 8/285 (2.8%) in the BKZ 320 mg Q4W group, and 2/146 (1.4%) in the placebo group. This corresponds to the observed imbalance in TEAEs in the system-organ class Infections and Infestations reported above. Pyrexia is included in Section 6.1 (Adverse Reactions) of approved labeling for BKZ.

Electrocardiograms (ECGs)

The review team evaluated cardiovascular safety in conjunction with consultants from the Division of Cardiology and Nephrology (DCN). Refer to section 8.2.5.6 of this review. During the development program, the Applicant evaluated the effect of BKZ on ECG parameters. Effects on the corrected QT interval (QTc) are discussed in the subsection below. No clinically meaningful trends were observed in ECG parameters during the phase 3 trials.

The review team also evaluated TEAEs related to ECG findings, which are presented in the table below. None of these TEAEs were serious or led to discontinuation. The review team, in consultation with reviewers from the Division of Cardiology and Nephrology (DCN) concluded that these events did not represent a cardiac safety signal for BKZ. Refer to the review by Selena DeConti, PharmD, MPH dated July 16, 2024.

Table 31: TEAEs Related to ECG Abnormalities, Pool S1

Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Atrioventricular block first degree	1 (0.2)	1 (0.4)	0 (0.0)
Bradycardia	1 (0.2)	0 (0.0)	0 (0.0)
Tachycardia	1 (0.2)	4 (1.4)	1 (0.7)
Bundle branch block left	0 (0.0)	1 (0.4)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S1" and TRT01A = "BKZ 320mg Q2W" (BKZ 320mg Q2W); TRT01A = "BKZ 320mg Q4W" and POOL = "S1" (BKZ 320mg Q4W); TRT01A = "Placebo" and POOL = "S1" (Placebo); TRTEMFL = "Y" and ANL01FL = "Y" (Adverse Events).

QT

The ICH E14 guideline regarding the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs does not specifically address QT assessments for biologic agents. Because of their large size and high target specificity, mAbs such as bimekizumab have a very low likelihood for ion channel interactions and therefore thorough QT/QTc studies are not generally needed.

Although a thorough QT study was not performed for bimekizumab, the Applicant nonetheless explored a relationship between BKZ and QTc during the development program for HS. In Pool S1 and S3, no trend in QTc was observed and no subjects had QT interval corrected for heart rate (Fridericia's formula) (QTcF) >480 ms.

In a consult review dated July 16, 2024, Dr. Selena DeConti from DCN stated the following:

> "Two subjects in the bimekizumab arms (1 subject each in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W) experienced prolonged QT (at one visit) compared with none in the placebo arm. Both events were reported as non-serious and reviewed by the CV-CAC; neither of these events led to study discontinuation or withdrawal of

> bimekizumab. Review of the ECG data did not raise concern for proarrhythmic potential."

Immunogenicity

Because therapeutic proteins have the potential to elicit an immune response, the Applicant evaluated subjects for the presence of anti-drug antibodies (ADAb) during the development program. During phase 3 trials, this included the evaluation of neutralizing antibodies (NAb). The assessment of immunogenicity is discussed in more detail in Sections 6.3.2 of this review.

Although frequencies for certain TEAEs were greater for subjects who were ADAb-positive, the 95% confidence intervals for the EAIRs overlap. As such, the review team concluded that the differences in TEAEs between ADAb-positive and ADAb-negative subjects were not clinically meaningful.

Per the Clinical Pharmacology team, based on the available data, the presence of ADAb and NAb had no clinically meaningful impact on the safety profile of bimekizumab in HS and was not associated with serious or severe hypersensitivity events.

8.2.5. Analysis of Submission-Specific Safety Issues

During the development program for HS, the Applicant monitored the adverse events of special interest (AESIs) identified during the development program for PsO. AESIs were events that were potentially related to the proposed mechanism of action for bimekizumab (immunomodulation via cytokine blockade, specifically IL-17A and IL-17F), effects associated with other anti-cytokine antibody therapies (including anti-IL-17A), and the specific risks and co-morbidities observed in the target population. The following were identified as AESIs:

- Suicidal Ideation/Behavior (SI/B)
- Inflammatory Bowel Disease
- Hepatotoxicity/DILI
- Infections (serious, opportunistic, fungal, and TB)
- Malignancies
- Major Adverse Cardiovascular Events (MACE)
- Neutropenia
- Hypersensitivity (including anaphylaxis) and Injection Site Reactions

The subsections below will present data regarding AESIs in the development program for HS.

8.2.5.1. Suicidal Ideation and Behavior

The Applicant evaluated suicidal ideation and behavior (SI/B) as an AESI in the HS development program because the data to support approval of BKZ for the treatment of moderate to severe plaque psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy included 1 completed suicide in a subject with no prior psychiatric history and 3 subjects with suicide attempts. To convey this potential risk to healthcare providers, currently approved labeling for BKZ includes the following language in Sections 5.1 and 6.1:

> 5.1 Suicidal Ideation and Behavior
> During the 16-week, placebo-controlled period of Trials Ps-1 and Ps-2, higher rates of suicidal ideation were reported in BIMZELX-treated subjects than in placebo-treated subjects.
>
> Suicidal ideation and behavior were prospectively monitored using the Columbia Suicide Severity Rating Scale (C-SSRS) in clinical trials of psoriasis. The C-SSRS is an interview-based instrument used to monitor for the presence and severity of suicidal ideation (ranging from "none" to "active suicidal ideation with specific plan and intent") and behaviors (rating the injury and potential lethality of self-injury, if present). Pooled analysis of C-SSRS data from two 16-week, placebo-controlled clinical trials indicated that 12/670 (1.8%) BIMZELX-treated subjects and 1/169 (0.6%) placebo-treated subjects reported passive suicidal ideation with an estimated relative risk of 3.0 (95% confidence interval: 0.39, 22.74). Subjects without a prior history of SI/B treated with BIMZELX also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects treated with placebo (1.3% vs. 0.6%). During the open-label extension trial, one completed suicide was reported in a BIMZELX-treated subject. *[see Adverse Reactions (6.1)].* A causal association between treatment with BIMZELX and increased risk of suicidal ideation and behavior has not been established.
>
> Prescribers should weigh the potential risks and benefits before using BIMZELX in patients with a history of severe depression or suicidal ideation or behavior. Advise patients, their caregivers, and families to monitor for the emergence or worsening of depression, suicidal ideation, or other mood changes. If such changes occur, advise them to promptly seek medical attention or ca l the National Suicide and Crisis Lifeline at 988 *[see Patient Counseling Information (17)]*. BIMZELX-treated patients with new or worsening symptoms of depression or suicidal ideation and/or behavior should be referred to a mental health professional, as appropriate. Prescribers should also re-evaluate the risks and benefits of continuing treatment with BIMZELX if such events occur.
>
> 6.1 Clinical Trials Experience, Specific Adverse Reactions

Suicidal Ideation and Behavior: The study populations of Trial Ps-1, Trial Ps-2, Trial Ps-3 and Trial Ps-4 excluded subjects with active suicidal ideation, suicidal ideation within the month prior to screening, a history of suicide attempt within the past 5 years prior to screening, or moderately severe to severe major depression (i.e., score of ≥15 on the screening Patient Health Questionnaire-9 (PHQ-9)).

Based on a pooled analysis of the first 16 weeks of the placebo controlled clinical trials, 12 of the 670 subjects in the BIMZELX group (1.8%) reported passive suicidal ideation on the C-SSRS compared to 1 of 169 subjects in the placebo group (0.6%).

During the course of the clinical trials for plaque psoriasis, there was 1 completed suicide in the open label extension trial after 718 days of treatment (1/2480; 0.01/100 patient-years). The completed suicide was reported in a subject without a past reported psychiatric history. There were also 3 suicide attempts (3/2480; 0.04/100 patient-years); 2 of these subjects had a history of prior suicide attempts.

To ensure the safety of enrolled subjects and to allow identification of a potential safety signal for SI/B in the development program for HS, the phase 3 Trials HS0003 and HS0004 included the following neuropsychiatric exclusion criteria:

- Presence of active SI or positive suicidal behavior (SB) using the "Screening" version of the eC-SSRS and with either of the following criteria:
    - History of suicide attempt within the past 5 years prior to Screening (subjects with a history of suicide attempt more than 5 years should be evaluated by a mental healthcare practitioner prior to enrolling)
    - SI in the past month prior to Screening based on a positive response to either question 4 or 5 of the "Screening" version of the eC-SSRS
- Moderately severe major depression or severe depression indicated by a PHQ-9 total score ≥ 15 at Screening
- In addition, medications used to treatment depression should be stable for 8 weeks prior to Baseline.

Safety monitoring in the phase 3 trials for BKZ for HS included active assessments for SI/B and depression. The protocol specified the administration of the eC-SSRS and PHQ-9 at Screening and Baseline, and then every 4 weeks throughout the trials. These instruments were also administered periodically throughout OLE Trial HS0005. These trials also included the following neuropsychiatric stopping criteria:

- Subjects must be referred immediately to a mental healthcare professional and must be withdrawn from the trial in the case of:
    - Active SI as indicated by a positive response to Question 5 on the "Since Last Visit" version of the eC-SSRS
    - Any SB since last visit

    - Severe major depression as indicated by PHQ-9 total score ≥ 20
- Subjects must be referred immediately to a mental healthcare professional and may be withdrawn from the trial based on Investigator's judgement for:
    - Active SI as indicated by a positive response to Question 4 on the "Since Last Visit" version of the eC-SSRS
    - Moderately severe major depression as indicated by PHQ-9 total score between 15 to 19, if this represents an increase of at least 3 points compared to last visit

We reviewed the neuropsychiatric AEs in the HS program in conjunction with consultants from the Division of Psychiatry (DP Review dated May 2, 2024). A brief summary of the review and analysis by consultants from DP is presented below:

> "The presented analysis included pooled data from two phase 3 studies (HS0003 and HS0004), and an independent description of study results from one phase 2 study (HS0001) and one open-label extension safety study (HS0005). Similar to the PsO development program, the results of the pooled analysis confirmed an increased risk for SI/B among subjects treated with bimekizumab relative to placebo (relative risk: 2.7). The Applicant also reported three suicidal attempts that occurred 1 to 2 years after treatment initiation. Although a casual association between treatment with bimekizumab and increased risk for SI/B cannot be definitely established, the consistent signal between the PsO and HS development program does support the Applicant's proposal to communicate the SI/B risk as a Warning and Precaution statement in the product label."

Additional information from the DP consult review, including subject narratives, is presented in Appendix 19.6.3 of this review.

Applicant's Proposed Labeling Changes (new text in red font, deleted text in strikethrough)

> 5.1 Suicidal Ideation and Behavior
>
> (b) (4)
>
> Suicidal ideation and behavior were prospectively monitored using the Columbia Suicide Severity Rating Scale (C-SSRS) in clinical trials. The C-SSRS is an interview-based instrument used to monitor for the presence and severity of suicidal ideation (ranging from "none" to "active suicidal ideation with specific plan and intent") and behaviors (rating the injury and potential lethality of self-injury, if present).
>
> During the placebo-controlled periods of Trials Ps-1, Ps-2, HS-1, and HS-2, higher rates of suicidal ideation as assessed by C-SSRS were reported in BIMZELX treated subjects than

in placebo treated subjects. A causal association between treatment with BIMZELX and increased risk of suicidal ideation and behavior has not been established.

(b) (4)

(b) (4)

Pooled analysis of C-SSRS data from two 16-week, placebo-controlled periods of Trials HS-1 and HS-2 indicated that 16/861 (1.9%) BIMZELX-treated subjects and 1/146 (0.7%) placebo-treated subjects reported suicidal ideation with an estimated relative risk of 2.70 (95% confidence interval: 0.36, 20.12). Subjects without a prior history of SI/B treated with BIMZELX also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects treated with placebo (0.9% vs. 0%). There were no completed suicides reported in Trials HS-1 and HS2*[see Adverse Reactions (6.1)]*.

(b) (4)

6.1 Adverse Reactions, Clinical Trials Experience

Hidradenitis Suppurativa Clinical Trials

Specific Adverse Reactions

(b) (4)

Consultants from DP stated their agreement with the Applicant's proposed labeling changes. From the DP consult review:

> "Because the risk for SI/B associated with bimekizumab appears to be similar between patients with PsO and HS, DP agrees with the Applicant's proposal to include language in Sections 5 (Warning and Precautions) and 6 (Adverse Drug Reactions) that parallels the description of the SI/B signal observed in the PsO development program. DP does not recommend any further labeling changes or additional risk mitigation strategies."

Refer to the Approval Letter for the final approved labeling text.

8.2.5.2. Inflammatory Bowel Disease

New onset or worsening of inflammatory bowel disease (IBD) is a known risk associated with IL-17A inhibitors. The Applicant conducted a proof-of-concept trial to evaluate BKZ for the treatment of active, moderate to severe ulcerative colitis (UC). However, this trial was terminated early based on an on an imbalance in TEAEs and SAEs between bimekizumab and placebo treatment together with an observed increase in clinical signs of UC. Because of this imbalance, both the PsO and HS development programs for BKZ identified IBD as an AESI. Currently approved labeling for BKZ includes the following:

> 5.5 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.
>
> 6.1 Clinical Trials Experience
>
> Specific Adverse Reactions
>
> *Inflammatory Bowel Disease:* In clinical trials in subjects with plaque psoriasis, subjects with active inflammatory bowel disease were excluded. In these trials, which included

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

To ensure the safety of enrolled subjects and to evaluate a potential safety signal for IBD in the development program for HS, the phase 3 Trials HS0003 and HS0004 included the following exclusion criterion:

- Subject has a diagnosis of sarcoidosis, systemic lupus erythematosus, or active IBD. Note: Subjects with a diagnosis of Crohn's disease or ulcerative colitis are allowed if they have no active symptomatic disease at Screening or Baseline.

In addition, the protocols required that subjects with newly diagnosed IBD or IBD flares during the trials must:

- Be referred, as appropriate, to a healthcare professional treating IBD, such as a gastroenterologist
- Discontinue IMP and be followed-up until resolution of active IBD symptoms

The review team evaluated AEs of IBD in conjunction with consultants from the Division of Gastroenterology (DG). In a review dated October 31, 2024, Dr. Arushi deFonseka stated the following:

> "In general, based on the clinical summaries/narratives provided by the (Applicant), the 8 cases that were adjudicated as "definite" or "probable" appear reasonably likely to represent IBD. Three of the cases occurred in subjects with a history of IBD, two of whom were on concomitant medications for the treatment and maintenance of IBD. Of the three cases that occurred in subjects with a history of IBD, two resulted in discontinuation of therapy, and in one case flare symptoms were successfully treated and study therapy was continued. A clear relationship between every 2 week dosing vs every 4 week dosing and development of IBD symptoms wasn't observed; however, the numbers of subjects in the study who developed new onset IBD or who had preexisting IBD were too small to draw definitive conclusions."

The Applicant proposed no changes to the labeling language in subsection 5.5 (Warnings and Precautions, Inflammatory Bowel Disease), and DG agreed that this was reasonable. DG proposed the following for inclusion in subsection 6.1 (~~strikeout~~ = deletion; <u>double underline</u> = addition):

Inflammatory Bowel Disease: In clinical trials in subjects with hidradenitis suppurativa, subjects with active inflammatory bowel disease were excluded. In these trials, which included (b) (4) 995 subjects exposed to BIMZELX accounting for (b) (4) 1272 patient-years, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC), Crohn's disease (CD) and (b) (4) BD-undetermined) occurred in (b) (4) 5 subjects (0. (b) (4) 39 per 100 patient-years); the majority of these cases were serious, and all resulted in discontinuation of therapy. Additionally, flares of pre-existing IBD occurred in 2 subjects, which resulted in discontinuation of therapy in both.

DDD concurs with the labeling recommendation from DG.

8.2.5.3. Hepatotoxicity/DILI

The phase 3 protocols for HS specified hepatotoxicity as an AESI because of data submitted to support approval of BKZ for the treatment of moderate to severe PsO. During review of the original BLA for PsO, the review team, in conjunction with consultants from the Drug-Induced Liver Injury (DILI) team from the Division of Hepatology and Nutrition (DHN), identified a safety signal for transaminase elevations and potential hepatocellular injury. Currently approved labeling for BKZ includes the following:

2.1 Recommended Evaluations and Immunization Prior to Treatment Initiation

- Test liver enzymes, alkaline phosphatase and bilirubin prior to initiating treatment with BIMZELX *[see Warnings and Precautions (5.4)]*.

5.4 Liver Biochemical Abnormalities

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

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

6.1 Adverse Reactions, Clinical Trials Experience

Specific Adverse Reactions

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

To ensure the safety of enrolled subjects and to allow identification of a potential safety signal for hepatoxicity in the development program for HS, the phase 3 Trials HS0003 and HS0004 included the following exclusion criteria:

- Subject has any systemic disease (i.e., cardiovascular, neurological, renal, liver, metabolic, gastrointestinal, hematological, immunological, etc.) considered by the Investigator to be uncontrolled, unstable, or likely to progress to a clinically significant degree during the course of the trial.
- Subject has laboratory abnormalities at Screening, including any of the following:
    - ≥3× the upper limit of normal (ULN) of any of the following: alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP)
    - Bilirubin >1.5×ULN (isolated bilirubin >1.5×ULN is acceptable if bilirubin is fractionated and direct bilirubin <35%)

Safety monitoring in the phase 3 trials for BKZ for HS included periodic evaluation of liver enzymes and bilirubin. The protocols also included criteria for discontinuation of IMP for potential DILI.

In Pool S1 (the 16-week placebo-controlled periods of Trials HS0003 and HS0004) the review team noted an imbalance for aminotransferase (AT) elevations in the BKZ treatment arms compared to placebo. We reviewed these in conjunction with the DILI team to determine the need for updates to labeling. A summary of the DILI team's conclusions and recommendations, excerpted from the consult review dated May 31, 2024 (DARRTS Reference ID: 5390131), is presented below. Refer to the consult review for more details regarding the DILI team analyses. Additional information from the DILI Team consult review is also presented in Appendix 19.6.2 of this review.

"Executive Summary

We did not detect a liver injury risk that would preclude approval of BKZ for HS treatment. The liver injury signal was less in this supplemental BLA compared to the original BLA for PSO. While there were more aminotransferase (AT) elevations in the

BKZ treated arms compared to placebo, we often did not attribute the elevations to BKZ on case level assessments. There were no Hy's Law or cholestatic jaundice cases. However, the number exposed in HS trials was only half as many as those in the PSO trials, so underpowering is a possible explanation for less liver injury seen. Nevertheless, the liver injuries in the HS trials tended to be modest and resolved quickly. In many cases resolution occurred while continuing BKZ. Therefore, the current label's highlighted Warnings and Precautions section regarding "Liver Biochemical Abnormalities" is sufficient. Additional liver analyte data from the HS trials will need to be added in the non-highlighted sections of the label. Our full assessment and recommendations are in Section 5.0 of this consult.

Assessment

Non-clinical data do not support a substantial DILI risk for BKZ. Post-market data include just three reports to FAERS for hepatobiliary adverse events so far; none are specifically labeled as DILI or hepatotoxicity. The estimated rates hepatobiliary reports per patient are low (<1%) for all four marketed monoclonal anti-IL17 antibodies. The three other marketed anti-IL17 monoclonal antibodies are not labeled for liver injury and considered low risk for DILI by LiverTox®.

eDISH plots for the two phase 3, randomized placebo-controlled trials, which exposed 861 HS subjects to BKZ, did not have subjects in the potential Hy's Law quadrant, but several were in Temple's. Accordingly, the BKZ arms had higher rates of elevated aminotransferases (AT; ALT or AST) compared to placebo during the first 16-weeks of treatment with some correlation with q2 week dosing over q4 weeks. The differences in AT elevations were mainly due to AST. The rates of AST $\geq$3x ULN were 0.7% and 1.4% in the q4 week and q2 week dosing arms versus 0% in the placebo arms. The respective rates for ALT$\geq$3x ULN were 0%, 0.5% and 0%. The rates increase when the maintenance phase data (48 weeks) are included, but AST elevations were still more common than ALT elevations.

We considered only one subject in Temple's (corollary) quadrant as probable DILI due to BKZ. The injury had a latency of 129 days, gradual onset, gradual resolution, modest peak enzymes (ALT 243 U/L, AST 82 U/L) without hyperbilirubinemia, and mixed pattern injury (R-value 2 to 5). Enzymes returned to near normal with holding BKZ. There were three subjects with possible DILI, but they all had competing alternative diagnoses. The remaining cases we assessed as unlikely DILI.

…the imbalance during the first 16-weeks is due to BKZ. Lack of attribution to DILI may be partly explained if some of the AT elevations are due to non-DILI events that are linked to BKZ. Myopathy and hemolysis would explain more AST over ALT elevations. At least two of twelve unlikely DILI cases had myopathy. There were four more that had

similar patterns of AST > ALT with low GGT suggesting non-liver events. CK levels were not checked in these cases.

Compared to the PSO trials, the liver injury signal was less prominent. The rate of ALT >5x ULN was up to 4.7% in the PSO trials while only 0.4% in the HS trials. Thus, the enzyme elevations were modest, and they typically resolved rapidly in the HS trials…

Overall, we do not see a substantial DILI risk with this supplemental BLA. The signal for liver injury is less in the HS trials compared to PSO trials. The current labeling for PSO does not need substantial changes, other than description of liver analyte changes in the HS trial.

Recommendations

- DILI concerns should not preclude approval.
- Labeling recommendations should BKZ be approved for HS
    - Would not change wording on Liver Biochemical Abnormalities in the Highlights for Warnings and Precautions
    - In section 5.0, point out imbalance in AT elevations during the randomized control trial portion, but no appearance of jaundice. Consider describing the one subject with slow onset and slow resolution liver injury.
    - In section 6.0, describe the percentages of AT elevations across treatment and placebo arms."

Applicant's Proposed Labeling Changes (new text in red font, deleted text in strikethrough)

- Sections 2.1, 5.4: No changes proposed

- Section 6.1, Clinical Trials Experience

  Hidradenitis Suppurativa Clinical Trials

  Specific Adverse Reactions

  Liver Biochemical Abnormalities: During the placebo-controlled period of Trials HS-1 and HS-2, liver serum transaminase elevations (> 3 times the upper limit of normal [ULN]) occurred in 1.2% of subjects treated with BIMZELX versus 0% of subjects treated with placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BIMZELX.

The DILI team concurred with the Applicant's proposed changes to labeling.

8.2.5.4. Infections

Overall Infections

The Applicant reported that in Pool S1 (the 16-week placebo-controlled periods of Trials HS0003 and HS0004), TEAEs from the SOC Infections and infestations occurred in 33% (EAIR 132.2/100 pt-yrs) of subjects in the combined BKZ group and 21% (EAIR 76.4/100 pt-yrs) in the placebo group. In Pool S1 , serious infections occurred in 0.1% (EAIR 0.4/100 pt-yrs) of subjects in the combined BKZ group and no subjects in the placebo group.

In Pool S3 (the combined Initial, Maintenance, and Open-Label periods of Trials HS0003, HS0004, and HS0005), infections were reported in 68% (EAIR 104.7/100 pt-yrs) of subjects in the combined BKZ group. Serious infections occurred in 2.1% (1.7/100 pt-yrs) of subjects in the combined BKZ group. The review team conducted additional analyses to compare the rate of infections between short-term (Pool S1) and long-term (Pool S3) exposure to BKZ as well as between the Q2W and Q4W dosing regimens. Results of these analyses are presented below.

In Pool S1, infections were reported by treatment group as follows:

- BKZ 320 mg Q2W: 193/576 (33.5%), EAIR 135.3/100 pt-yrs
- BKZ 320 mg Q4W: 91/285 (31.9%), EAIR 126.6/100 pt-yrs
- Placebo: 30/146 (20.5%), EAIR 75.6/100 pt-yrs

Based on the proportions and EAIRs, infections were more common in the Q2W group than the Q4W group. The most commonly reported PTs in Pool S1 were Oral candidiasis, Nasopharyngitis, Corona virus infection, Folliculitis, and Vulvovaginal mycotic infection. Overall, infections reported in Pool S1 were consistent with the established safety profile of BKZ.

In Pool S3, infections were reported by treatment group as follows:

- BKZ 320 mg Q2W: 473/823 (57.5%), EAIR 114.7/100 pt-yrs
- BKZ 320 mg Q4W: 362/650 (55.7%), EAIR 109.9/100 pt-yrs

Based on the proportions and EAIRs, infections were more common in the Q2W group than the Q4W group and were not increased with longer exposure to BKZ. However, the Applicant is not seeking approval for Q2W dosing beyond Week 16. The most commonly reported PTs in Pool S3 were Corona virus infection, Oral candidiasis, Nasopharyngitis, Folliculitis, and Upper respiratory infection. Overall, infections in Pool S3 were consistent with the established safety profile of BKZ.

Serious Infections

In Pool S1, only 1 subject in the BKZ 320 mg Q2W group (1/576, 0.2%; EAIR 0.6/100 pt-yrs) developed a serious infection (PT Cellulitis). In Pool S3, serious infections by treatment group were as follows:

- BKZ 320 mg Q2W: 13/823 (1.6%), EAIR 1.8/100 pt-yrs
- BKZ 320 mg Q4W: 9/650 (1.4%), EAIR 1.7/100 pt-yrs

Although the overall frequency of serious infections was low, based on the EAIRs, the rate of serious infections was increased with longer exposure to BKZ. This is consistent with the expected immunosuppression from treatment with a biologic immunomodulator. The only serious infection PTs reported in more than 1 subject in Pool S3 were cellulitis, reported in 2/823 (0.2%; EAIR 1.8/100 pt-yrs) in the BKZ 320 mg Q2W group and 1/650 (0.2%; EAIR 0.2/100 pt-yrs) in the BKZ 320 mg Q4W group, and Corona virus infection, which was reported in 1 subject each in the BKZ 320 mg Q2W and BKZ 320 mg Q4W groups, respectively.

Opportunistic infections and Tuberculosis (TB)

No subjects developed active TB during clinical trials for HS. In Pool S1, all opportunistic infections were reported in the BKZ treatment groups and consisted of mucocutaneous candidal or herpes infections. Opportunistic infections reported in Pool S1 are presented in the table below.

Table 32: Opportunistic Infections in Pool S1

Group Term	BKZ 320mg Q2W N = 576		BKZ 320mg Q4W N = 285		Placebo N = 146	
Preferred Term	n	(%) EAIR	n	(%) EAIR	n	(%) EAIR
Opportunistic Infection	4	(0.7) 2.3	6	(2.1) 6.9	0	(0.0) 0
Oral herpes	3	(0.5) 1.7	1	(0.4) 1.2	0	(0.0) 0
Genital candidiasis	1	(0.2) 0.6	2	(0.7) 2.3	0	(0.0) 0
Esophageal candidiasis	1	(0.2) 0.6	1	(0.4) 1.2	0	(0.0) 0
Genital herpes	0	(0.0) 0	1	(0.4) 1.2	0	(0.0) 0
Oropharyngeal candidiasis	0	(0.0) 0	1	(0.4) 1.2	0	(0.0) 0

Abbreviations: BKZ-Bimekizumab, EAIR- exposure adjusted incidence rate/100 pt-yrs
Source: Reviewer's Table

As noted in the table, opportunistic infections occurred more frequently in the BKZ 320 mg Q4W group than the BKZ 320 mg Q2W group. Both Candida and Herpes Simplex infections are listed in Section 6 (Adverse Reactions) of labeling based on data from the PsO program.

Similar to Pool S1, opportunistic infections consisted of mucocutaneous fungal and herpes infections. Opportunistic infections reported in Pool S3 are presented in the table below.

Table 33: Opportunistic Infections in Pool S3

Group Term Preferred Term	BKZ 320mg Q2W N = 823 n	 (%) EAIR	BKZ 320mg Q4W N = 650 n	 (%) EAIR
Opportunistic Infection	13	(1.6) 1.8	19	(2.9) 3.6
Oral herpes	6	(0.7) 0.8	6	(0.9) 1.1
Herpes Zoster	2	(0.2) 0.3	1	(0.2) 0.2
Oropharyngeal candidiasis	2	(0.2) 0.3	4	(0.6) 0.7
Cutaneous coccidioidomycosis	1	(0.1) 0.1	0	(0) 0
Genital candidiasis	1	(0.1) 0.1	3	(0.5) 0.6
Herpes dermatitis	1	(0.1) 0.1	0	(0) 0
Herpes virus infection	1	(0.1) 0.1	0	(0) 0
Esophageal candidiasis	1	(0.1) 0.1	1	(0.2) 0.2
Genital herpes	0	(0) 0	1	(0.2) 0.2
Genital herpes simplex	0	(0) 0	1	(0.2) 0.2
Oropharyngitis fungal	0	(0) 0	1	(0.2) 0.2
Superinfection fungal	0	(0) 0	1	(0.2) 0.2

Abbreviations: BKZ-Bimekizumab, EAIR- exposure adjusted incidence rate/100 pt-yrs
Source: Reviewer's Table

As in Pool S1, opportunistic infections overall occurred more frequently in the BKZ 320 mg Q4W group than the BKZ 320 mg Q2W group. However, based on the EAIRs, the rate of opportunistic infections did not increase with longer exposure to BKZ.

Labeling Recommendations

The Applicant proposes the following changes to labeling regarding infections (new text in red font, deletions in ~~strikethrough~~):

5.2 Infections

BIMZELX may increase the risk of infections. (b) (4)

(b) (4)

Do not initiate treatment with BIMZELX in patients with any clinically important active infection until the infection resolves or is adequately treated.

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

6.1 Adverse Reactions, Clinical Trials Experience

Hidradenitis Suppurativa Clinical Trials
BIMZELX was evaluated in two placebo-controlled trials (Trial HS-1 and Trial HS-2) in 1014 subjects with moderate to severe hidradenitis suppurativa (868 subjects on BIMZELX and 146 subjects on placebo). The safety profile observed in subjects with hidradenitis suppurativa treated with BIMZELX was overall similar to the safety profile seen in subjects with plaque psoriasis.

Specific Adverse Reactions

Infections: During the placebo-controlled period of Trials HS-1 and HS-2, infections were reported in 33% of subjects (132.2 per 100 patient-years) treated with BIMZELX compared with 21% of subjects (76.4 per 100 patient-years) treated with placebo. Serious infections occurred in 0.1% of subjects (0.4 per 100 patient-years) treated with BIMZELX and 0% treated with placebo.

During the combined placebo-controlled, maintenance treatment periods and open-label extension treatment periods of Trials HS-1 and HS-2, infections were reported in 68% of subjects treated with BIMZELX (104.7 per 100 patient-years). Serious infections were reported in 2.1% of subjects treated with BIMZELX (1.7 per 100 patient-years).

The review team also added data regarding the most commonly reported infections by dosing regimen for Pool S1 to subsection 6.1 of labeling.

8.2.5.5. Malignancies

Subjects with any active malignancy or history of malignancy within 5 years prior to the Screening Visit were excluded from phase 3 trials. The only exceptions to the exclusion criteria were cutaneous squamous or basal cell carcinoma , or in situ cervical cancer that were treated and considered cured. Overall, the frequency of malignancies was low during the development program. This review will focus on comparison of malignancy rates during Pool S1 (the 16-week placebo-controlled periods of Trials HS0003 and HS0004) and Pool S3 (the combined Initial, Maintenance, and Open-Label periods of Trials HS0003, HS0004, and HS0005).

In Pool S1, only one subject (1/576, 0.2%, EAIR 0.6/100 pt-yrs) developed a TEAE of malignancy. The subject, who was treated with BKZ 320 mg Q2W, developed a TEAE of Breast cancer on Day

15. The event was serious, severe, led to discontinuation, and was not resolved at the time of submission. The investigator considered the event not related to treatment with BKZ.

In Pool S3, malignancies occurred in 6/823 (0.7%; EAIR 0.8/100 pt-yrs) subjects in the BKZ 320 mg Q2W group and 3/650 (0.5%; EAIR 0.6/100 pt-yrs) in the BKZ 320 mg Q4W group. Each PT for malignancies was reported in only one subject. No malignancies had a fatal outcome. In addition to the subject with breast cancer as discussed above, malignancy PTs (including subject age/race, Study Day at onset, intensity, action taken with BKZ, outcome, and relationship to BKZ as assessed by the investigator) reported in Pool S3 included the following:

BKZ 320 mg Q2W

- 61 y/o white female with Intraductal proliferative breast lesion, Day 301 (192 days after last dose of BKZ), severe, action taken with BKZ not applicable (N/A) as subject had already discontinued, not resolved, not related.
- 54 y/o white male with Adrenal gland cancer, Day 406, severe, drug withdrawn, not resolved, not related.
- 62 y/o black or African-American male with Clear renal cell carcinoma, Day 365, severe, drug withdrawn, not resolved, not related
- 55 y/o white female with keratoacanthoma, Day 328, mild, action taken with BKZ N/A (subject had completed Trial HS0004 and went on to enroll in OLE Trial HS0005), resolved, not related
- 51 y/o white male with Squamous cell carcinoma of the tongue, Day 400, moderate, action taken with BKZ N/A as subject had discontinued on Day 340 due to an AE of Seborrheic dermatitis, resolved, considered related by the investigator, considered not related by the Applicant due to subjects' h/o tobacco use.

BKZ 320 mg Q4W

- 57 y/o white female with Basal cell carcinoma, Day 197, moderate, action taken with BKZ N/A (event occurred at Early Termination visit), not resolved, not related
- 49 y/o white female with papillary thyroid cancer, Day 464, severe, drug withdrawn, resolved, not related.
- 41 y/o white female with Hodgkin's disease, Day 627, severe, drug withdrawn, not resolved, not related.

Because of the overall low rate of malignancies in the HS program, and that each malignancy PT was only reported by one subject, these data do not appear to be consistent with a safety signal for malignancy. Because of the long latency period associated with malignancy, this is currently being monitored as an outcome of interest in a long-term safety study to be conducted under PMR 4268-6 which was issued in the Approval Letter dated October 18, 2023. In addition, the risk of lymphoma is being evaluated via Active Risk and Identification Analysis (ARIA) system.

8.2.5.6. Major Adverse Cardiovascular Events

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

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

Subjects with stable CV disease were not excluded from the clinical trials unless they had a history of MI or stroke within 6 months prior to Screening. Baseline CV risk factors and history of CV events were relatively evenly distributed between the randomized treatment arms. The demographics were representative of the HS population. Overall, in Pool S1, 36% of subjects had Class III Obesity (morbidly obese), 45% of subjects were current smokers, and 20% had previous or ongoing hypertension. Six subjects in the bimekizumab arms (0.7%) versus none in the placebo arm had previous or ongoing heart failure.

The review team evaluated MACE events in conjunction with consultants from the Division of Cardiology and Nephrology (DCN). Refer the Consult Review dated July 16, 2024 by Selena DeConti, PharmD, MPH. The results of Dr. DeConti's analysis of CV events in Pool S1 included the following:

- The patient characteristics, baseline cardiac risk factors, and baseline history of CV disease were relatively evenly distributed between the treatment arms.
- The CV events were reported similarly in the treatment arms; placebo (6%) versus bimekizumab Q2W or Q4W (6% and 5%, respectively). No trend was observed with respect to the type of CV event or time to onset.
- Serious CV adverse events were reported similarly between treatment arms; placebo (0.7%) versus bimekizumab Q2W or Q4W (0.7% and 0.4%, respectively). No trend was observed with respect to the type of CV event or time to onset.
- There were no adjudicated major adverse cardiac events (MACE) reported in the bimekizumab arms or placebo arm.
- One subject in the bimekizumab Q2W group (0.1%) experienced two adjudicated extended MACE (heart failure exacerbation; acute on chronic heart failure) versus none in the bimekizumab Q4W or placebo arms. This subject had a previous history of heart failure and eventually died due to heart failure at Week 36 of the study. Dr. DeConti noted that the subject had multiple CV comorbidities and risk factors for CV disease. A narrative for this subject is presented in Section 8.2.4 of this review.

- The incidence of adjudicated CV adverse events was low, 1% in the bimekizumab Q2W arm versus none in the bimekizumab Q4W or placebo arms.

Dr. DeConti's review provided the following comments regarding MACE events in Pool S3:

> "During the combined maintenance treatment periods and OLE, there were four adjudicated MACE, including one subject experiencing fatal congestive heart failure (discussed in the Appendix of Dr. DeConti's review). The remaining adjudicated MACE included one subject with acute coronary syndrome, one subject with cerebral infarction, and one subject with ruptured cerebral aneurysm; none of these events led to study discontinuation or withdrawal of bimekizumab."

Dr. DeConti also stated that "A review of the CV events described in the periodic safety reports since approval did not identify CV findings of concern." In addition, the consult review provided the following conclusions:

> "There is no clinical concern from the cardiovascular perspective and no safety labeling language is necessary. Consider eliminating the need for CV AEs to be collected as AESI and event adjudication in future development programs for bimekizumab."

The review team concurs with the conclusions of consultants from DCN and does not recommend inclusion of cardiovascular events in labeling for BKZ.

8.2.5.7. Neutropenia

Based on the mechanism of action and observed effects of bimekizumab in the population with PsO, the Applicant evaluated neutropenia as an AESI. Per the Applicant, TEAEs of neutropenia and abnormal laboratory values of decreased neutrophil counts occurred as expected per bimekizumab mode of action and in line with the IL-17 class. Neutropenia is listed in Section 6 (Adverse Reactions) of approved labeling for BKZ under adverse reactions occurring in <1% but >0.1% of subjects with PsO.

The review team evaluated TEAEs related to neutropenia. In Pool S1 (the 16-week placebo-controlled periods of Trials HS0003 and HS0004), there were no TEAEs related to neutropenia or decreased neutrophil count in any treatment group. In Pool S3 (the combined Initial, Maintenance, and Open-Label periods of Trials HS0003, HS0004, and HS0005), the following TEAEs related to neutropenia were reported:

- Neutrophil count decreased: 1/823 (0.1%, EAIR 0.1/100 pt-yrs) in BKZ 320 mg Q2W group
- Neutropenia: 1/650 (0.2%; EAIR 0.2/100 pt-yrs in BKZ 320 mg Q4W group

None of the TEAEs were serious or led to discontinuation of BKZ. All were mild in intensity and resolved.

Based on data from the HS program, the review team recommends no changes to labeling regarding neutropenia.

8.2.5.8. Hypersensitivity and Injection Site Reactions

The review team evaluated potential hypersensitivity reactions reported during the development program for HS. Overall, the review team did not identify a safety signal for hypersensitivity. No cases of anaphylaxis occurred during clinical trials for HS.

Pool S1
In Pool S1 (the placebo-controlled periods of Trials HS0003 and HS0004), there were no TEAEs of angioedema. TEAE PTs of urticaria occurred in Pool S1 as follows:

- Urticaria:
  - BKZ 320 mg Q2W: 8/576 (1.4%); EAIR 4.6/100 pt-yrs, 7 mild, 1 moderate
  - BKZ 320 mg Q4W: 1/285 (0.4%); EAIR 1.1/100 pt-yrs, mild
  - Placebo: 0
- Idiopathic urticaria:
  - BKZ 320 mg Q2W: 1/576 (0.2%); EAIR 0.6/100 pt-yrs, mild
  - BKZ 320 mg Q4W: 0
  - Placebo: 0
- Injection site urticaria
  - BKZ 320 mg Q2W: 2/576 (0.3%); EAIR 1.1/100 pt-yrs, both mild
  - BKZ 320 mg Q4W: 0
  - Placebo: 0

One TEAE of urticaria was of moderate severity. The other TEAEs of urticaria were mild in severity. No TEAEs of urticaria were serious AEs or led to discontinuation. As such, the review team did not consider the imbalance in urticaria TEAEs to be clinically meaningful.

Pool S3
Pool S3 (the combined Initial, Maintenance, and Open-Label periods of Trials HS0003, HS0004, and HS0005) included the following TEAEs of angioedema or urticaria:

Angioedemas

- Angioedema:
  - BKZ 320 mg Q2W: 3/823 (0.4%); EAIR 0.4/100 pt-yrs; 1 mild, 2 moderate
  - BKZ 320 mg Q4W: 1/650 (0.2%); EAIR 0.2/100 pt-yrs, moderate

Urticarias

- Urticaria:
  - BKZ 320 mg Q2W: 14/823 (1.7%); EAIR 2.0/100 pt-yrs; 12 mild, 2 moderate
  - BKZ 320 mg Q4W: 6/650 (0.9%; EAIR 1.1 /100 pt-yrs; 3 mild, 3 moderate
- Idiopathic urticaria:
  - BKZ 320 mg Q2W: 1/823 (0.1%); EAIR 0.1/100 pt-yrs; mild
  - BKZ 320 mg Q4W: 0
- Urticaria cholinergic:
  - BKZ 320 mg Q2W: 1/823 (0.1%); EAIR 0.1/100 pt-yrs; moderate
  - BKZ 320 mg Q4W: 0
- Urticaria papular:
  - BKZ 320 mg Q2W: 1/823 (0.1%); EAIR 0.1/100 pt-yrs; mild
  - BKZ 320 mg Q4W: 0
- Mechanical urticaria:
  - BKZ 320 mg Q2W: 0
  - BKZ 320 mg Q4W: 1/650 (0.2%); EAIR 0.2/100 pt-yrs; mild
- Injection site urticaria:
  - BKZ 320 mg Q2W: 2/823 (0.2%); EAIR 0.3/100 pt-yrs; mild
  - BKZ 320 mg Q4W: 0

Because none of the TEAEs of angioedema were serious or resulted in discontinuation of BKZ, the Applicant did not provide narratives for these subjects. However, the Applicant provided the following limited information regarding subjects with angioedema in AE listings:

- Subject H (b) (6) BKZ Q2W/Q2W, TEAE Angioedema Day 238, 237 days after 1st and 1 day after most recent BKZ dose, not related, resolved, dose not changed.
- Subject (b) (6): BKZ Q2W; TEAE Angioedema (unknown etiology per verbatim term) Day 452, 451 days after 1st and 1 day after most recent BKZ dose, not related, resolved, dose not changed
- Subject (b) (6) BKZ Q2W, TEAE Angioedema (verbatim term: food allergic reaction [melon] with mouth angioedema) Day 433, 432 days after first and 5 days after most recent dose of BKZ, not related, dose not changed, resolved
- Subject (b) (6) BKZ Q4W/Q4W, TEAE Angioedema (cause unknown per verbatim term) on Day 236, 235 days after first and 67 days after most recent BKZ dose, not related, resolved, action taken not applicable (Subject d/c'd Day 169 d/t lack of efficacy per HS0004 CSR disposition listing); had AE of allergy to nuts 10 days later

Similar to Pool S1, TEAEs of angioedema and urticaria were mild or moderate in severity. None were serious AEs nor resulted in discontinuation. As such, the review team concluded that these TEAEs do not indicate a safety signal for hypersensitivity.

Injection Site Reactions

Injection site reactions were reported under multiple PTs. To better characterize the overall frequency of injection site reactions, the review team pooled PTs for these TEAEs. The PTs for injection site reactions included: injection site reaction, pain, erythema, pruritus, swelling, bruising, rash, urticaria, discoloration, and hemorrhage. In Pool S1, pooled injection site reactions were reported as follows:

- BKZ 320 mg Q2W: 37/576 (6.4%), EAIR 22.2/100 pt-yrs
- BKZ 320 mg Q4W: 13/285 (4.6%), EAIR 15.4/100 pt-yrs
- Placebo: 2/146 (1.4%). EAIR 4.5/100 pt-yrs

In Pool S3, injection site reactions were reported as follows:

- BKZ 320 mg Q2W: 52/823 (6.3%), EAIR 7.5/100 pt-yrs
- BKZ 320 mg Q4W: 25/650 (3.8%), EAIR 4.7/100 pt-yrs

The most commonly reported PTs in both Pool S1 and Pool S3 were Injection site reaction, Injection site pain, and Injection site erythema. Based on comparison of the EAIRs between Pool S1 and S3, the frequency of injection site reactions did not increase with longer exposure to BKZ. Although there appears to be a dose-response for injection site reactions, the Applicant is not seeking approval for Q2W dosing beyond Week 16. As such, the review team recommends no changes to labeling regarding injection site reactions.

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

There were no patient-reported outcome (PRO) assessments that measured safety parameters. Refer to Section 8.1.10 for PRO and COA analyses informing efficacy, as well as the DCOA consult review by Dr. Yasmin Choudhry dated October 11, 2024.

8.2.7. Safety Analyses by Demographic Subgroups

The review team conducted analyses of common adverse reactions (ARs) by race, age group, and sex using data from Pool S1 (the placebo-controlled periods of Trials HS0003 and HS0004). We conducted separate analyses for ARs defined by a single Preferred Term (PT) and for ARs defined by pooled PTs. The results of these analyses are presented below.

Race

ARs defined by a single PT and by pooled terms by racial subgroups are presented in the tables below.

Table 34: ARs Reported as Single Preferred Terms by Race, Pool S1

Event/ Race	BKZ 320 mg Q2W (N=573) n (%) EAIR				BKZ 320 mg Q4W (N=284) n (%) EAIR				Placebo (N=145) n (%) EAIR			
	White (N=463)	Black (N=61)	Asian (N=24)	Other (N=25)	White (N=221)	Black (N=34)	Asian (N=10)	Other (N=19)	White (N=119)	Black (N=13)	Asian (N=8)	Other (N=5)
Pyrexia	15 (3.2) 10.8	2 (3.3) 11.1	2 (8.3) 27.6	0	6 (2.7) 9.1	0	0	2 (10.5) 36.6	2 (1.7) 5.5	0	0	0
Fatigue	16 (3.5) 11.6	0	0	0	8 (3.6) 12.3	0	0	0	1 (0.8) 2.7	0	0	1 (20.0) 93.7
Folliculitis	13 (2.8) 9.3	2 (3.3) 11.0	0	1 (4.0) 14.0	6 (2.7) 9.0	2 (5.9) 20.1	0	0	0	0	0	0
Otitis Externa	9 (1.9) 6.4	0	0	0	1 (0.5) 1.5	0	0	1 (5.3) 17.9	1 (0.8) 2.7	0	0	0
Acne	6 (1.3) 4.3	3 (4.9) 16.5	0	0	2 (0.9) 3.0	1 (2.9) 10.0	0	0	0	0	0	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
Source: Reviewer's Table, data from ISS

Table 35: ARs Reported with Pooled Preferred Terms by Race, Pool S1

Pooled Term/ Race	BKZ 320 mg Q2W (N=573) n (%) EAIR				BKZ 320 mg Q4W (N=284) n (%) EAIR				Placebo (N=145) n (%) EAIR			
	White (N=463)	Black (n=61)	Asian (N=24)	Other (N=25)	White (N=221)	Black (N=34)	Asian (N=10)	Other (N=19)	White (N=119)	Black (N=13)	Asian (N=8)	Other (N=5)
Upper respiratory infections [a]	55 (11.9) 41.6	1 (1.6) 5.4	0	3 (12.0) 45.2	21 (9.5) 32.9	0	0	2 (10.5) 36.1	7 (5.9) 19.7	1 (7.7) 28.2	1 (12.5) 42.5	0

Pooled Term/ Race	BKZ 320 mg Q2W (N=573) n (%) EAIR				BKZ 320 mg Q4W (N=284) n (%) EAIR				Placebo (N=145) n (%) EAIR			
	White (N=463)	Black (n=61)	Asian (N=24)	Other (N=25)	White (N=221)	Black (N=34)	Asian (N=10)	Other (N=19)	White (N=119)	Black (N=13)	Asian (N=8)	Other (N=5)
Oral candidiasis [b]	36 (7.8) 26.4	4 (6.6) 22.4	3 (12.5) 43.6	2 (8.0) 29.1	11 (5.0) 16.7	0	0	0	0	0	0	0
Injection site reactions [c]	30 (6.5) 22.2	3 (4.9) 17.0	1 (4.2) 14.2	3 (12.0) 47.1	10 (4.5) 15.3	2 (5.9) 19.9	0	1 (5.3) 17.2	2 (1.7) 5.5	0	0	0
Other Candida infections [d]	13 (2.8) 9.3	6 (9.8) 34.0	0	2 (8.0) 28.9	13 (5.9) 19.8	4 (11.8) 42.6	0	2 (10.5) 35.4	0	0	0	0
Tinea infections [e]	16 (3.5) 11.5	1 (1.6) 5.5	1 (4.2) 13.8	0	5 (2.3) 7.5	2 (5.9) 19.7	0	0	1 (0.8) 2.7	0	0	0
Herpes simplex infections [f]	2 (0.4) 1.4	1 (1.6) 5.5	0	0	2 (0.9) 3.0	0	0	0	0	0	0	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks

[a] Upper Respiratory Infections - Includes high level term Upper respiratory tract infections plus the preferred terms Pharyngitis streptococcal, Pharyngitis bacterial, Influenza, and Viral upper respiratory tract infection.

[b] Oral Candidiasis - Includes the preferred terms Oral candidiasis, Esophageal candidiasis, Oropharyngeal candidiasis, and Oral fungal infection.

[c] Injection site reactions- Includes preferred terms Injection site pain, Injection site reaction, Injection site erythema, Injection site swelling, Injection site pruritus, Injection site bruising, Injection site urticaria, Injection site rash, Injection site discoloration, and Injection site hemorrhage

[d] Other Candida Infections - Includes preferred terms Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Skin candida, Genital candidiasis, Anal fungal infection, and Genital infection fungal.

[e] Tinea infections- Includes Tinea pedis, Body tinea, Dermatophytosis, Tinea capitis, Tinea cruris, Tinea manuum, Tinea versicolor, and Fungal skin infection.

[f] Herpes Simplex Infections - Includes preferred terms Oral herpes and Genital herpes

Source: Reviewer's Table, data from Applicant's Response to Information request dated July 31, 2024

The numbers of subjects in the Black, Asian, and Other races subgroups are not sufficient to allow for meaningful comparisons of AR rates between the racial subgroups.

Age

ARs defined by a single PT and by pooled terms by age group are presented in the tables below.

Table 36: ARs Reported as Single Preferred Terms by Age Group, Pool S1

Event/ Age Group	BKZ 320 mg Q2W (N=576) n (%) EAIR			BKZ 320 mg Q4W (N=285) n (%) EAIR			Placebo (N=146) n (%) EAIR		
	<40 years (N=352)	40-<65 years (N=214)	**≥65** years (N=10)	<40 years (N=188)	40-<65 years (N=94)	**≥65** years (N=3)	<40 years (N=91)	40-<65 years (N=60)	**≥65** years (N=5)
Pyrexia	12 (3.4) 11.4	7 (3.3) 10.9	0	8 (4.3) 14.3	0	0	2 (2.2) 7.3	0	0
Fatigue	9 (2.6) 8.6	7 (3.3) 11	0	5 (2.7) 8.9	3 (3.2) 10.8	0	3 (3.3) 11.0	0	0
Folliculitis	11 (3.1)10.4	5 (2.3) 7.8	0	7 (3.7) 12.4	1 (1.1) 3.5	0	0	0	0
Otitis externa	6 (1.7) 5.6	3 (1.4) 4.6	0	1 (0.5) 1.8	1 (1.1) 3.5	0	0	1 (2.0) 6.7	0
Acne	6 (1.7) 5.7	3 (1.4) 4.6	0	3 (1.6) 5.3	0	0	0	0	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
Source: Reviewer's Table, data from ISS

Table 37: ARs Reported with Pooled Preferred Terms by Age Group, Pool S1

Pooled Term/ Age Group	BKZ 320 mg Q2W (N=576) n (%) EAIR			BKZ 320 mg Q4W (N=285) n (%) EAIR			Placebo (N=146) n (%) EAIR		
	<40 years (N=352)	40-<65 years (N=214)	**≥65** years (N=10)	<40 years (N=188)	40-<65 years (N=94)	**≥65** years (N=3)	<40 years (N=91)	40-<65 years (N=50)	**≥65** years (N=5)
Upper respiratory infections [a]	39 (11.1) 38.7	19 (8.9) 30.8	1 (10.0) 33.3	11 (5.9) 19.8	12 (12.8) 45.4	0	6 (6.6) 22.3	3 (6.0) 20.5	0
Oral candidiasis [b]	23 (6.5) 22.1	21 (9.8) 34.0	1 (10.0) 35.6	6 (3.2) 10.6	5 (5.3) 18.0	0	0	0	0
Injection site reactions [c]	23 (6.5) 22.5	14 (6.5) 22.6	0	8 (4.3) 14.3	5 (5.3) 18.0	0	0	2 (4.0) 13.4	0
Other Candida infections [d]	10 (2.8) 9.5	11 (5.1) 17.3	0	12 (6.4) 21.5	7 (7.4) 25.6	0	0	0	0
Tinea infections [e]	6 (1.7) 5.6	12 (5.6) 18.9	0	6 (3.2) 10.6	1 (1.1) 3.5	0	1 (1.1) 3.6	0	0
Herpes simplex infections [f]	3 (0.9) 2.8	0	0	2 (1.1) 3.5	0	0	0	0	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
[a] Upper Respiratory Infections - Includes high level term Upper respiratory tract infections plus the preferred terms Pharyngitis streptococcal, Pharyngitis bacterial, Influenza, and Viral upper respiratory tract infection.
[b] Oral Candidiasis - Includes the preferred terms Oral candidiasis, Esophageal candidiasis, Oropharyngeal candidiasis, and Oral fungal infection.

[c] Injection site reactions- Includes preferred terms Injection site pain, Injection site reaction, Injection site erythema, Injection site swelling, Injection site pruritus, Injection site bruising, Injection site urticaria, Injection site rash, Injection site discoloration, and Injection site hemorrhage
[d] Other Candida Infections - Includes preferred terms Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Skin candida, Genital candidiasis, Anal fungal infection, and Genital infection fungal.
[e] Tinea infections- Includes Tinea pedis, Body tinea, Dermatophytosis, Tinea capitis, Tinea cruris, Tinea manuum, Tinea versicolor, and Fungal skin infection.
[f] Herpes Simplex Infections - Includes preferred terms Oral herpes and Genital herpes
Source: Reviewer's Table, data from Applicant's Response to Information request dated July 31, 2024

Oral candidiasis and Other candida infections occurred more frequently in subjects 40-<65 years of age in both BKZ treatment groups. Although there is no clear explanation for this imbalance, it is plausible that subjects 40-<65 years of age may have had a longer history of exposure to potentially immunosuppressive treatments for HS. The rates of Injection site reactions were identical between age groups in the BKZ 320 mg Q2W group and slightly more common in subjects 40-<65 years of age in the BKZ 320 mg Q4W group. Herpes simplex infections were more common in subjects <40 years of age in both BKZ treatment groups.

Subgroup analyses for the ARs of Pyrexia, Folliculitis, Upper respiratory infections (URIs), and Tinea infections were inconsistent. Pyrexia and folliculitis were more common in subjects <40 years of age than in subjects 40-<65-years of age in the 320 mg Q4W group. However, the proportion of these ARs were similar between these age groups in the 320 mg Q2W group. As shown in the table, URIs occurred more frequently in subjects <40 years of age in the BKZ 320 mg Q2W group but were more frequent in the 40-<65 years age group in the BKZ 320 mg Q4W group. On the other hand, Tinea infections were more common in subjects 40-<65 years of age in the BKZ 320 mg Q2W group but more common in subjects <40 years of age in the BKZ 320 mg Q4W group. The proportion of subjects with fatigue was similar between the <40 years and the 40-<65-years age groups across both BKZ treatment groups.

Overall, the data do not clearly demonstrate an increase in risk for a particular adverse reaction in any age subgroup. The number of subjects in the age 65 years and older subgroup are insufficient to draw meaningful conclusions regarding this population.

Sex

ARs defined by a single PT and by pooled terms by sex are presented in the tables below.

ARs Reported as Single Preferred Terms by Sex, Pool S1

Table 38: ARs Reported as Single Preferred Terms by Sex, Pool S1

Event/Sex	BKZ 320 mg Q2W (N=576) n (%) EAIR		BKZ 320 mg Q4W (N=285) n (%) EAIR		Placebo (N=146) n (%) EAIR	
	Male (N=254)	Female (N=322)	Male (N=111)	Female (N=174)	Male (N=71)	Female (N=75)
Pyrexia	11 (4.3) 14.5	8 (2.5) 8.3	2 (1.8) 5.9	6 (3.4) 11.6	1 (1.4) 4.6	1 (1.3) 4.4
Fatigue	2 (0.8) 2.6	14 (4.3) 14.7	1 (0.9) 3.0	7 (4.0) 13.8	1 (1.4) 4.7	2 (2.7) 8.9
Folliculitis	8 (3.1) 10.5	8 (2.5) 8.3	4 (3.6) 11.8	4 (2.3) 7.7	0	0
Otitis externa	3 (1.2) 3.9	6 (1.9) 6.1	1 (0.9) 2.9	1 (0.6) 1.9	1 (1.4) 4.6	0
Acne	2 (0.8) 2.6	7 (2.2) 7.2	0	3 (1.7) 5.8	0	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
Source: Reviewer's Table, data from ISS

Table 39: ARs Reported with Pooled Preferred Terms by Sex, Pool S1

Pooled term /Sex	BKZ 320 mg Q2W (N=576) n (%) EAIR		BKZ 320 mg Q4W (N=285) n (%) EAIR		Placebo (N=146) n (%) EAIR	
	Male (N=254)	Female (N=322)	Male (N=111)	Female (N=174)	Male (N=71)	Female (N=75)
Upper respiratory infections [a]	22 (8.7) 29.9	37 (11.5) 40.3	7 (6.3) 21.2	16 (9.2) 32.0	6 (8.5) 28.7	3 (4.0) 13.5
Oral candidiasis [b]	24 (9.4) 32.6	21 (6.5) 22.1	4 (3.6) 11.9	7 (4.0) 13.5	0	0
Injection site reactions [c]	6 (2.4) 7.9	31 (9.6) 34.0	3 (2.7) 9.0	10 (5.7) 19.6	1 (1.4) 4.6	1 (1.3) 4.4
Other Candida infections [d]	4 (1.6) 5.2	17 (5.3) 17.8	2 (1.8) 5.9	17 (9.8) 33.9	0	0
Tinea infections [e]	12 (4.7) 15.8	6 (1.9) 6.2	1 (0.9) 2.9	6 (3.4) 11.5	0	1 (1.3) 4.4
Herpes simplex infections [f]	0	3 (0.9) 3.1	1 (0.9) 2.9	1 (0.6) 1.9	0	0

Abbreviations: BKZ-bimekizumab, EAIR-exposure-adjusted incidence rate/100 patient-years, n-number of subjects with event, Q2W-every 2 weeks, Q4W- every 4 weeks
[a] Upper Respiratory Infections - Includes high level term Upper respiratory tract infections plus the preferred terms Pharyngitis streptococcal, Pharyngitis bacterial, Influenza, and Viral upper respiratory tract infection.
[b] Oral Candidiasis - Includes the preferred terms Oral candidiasis, Esophageal candidiasis, Oropharyngeal candidiasis, and Oral fungal infection.
[c] Injection site reactions- Includes preferred terms Injection site pain, Injection site reaction, Injection site erythema, Injection site swelling, Injection site pruritus, Injection site bruising, Injection site urticaria, Injection site rash, Injection site discoloration, and Injection site hemorrhage
[d] Other Candida Infections - Includes preferred terms Vulvovaginal candidiasis, Vulvovaginal mycotic infection, Skin candida, Genital candidiasis, Anal fungal infection, and Genital infection fungal.
[e] Tinea infections- Includes Tinea pedis, Body tinea, Dermatophytosis, Tinea capitis, Tinea cruris, Tinea manuum, Tinea versicolor, and Fungal skin infection.
[f] Herpes Simplex Infections - Includes preferred terms Oral herpes and Genital herpes
Source: Reviewer's Table, data from Applicant's Response to Information request dated July 31, 2024

Other candida infections were more common in females for both BKZ treatment groups, which would be expected as this category is mostly driven by preferred terms for vulvovaginal fungal infections.

Fatigue, Upper respiratory infections, and Injection site reactions occurred more frequently in female subjects in both BKZ treatment groups, while Folliculitis was reported more frequently in males in both BKZ treatment groups. The reason for these imbalances is unclear as there is no clear biologically plausible explanation for the differences. The number of subjects with ARs of Otitis externa and Acne was insufficient to permit detection of meaningful differences between the sexes.

Subgroup analyses for Pyrexia, Oral candidiasis, Tinea infections, and Herpes simplex infections were inconsistent. Pyrexia was reported more frequently by males in the 320 mg Q2W arm and females in the 320 mg Q4W arm. Both Oral candidiasis and Tinea infections occurred more frequently in males in the BKZ 320 mg Q2W group but more frequently in females in the BKZ 320 mg Q4W group. However, Herpes simplex infections occurred more frequently in females in the BKZ 320 mg Q2W group and in males in the 320 mg Q4W group.

Overall, subgroup analyses by sex do not demonstrate clinically meaningful differences in risk between these subgroups.

8.2.8. Specific Safety Studies/Clinical Trials

In addition to the phase 3 trials, the Applicant submitted data from the 32- week, phase 2 Trial HS0001. This was a multicenter, randomized, investigator-blind, subject-blind, placebo- and active comparator-controlled trial to assess the efficacy, safety, and PK of BKZ in adult subjects with moderate to severe HS. The inclusion criteria for baseline disease severity were different than the phase 3 trials. In Trial HS0001, moderate to severe HS was defined as:

- Total abscess and inflammatory nodule count $\geq$3 (as opposed to $\geq$5 in the phase 3 trials)
- Diagnosis of HS for at least 1 year prior to Baseline
- Inadequate response to at least a 3-month treatment with an oral antibiotic for treatment of HS
- Draining fistula count <20 at the Baseline Visit

The trial was comprised of a Screening Period, a 12-week Treatment Period, and a 20-week Safety Follow-up Period. Eligible subjects were randomized 2:1:1 to one of the following treatment regimens:

- BKZ 640mg at Baseline (loading dose), followed by 320mg every 2 weeks (Q2W) x 5 doses from Week 2 to 10

- Adalimumab 160mg at Baseline (loading dose), followed by 80mg at Week 2 and 40mg once weekly x 7 doses at Weeks 4-10
- Placebo at Baseline, Week 2, then once weekly x 7 doses from Weeks 4-10

Results

The trial enrolled 88 subjects. The majority were female (69.3%), white (69.3%), not Hispanic/Latino (88.6%) with a mean age of 36.7 years.

The Applicant reported no deaths during the trial. One subject, a 53-year-old (y/o) white male (Subject (b) (6) in the BKZ group discontinued due to an adverse event (AE) of hidradenitis that began 26 days after the first dose and 1 day after the most recent dose of BKZ. The Investigator characterized the AE as mild in intensity and considered the AE not related to treatment. The outcome of the AE was unknown.

A total of 5 subjects in Trial HS0001 reported 8 serious AEs (SAEs); none resulted in discontinuation. SAEs reported by subjects treated with BKZ that required hospitalization included one subject with empyema and one with severe anemia. Brief narratives of the SAEs are below:

- 59 y/o white male (Subject (b) (6) with a noncontributory past medical history developed empyema 128 days after the first bimekizumab injection and 58 days after the most recent BKZ injection (this was the final dose at Week 10). He was treated with thoracentesis and antibiotics. The investigator classified the SAE of empyema as severe in intensity and not related to treatment with BKZ. The outcome of the event was resolved with sequelae.

- 31 y/o white male (Subject (b) (6) with a noncontributory past medical history developed severe anemia 156 days after the first BKZ dose and 96 days after the most recent dose. At the time of admission, the subject also had rectal bleeding from hemorrhoids. The etiology of the anemia was determined to be iron deficiency and blood loss from the rectal bleeding. The investigator considered the SAE of severe anemia not related to treatment. The outcome of the SAE was resolved.

Other than the serious infection (empyema), no other adverse events of special interest (AESIs) were reported, including Hy's Law, infections (opportunistic, fungal, and tuberculosis [TB]), neutropenia, hypersensitivity, suicidal ideation and behavior, depression, major cardiovascular events, liver function test changes/enzyme elevations, malignancies, and inflammatory bowel disease (IBD).

Treatment-emergent AEs (TEAEs) were reported in 13/21 (61.9%) of subjects in the placebo group, 15/21 (71.4%) of subject in the adalimumab group, and 32/46 (69.6%) of subjects in the BKZ group. The most common System-Organ Classes (SOC) in which TEAE were reported in the BKZ group were Infections and Infestations (20/46; 43.5%) and Skin and Subcutaneous Tissue

Disorders (13/46; 28.3%). The most commonly reported Preferred Terms (PT) in the BKZ group were hidradenitis (8/46; 17.4%) and fatigue (4/46; 8.7%). A summary of TEAEs reported by 2 or more subjects in any treatment group is presented in the table below.

Table 40:TEAEs by Preferred Term Reported in **≥2** Subjects in any Treatment Group

MedDRA (v19.0) System Organ Class PT	PBO N=21 n (%) [#]	ADA N=21 n (%) [#]	BKZ N=46 n (%) [#]
Any TEAE	13 (61.9) [30]	15 (71.4) [60]	32 (69.6) [150]
Gastrointestinal disorders	3 (14.3) [3]	3 (14.3) [7]	8 (17.4) [15]
Diarrhoea	0	1 (4.8) [2]	3 (6.5) [5]
Nausea	0	1 (4.8) [1]	3 (6.5) [3]
General disorders and administration site conditions	2 (9.5) [3]	5 (23.8) [11]	10 (21.7) [20]
Fatigue	0	2 (9.5) [2]	4 (8.7) [4]
Pyrexia	0	2 (9.5) [2]	1 (2.2) [2]
Injection site reaction	0	0	3 (6.5) [4]
Injection site pain	0	0	3 (6.5) [3]
Injection site pruritus	0	2 (9.5) [2]	2 (4.3) [2]
Infections and infestations	4 (19.0) [4]	9 (42.9) [19]	20 (43.5) [41]
Oral candidiasis	0	1 (4.8) [1]	3 (6.5) [4]
Influenza	0	3 (14.3) [3]	0
Nasopharyngitis	0	1 (4.8) [1]	3 (6.5) [4]
Rhinitis	0	0	2 (4.3) [2]
Upper respiratory tract infection	0	2 (9.5) [2]	2 (4.3) [2]
Musculoskeletal and connective tissue disorders	2 (9.5) [2]	2 (9.5) [2]	5 (10.9) [10]
Arthralgia	1 (4.8) [1]	2 (9.5) [2]	1 (2.2) [3]
Back pain	0	0	2 (4.3) [2]
Nervous system disorders	6 (28.6) [9]	2 (9.5) [2]	5 (10.9) [6]
Headache	3 (14.3) [5]	0	3 (6.5) [4]
Renal and urinary disorders	0	0	2 (4.3) [2]

Acute kidney injury	0	0	2 (4.3) [2]
Skin and subcutaneous tissue disorders	4 (19.0) [4]	9 (42.9) [12]	13 (28.3) [22]
Hidradenitis	3 (14.3) [3]	7 (33.3) [8]	8 (17.4) [9]
Intertrigo	0	1 (4.8) [1]	3 (6.5) [3]
Dermatitis contact	0	0	2 (4.3) [2]
Vascular disorders	0	1 (4.8) [1]	6 (13.0) [6]
Hypertension	0	0	3 (6.5) [3]

ADA=adalimumab; BKZ=bimekizumab; MedDRA=Medical Dictionary for Regulatory Activities; PBO=placebo; PT=preferred term; SS=Safety Set; TEAE=treatment-emergent adverse event
Note: n=number of study subjects reporting at least one TEAE within system organ class/high level term/preferred term.
Note: [#] was the number of individual occurrences of the TEAE.
Source: HS0001 CSR, Table 11-3, pp.153-153

8.2.9. Additional Safety Explorations

Human Carcinogenicity or Tumor Development

Because they are large proteins, monoclonal antibodies are not expected to gain access to the nucleus and directly interact with DNA to promote carcinogenesis. BKZ will be catabolized to peptides and constituent amino acids via normal metabolic pathways. However, for any product that produces immunosuppression, and which is indicated for chronic administration, there is a theoretical risk of increased malignancy.

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

AEs of malignancy reported during the development program for HS were discussed in Section 8.2.5.5 of this review. The data available, to date, do not support the conclusion that chronic administration of BKZ is associated with an increased risk of carcinogenesis. However, the limited duration of observation during the drug development program is unlikely to allow detection of rare events with a long latency period such as malignancy. Malignancy is an outcome of interest in a long-term safety study to be conducted under PMR 4268-6 which was issued in the Approval Letter dated October 18, 2023.

Human Reproduction and Pregnancy

Female subjects of reproductive potential were required to have a negative pregnancy test at Screening and to use a highly effective method of birth control. Pregnancy testing was

performed at appropriate intervals. Per pre-specified withdrawal criteria, the study drug was discontinued if pregnancy occurred. Wherever possible, subjects who were pregnant were followed until delivery. The Applicant considered the following abnormal pregnancy outcomes to be SAEs:

- Spontaneous abortion
- Fetal death
- Stillbirth
- Congenital anomalies
- Ectopic pregnancy

In the initial sBLA submission and the 120-day Safety Update, the Applicant reported a total of 10 pregnancies in 9 subjects in the development program for HS, with the following outcomes:

- 3 pregnancies resulted in live birth of 4 heathy infants, with no congenital anomalies or major maternal complications
- 3 pregnancies ended due to induced abortion
- 2 pregnancies ended due to spontaneous abortion
- 1 pregnancy was ongoing
- 1 pregnancy had an unknown outcome

No congenital anomalies were identified. In a review dated March 20, 2024 by Wenjie Sun, MD, of the Division of Pediatrics and Maternal Health (DPMH) provided the following discussion and conclusions:

> "There is a pregnancy registry and database study for use of BKZ in pregnant women. However, the pregnancy registry has not initiated enrollment of patients at the time of this review. Results from additional eight BKZ exposed pregnancies to the 20 exposed pregnancies that were reviewed for the initial approval are not sufficient to change the approved labeling language at the current time. DPMH agrees with the previous conclusions on bimekizumab use during pregnancy, which states there are insufficient data to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. DPMH does not recommend labeling change at the current time…
>
> Because bimekizumab will be used in females of reproductive potential with the diagnosis of HD and there are insufficient data to inform drug-associated effects on maternal and infant outcomes with bimekizumab *in utero* exposure, DPMH recommends issuing postmarketing requirements (PMRs) for a pregnancy registry and database study to obtain additional data for this population. Since there is an existing pregnancy registry and database study for bimekizumab, the Applicant may enroll patients taking bimekizumab for HD into the existing bimekizumab pregnancy registry that is enrolling patients with moderate to severe plaque psoriasis. Additionally,

> because many patients with HS are also obese, obesity should be included as a confounder in the study design."

Refer to Section 13 (Postmarketing Requirements and Commitments) of this review for more details regarding the PMRs and proposed timelines.

Pediatrics and Assessment of Effects on Growth

The Applicant has not evaluated the safety and efficacy of BKZ in the pediatric population with moderate to severe HS. Because the Applicant is seeking approval of BKZ for the new indication of moderate to severe HS, approval of BKZ for this indication triggers the Pediatric Research Equity Act (PREA)(21 U.S.C. 355c).

The Applicant submitted an initial Pediatric Study Plan (iPSP) on 8/1/2019. A written response was sent to the Applicant on 10/25/2019. The Written Response included the following comment:

> "Your plan to request a waiver of the requirement to conduct studies in pediatric subjects from birth to less than 12 years of age is reasonable. We acknowledge the potential difficulty in recruiting (for a standalone, randomized, controlled clinical trial) sufficient numbers of adolescent subjects with moderate to severe hidradenitis suppurativa (HS) who would meet clinical criteria to receive treatment with your product. Therefore, in light of the safety and efficacy data from your Phase 2 trial, include pediatric subjects age 12 years to less than 17 years of age in your Phase 3 trials. Alternatively, you may consider conducting a separate open-label PK and safety trial in adolescent subjects (age 12 years to 17 years), to run in parallel with your Phase 3 trials in adults. The dosing in adolescent subjects should be supported by adequate justification."

In the final Agreed iPSP (dated April 7, 2020), the Applicant planned to request a deferral of studies in pediatric subjects ages 12 years to <18 years until population pharmacokinetic (PopPK) and population PK/pharmacodynamic (PopPK/PD) data was available from the phase 3 trials in adult subjects with HS. The Agency agreed with the Applicant's proposal and agreed with the iPSP (letter dated May 7, 2020).

In the Agreed iPSP as well as the BLA submission, the Applicant requested a partial waiver for studies in the pediatric population from birth to less than 12 years of age. The waiver was requested because the necessary studies are impossible or highly impracticable (Section 505B (a)(4)(B)(i) of the Act) due to the low prevalence of moderate to severe HS in this population. The Applicant requested a deferral of studies in the pediatric population age 12 years to less than 18 years until the safety, efficacy, and PopPK/PD data from the phase 3 trials in the adult population with moderate to severe HS was submitted and reviewed. (Section 505B(a)(3)(A)(ii) of the Act).

In the discussion with the Pediatric Review Committee (PeRC) on September 10, 2024, the PeRC agreed with the proposed partial waiver and deferral. DDD also discussed with the PeRC the Applicant's proposal to expand the study population to pediatric subjects ages 9 years and older who have attained Tanner Stage 2 or greater pubertal development. DDD and the PeRC agreed that, the Applicant's plan notwithstanding, a partial waiver would be granted for pediatric subjects from birth to <12 years of age.

Overdose, Drug Abuse Potential, Withdrawal, and Rebound

The Applicant reported that "to date, no intentional or accidental overdose has been reported during the clinical development program." The Applicant further noted that single doses of BKZ up to 640 mg SC were administered in phase 2 Trial HS0001 without dose-limiting toxicity. The Applicant did not propose language for inclusion in Section 10 (Overdosage) in product labeling.

Abuse, Withdrawal, and Rebound

There is no data to support an association of monoclonal antibodies including bimekizumab with the potential for addiction or abuse. Therefore, the Applicant did not evaluate abuse potential. The development program for HS did not evaluate for potential withdrawal or rebound effects. However, the development program for PsO included evaluation of withdrawal and rebound. No evidence of withdrawal or rebound was reported in the development program for PsO.

8.2.10. Safety in the Postmarket Setting

Safety Concerns Identified Through Postmarket Experience

In the 120-Day Safety Update, the Applicant stated that BKZ was first approved on August 20, 2021 in the EU (PsO indication) and is authorized in more than 40 countries as of February 19, 2024 (Periodic Safety Update Report [PSUR] submitted April 29, 2024 [SDN 228]). The axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) indications were first approved in the EU on June 5, 2023. Cumulatively since the approval up to February 19, 2024, the post-authorization patient exposure to BKZ outside of clinical trials is estimated to be approximately 24,360 patient-years.

In the most recent Periodic Adverse Experience Report (PAER) submitted to BLA 761151 and dated June 18, 2024, the Applicant reported no changes to the labeling. The PAER also stated that there was no new safety information to communicate during the reporting period. The PAER included 4 fatal cases. Except where noted, the dosage of BKZ was not reported. Brief summaries of the cases are presented below.

- A 29 y/o female from Canada with h/o hypothyroidism, anxiety, cholecystitis, coeliac disease, depression, hypertension, irritable bowel syndrome, and pancreatitis, developed severe gastroenteritis after her 4th dose of BKZ for PsO (interval between dose and onset of illness not reported). The following day she developed sepsis and had cardiac arrest and was revived. She developed multi-organ dysfunction syndrome and died. The cardiac arrest event was considered secondary to sepsis.
- A 35 y/o female from Canada with h/o HS was treated with BKZ off-label for her HS. Approximately 60 days after her first dose, she underwent surgery for an infected cyst on her back and reportedly died on the operating table. The cause of death was unknown and autopsy details were not reported.
- An "elderly" (age not reported) male patient from Canada receiving BKZ for PsO developed pneumonia, Crohn's disease, and inflammatory bowel disease unknown days after the initiation of BKZ for PsO. On an unspecified date, the patient died from complications of pneumonia. Per the narrative, "limited information regarding relevant medical history, onset latency, co-suspect drugs and concomitant medications, and autopsy details precluded an adequate medical assessment."
- A 30 y/o male from Slovakia was treated for PsO with BKZ 640 mg weekly (off-label dosage as per local labeling in Slovakia). The patient experienced COVID-19 infection and died due to hepatorenal failure 65 days after the initiation of BKZ.

Although the information in the narratives is not sufficient to definitively determine a relationship of these fatal event to treatment with BKZ, it should be noted that infection (including serious infection) and inflammatory bowel disease are known risks associated with treatment with BKZ and are communicated in labeling.

The PAER also included AESIs reported during the monitoring period. There were 3 cases with PTs of Liver function test increased. One patient also had a PT of Aspartate aminotransferase increased. There were also 6 SI/B events. These included 4 patients with PT suicidal ideation and 1 patient each with PT Self-injurious ideation and Suicide attempt. There were no completed suicides during the reporting period.

Overall, the safety events reported in the most recent PAER are consistent with the established safety profile of BKZ.

Expectations on Safety in the Postmarket Setting

The proposed dosing regimen of BKZ 320 mg SC Q2W from Weeks 0 to 16, then every 4 weeks thereafter, is different from the approved dosing regimen for PsO (320 mg SC Q4W from Weeks 0-16, then every 8 weeks thereafter [for patients weighing ≥ 120 kg, a dosage of 320 mg Q4W may be considered]). However, the safety profile of BKZ at the proposed dosing regimen in subjects with HS was consistent with the established safety profile of BKZ for the PsO indication. As such, based on the available safety data, we expect that the postmarketing safety

experience for patients with HS will be similar to that of patients with PsO for which BKZ is approved.

8.2.11. Integrated Assessment of Safety

The data provided with this sBLA submission was sufficient to characterize the safety of BKZ for the treatment of adults with moderate to severe HS. As of the 120-day Safety Update, exposure during the phase 3 trials in the HS program included 995 subjects exposed to BKZ. This includes 649 subjects with ≥12 months exposure and 496 with ≥24 months exposure. The primary analysis dataset (Pool S1) for the review of safety of BKZ for the treatment of moderate to severe HS included pooled data from the placebo-controlled Initial Treatment Period (Weeks 0-16) of phase 3 Trials HS0003 and HS0004. The review team evaluated long-term safety using Pool S3, which consists of data from the combined initial, maintenance, and open-label Periods of Trials HS0003, HS0004, and HS0005.

During the HS program, treatment with BKZ did not appear to increase the risk of mortality. The Applicant reported 2 deaths in subjects treated with BKZ. This included one subject with Cardiac failure congestive with sudden cardiac death, and one subject with CNS infection, septic shock and multiorgan failure. Treatment with BKZ did not appear to increase the risk for major adverse cardiovascular events (MACE).

In Pool S1, serious adverse events (SAEs) in each treatment group were reported by:

- BKZ 320 mg Q2W: 15/576 (2.6%; exposure-adjusted incidence rate [EAIR] 8.7/100 patient-years)
- BKZ 320 mg Q4W: 7/285 (2.5%; EAIR 8.1/100 pt-yrs)
- Placebo: 0

There was no clear safety signal for SAEs in Pool S1, with most SAE PTs reported in only one subject. In Pool S3, SAEs occurred in 6.9% (EAIR 8.0/100 subject years) of subjects treated with BKZ 320 mg Q2W and 6.0% (EAIR 7.2/100 subject years) of subjects treated with BKZ 320 mg Q4W. Based on the EAIRs, SAEs did not increase in frequency with longer exposure to BKZ. No cases of anaphylaxis, treatment-related angioedema, or serious hypersensitivity reactions related to treatment with BKZ were reported during the HS program.

In Pool S1, the most common ARs were Upper respiratory infections, Oral candidiasis, Injection site reactions, Other Candida infections, Pyrexia, Tinea infections, Fatigue, Folliculitis, Otitis externa, and Acne. These ARs are comparable to those identified during the development program for PsO and included in currently approved labeling for BKZ. As such, Section 6.1 of labeling for HS will include the statement "The safety profile observed in subjects with hidradenitis suppurativa treated with BIMZELX was comparable to the safety profile observed in subjects with plaque psoriasis treated with BIMZELX." Because of the small sample sizes for

demographic subgroups, it was not possible to detect clinically meaningful imbalances in ARs between the subgroups.

Treatment with BKZ is associated with a risk of suicidal ideation and behavior (SI/B), and this risk is conveyed in currently approved labeling for BKZ. Investigators assessed subjects for the development of SI/B using the Columbia Suicide Severity Rating Scale (C-SSRS) to monitor for treatment-emergent SI/B during the HS program. In Pool S1, 1.9% of subjects receiving BKZ and 0.7% of subjects receiving placebo reported SI on the C-SSRS. Subjects without a prior history of SI/B treated with BKZ also reported a higher rate of new-onset suicidal ideation on the C-SSRS than subjects receiving placebo (0.9% vs. 0%). In addition, there were 2 cases of SI that were adjudicated as suicide attempts. There were no completed suicides in the HS program. Data regarding SI/B in the HS program will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.

Infections occurred more frequently in subjects treated with BKZ than subjects receiving placebo. In Pool S1, TEAEs from the SOC Infections and infestations occurred in 33% (EAIR 132.2/100 pt-yrs) of subjects in the combined BKZ group and 21% (EAIR 76.4/100 pt-yrs) in the placebo group. Serious infections occurred in 0.1% (EAIR 0.4/100 pt-yrs) of subjects in the combined BKZ group and no subjects in the placebo group. In Pool S3, infections were reported in 68% (EAIR 104.7/100 pt-yrs) of subjects in the combined BKZ group. Serious infections occurred in 2.1% (1.7/100 pt-yrs) of subjects in the combined BKZ group. When analyzed by treatment group, based on the proportions and EAIRs, infections were more common in the Q2W group than the Q4W group and were not increased with longer exposure to BKZ.

The most commonly reported infections were comparable to those reported in subjects with plaque psoriasis. Oral candidiasis occurred in 7.8% of subjects (26.7 per 100 patient years) treated with BKZ 320 mg Q2W, 3.9% of subjects (12.9 per 100 patient years) treated with BKZ 320 mg Q4W, and 0 subjects receiving placebo. Other candida infections occurred in 3.6% of subjects (12.2 per 100 patient years) treated with BKZ 320 mg Q2W, 6.7% of subjects (22.6 per 100 patient years) treated with BIMZELX 320 mg Q4W, and 0 subjects receiving placebo. Tinea infections occurred in 3.1% of subjects (10.4 per 100 patient-years) treated with BIMZELX 320 mg Q2W, 2.5% of subjects (8.1 per 100 patient years) treated with BIMZELX 320 mg Q4W, and 0.7% (2.3 per 100 patient-years) receiving placebo. This information will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.

Elevated liver transaminases (>3xULN) occurred more frequently subjects treated with BKZ than subjects receiving placebo. In Pool S1, such elevations occurred in 1.2% of subjects treated with BKZ and 0% receiving placebo. Elevated liver serum transaminases resolved during continued treatment or after discontinuation of BKZ. This information will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.
Inflammatory bowel disease is a known risk of treatment with IL-17 inhibitors, including BKZ, and this risk is conveyed in currently approved labeling for BKZ. In Pool S3, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC), Crohn's disease (CD)

and IBD-undetermined) occurred in 5 subjects (0.39 per 100 patient-years). The majority of these cases were serious, and all resulted in discontinuation of BKZ. Additionally, flares of pre-existing IBD occurred in 2 subjects, which resulted in discontinuation of BKZ in both. This information will be conveyed in subsection 6.1, Clinical Trials Experience of labeling under the HS subheading.

Because of the mechanism of action of BKZ, malignancy was included as an adverse event of special interest (AESI). The review team did not identify a safety signal for malignancy in the study population through Week 48 of the phase 3 trials or in the available data from the open-label extension.

In the initial sBLA submission for HS and the 120-day Safety Update, the Applicant reported a total of 10 pregnancies in 9 subjects in the development program for HS. Three pregnancies resulted in live birth of 4 heathy infants, with no congenital anomalies or major maternal complications, 3 pregnancies ended due to induced abortion, 2 pregnancies ended due to spontaneous abortion, 1 pregnancy was ongoing, and 1 pregnancy had an unknown outcome. The effect of BKZ on human reproduction and pregnancy is discussed in further detail in Section 8.2.9 of this review. Because the available data are insufficient to evaluate the risk of major birth defects, miscarriage, or adverse fetal or maternal outcomes associated with treatment with BKZ, we will require the Applicant to recruit pregnant women with HS into the post-approval prospective and retrospective studies to be conducted to fulfill postmarketing requirements (PMRs) issued with the initial approval of BKZ for the treatment of moderate to severe PsO. Refer to Section 13 (Postmarketing Requirements and Commitments) for further details.

The safety data currently available demonstrate that BKZ is safe for the treatment of adult patients with moderate to severe HS. Postmarketing risk management will include professional labeling (including a Medication Guide), prescription status and routine pharmacovigilance. The long-term risk of malignancy, inflammatory bowel disease, and elevated liver enzymes is being evaluated in a long-term safety study to be conducted to fulfill a PMR issued with the initial approval of BKZ for the treatment of moderate to severe PsO. The maternal, fetal, and infant outcomes of women with HS exposed to BKZ during pregnancy will be evaluated by recruitment of these patients into the post-approval prospective and retrospective studies to be conducted to fulfill PMRs issued with the initial approval of BKZ for the treatment of moderate to severe PsO.

8.3. Statistical Issues

There were no major statistical issues affecting the overall conclusions for Trials HS0003 and HS0004. For both trials, bimekizumab Q2W was statistical superior to placebo (p-values ≤ 0.006) for the primary efficacy endpoint of HiSCR50 at Week 16; however, statistical superiority

of bimekizumab Q4W over placebo could only be claimed in Trial HS0004 (see Table 19 in Section 8.1.6). Bimekizumab Q2W was also statistical superior to placebo (p-values ≤ 0.021) for the secondary efficacy endpoint of HiSCR75 at Week 16 (see Table 21 in Section 8.1.7).

For the handling of missing data, the results of the primary efficacy endpoint were generally similar across the methods used to input the missing data (Table 70 in Appendix 19.6.5). In addition, there were no substantial differences in efficacy among subgroups; however, for some subgroups (e.g., age subgroups), the sample sizes were relatively small, which makes it difficult to detect differences in efficacy between these subgroups and their complements (Table 22 and Table 23 in Section 8.1.9).

During the filing review, the statistical reviewer identified at least one instance where a lesion that received lesion intervention was not counted as permanently present per the protocol. This was considered a potential review issue, and an information request was included in the Filing Communication Letter sent on April 2, 2024. On April 26, 2024, the Applicant submitted their response to the potential review issue and information request in the Filing Communication Letter. The Applicant conducted two *post hoc* sensitivity analyses and the results were included in the response (see Table 20 in Section 8.1.6). The results for both analyses were similar to those of the main analysis (see Table 19). For Trial HS0003, the treatment effects were 1-2% larger in the *post hoc* analyses than in the main analysis. However, for Trial HS0004, the treatment effects were 1% smaller in the *post hoc* analyses than in the main analysis. Overall, the results of the *post hoc* analyses are supportive of the main analysis.

8.4. Conclusions and Recommendations

To establish the effectiveness of BKZ for the treatment of moderate to severe HS, the Applicant submitted data from two adequate and well-controlled trials HS0003 and HS0004. These trials were randomized, multicenter, double-blind, placebo-controlled, parallel-group trials of identical design. The trials evaluated 1014 adult subjects ages 18 years and older with moderate to severe HS. The protocol-specified definition for moderate to severe HS was ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules) at both the Screening and Baseline visits, HS lesions in at least 2 distinct anatomic locations, 1 of which must be Hurley Stage II or III, and no more than 20 draining tunnels at Baseline. Subjects were randomized in a 2:2:2:1 ratio to the following treatment arms: BKZ 320 mg Q2W from Week 0-48, BKZ 320 mg Q4W from Week 0-48, BKZ 320 mg Q2W from Week 0-16, then 320 mg Q4W from Week 16-48, and placebo.

The primary efficacy endpoint was the Hidradenitis Suppurativa Clinical Response 50 (HiSCR50) at Week 16, defined by at least a 50% reduction in total abscess and inflammatory nodule count with no increase in abscess or draining tunnel count relative to baseline. In both trials, a higher proportion of BKZ-treated subjects achieved HiSCR50 compared to placebo. In Trial HS0003, 48% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 at Week 16 compared to 29% of subjects receiving placebo (difference 18%, 95% confidence interval [CI] 65%, 30%). In Trial

HS0004, 52% of subjects treated with BKZ 320 mg Q2W achieved HiSCR50 compared to 32% of subjects receiving placebo (difference 20%, 95% CI 8%, 32%).

The protocol and Statistical Analysis Plan (SAP) list the following key secondary efficacy endpoints (multiplicity-controlled endpoints):

- Proportion of subjects achieving HiSCR75 at Week 16
- Proportion of subjects who experience at least one flare by Week 16, with flare defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to baseline [ONLY Trial HS0004]
- Absolute change from baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 16
- Absolute change from baseline in the Worst HS Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HS Symptom Daily Diary (HSSDD)
- Proportion of subjects with a ≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16 among subjects with a baseline score ≥ 3

BKZ was superior to placebo for the key secondary endpoint of HiSCR75 at Week 16.
Data from the phase 3 trials was also sufficient to support the safety of BKZ for the treatment of moderate to severe HS. Pooling of data from the phase 3 trials allowed for comparison of safety vs. placebo and well as the comparative safety of short vs longer term exposure for the proposed dosing regimen. The proposed dosing regimen is BKZ 320 mg Q2W for 16 weeks followed by BKZ 320 mg Q4W.

The Applicant conducted a comprehensive assessment of safety of bimekizumab in the target population. The size of the safety database and the safety evaluations were adequate to identify local and systemic treatment-emergent adverse reactions. Safety and efficacy data submitted by the Applicant support approval of this sBLA for BKZ for the treatment of adults with moderate to severe HS.

9 Advisory Committee Meeting and Other External Consultations

The Agency held no Advisory Committee Meeting for this efficacy supplement. No novel or complex regulatory issues were identified that required an open forum discussion for this supplement.

10 Pediatrics

Refer to the following sections of this review for the proposed development program for BKZ in the pediatric population with moderate to severe HS:

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

11 Labeling Recommendations

11.1. Prescription Drug Labeling

The Applicant submitted proposed prescribing information (PI) and carton/container labels for BIMZELX (bimekizumab) injection. The review team provided recommendations regarding the PI which are provided throughout this review. The Office of Prescription Drug Promotion (OPDP) reviewed and provided comments regarding the PI. Refer to the OPDP review by Montherson Saint Juste, PharmD, MS dated September 26, 2024. The following table provides the location of the labeling discussion for each section.

Table 41: Location of the Labeling Discussion

Summary of Significant High Level Labeling Changes	
Section	Location of Reviewer Comments on Proposed Labeling
1 INDICATIONS AND USAGE	Section 1.1
2 DOSAGE AND ADMINISTRATION	Section 6.2.2
4 CONTRAINDICATIONS	N/A
5 WARNINGS AND PRECAUTIONS	Section 8.2.5
6 ADVERSE REACTIONS	Section 8.2.4
7 DRUG INTERACTIONS	Section 6.3.3
8 USE IN SPECIFIC POPULATIONS	Section 8.2.9
12 CLINICAL PHARMACOLOGY	Section 6.2, 6.3
13 NONCLINICAL TOXICOLOGY	Section 19.3 of BLA 761151 Unireview dated May 11, 2022
14 CLINICAL STUDIES	Section 8.1
17 PATIENT COUNSELING INFORMATION	Reflects the data in other sections of labeling, Sections 4, 5, 6, 7 and 14.

Source: Reviewer's Table

The review team discussed Agency recommended labeling with leadership from the Office of Immunology and Inflammation. Dr. Nikolay Nikolov, Office Director, Dr. Kathleen Donohue, Deputy Office Director, and Dr. Jill Lindstrom, Division Director of Dermatology and Dentistry, agreed with the recommendations from the review team.

11.2. Patient Labeling

The Applicant submitted a proposed Medication Guide (MG) and Instructions for Use (IFU) for BIMZELX (bimekizumab). The Division of Medical Policy Programs (DMPP) and OPDP reviewed and provided comments regarding the MG and IFU. These comments are reflected in final labeling. Refer to the DMPP/OPDP reviews by Susan Redwood, MPH, BSN, RN and Montherson Saint Juste, PharmD, MS dated September 20, 2024.

12 Risk Evaluation and Mitigation Strategies (REMS)

Safety findings from this review are consistent with the established safety profile of BKZ. As such, risk mitigation measures beyond professional labeling and a Medication Guide are not required at this time. Under 21 CFR 208.1, the Medication Guide is required to help prevent serious adverse effects. See Section 11.1 (Labeling Recommendations).

13 Postmarketing Requirements

Clinical postmarketing requirements are intended to characterize the risks of bimekizumab use in special populations (e.g., pregnancy). Development of final pharmacovigilance plans is ongoing.

The available safety data regarding use of BKZ during pregnancy are limited. The study population as defined by the entry criteria excluded pregnant and breastfeeding females, as well as females planning to become pregnant or breastfeed during the trials. Because exposures to BKZ during pregnancy are likely to occur and the available data are insufficient to characterize the associated risk in pregnant women, the Agency will require the Applicant to conduct post-marketing assessments to characterize the drug associated risk. Because the Applicant is already planning to conduct prospective and retrospective pregnancy studies under PMRs issued with the Approval Letter for PsO, we will require the Applicant to recruit pregnant women with HS into the existing studies.

Based on review of the data in this submission, proposed postmarketing requirements (PMRs) were conveyed to the Applicant (letter dated September 24, 2024). On November 6, 2024, the Applicant submitted a response to the proposed PMRs. The Agency considered the Applicant's proposed edits reasonable. The final PMR language and milestone dates are as follows:

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

Conduct a prospective pregnancy exposure registry/registries in pregnant patients with hidradenitis suppurativa.

You can use the registry required under PMR 4268-3 issued in the BLA 761151 Approval letter dated October 17, 2023.

Final Protocol Submission:	06/2025
Study/Trial Completion:	06/2034
Final Report Submission:	06/2035

Conduct a retrospective pregnancy cohort study in patients with hidradenitis suppurativa using claims or electronic health record data with medical chart validation.

You can use the registry required under PMR 4268-4 issued in the BLA 761151 Approval letter dated October 17, 2023.

Final Protocol Submission: 06/2025
Study/Trial Completion: 12/2034
Final Report Submission: 12/2035

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

This sBLA triggers the Pediatric Research Equity Act (PREA) as a new indication. The following study in the pediatric population 12 years to <18 years of age were included in the Agreed iPSP and will be deferred:

Conduct a multicenter, open-label clinical trial to evaluate the PK and safety of bimekizumab in pediatric patients including those 12 years of age and older with moderate to severe HS.

Final Protocol Submission:	No later than 07/2025
Interim Report/sBLA Submission:	No later than 02/2029
Study/Trial Completion:	No later than 05/2031
Final Report Submission:	No later than 11/2031

We are waiving the pediatric study requirement for ages 0 to less than 12 years because necessary studies are impossible or highly impracticable. We are deferring submission of pediatric studies for ages 12 years to less than 18 years for this application because this product is ready for approval for use in adults and the pediatric studies have not been completed. Refer to Section 8.2.9 of this review for a more detailed discussion of the waiver and deferral of pediatric studies.

14 Division Director (DHOT) Comments

Not applicable.

15 Division Director (OCP) Comments

Not applicable.

16 Division Director (OB) Comments

Not applicable.

17 Associate Director for Therapeutic Review (Clinical) Comments

I agree with the conclusions of the review team, labeling recommendations and regulatory action.

18 Office Director (or designated signatory authority) Comments

Not applicable.

19 Appendices

19.1. References

Cotton CH, SX Chen, SH Hussain, I Lara-Corrales, and AL Zaenglein, 2023, Hidradenitis Suppurativa in Pediatric Patients, Pediatrics, 151(5): 1-16.

Garg A, Malviya N, Strunk A, et al. Comorbidity screening in hidradenitis suppurativa: evidence-based recommendations from the US and Canadian Hidradenitis Suppurativa Foundations. J Am Acad Dermatol. 2022;86(5):1092-1101.

Goldberg SR, BE Strober, and MJ Payette, 2020, Hidradenitis suppurativa: Epidemiology, clinical presentation, and pathogenesis, J Am Acad Dermatol, 82: 1045-1058.

Jenkins T, J Isaac, A Edwards, and GA Okoye, 2023, Hidradenitis Suppurativa, Dermatol Clin, 41: 471–479.

Saunte DML and GBE Jemec, 2017, Hidradenitis Suppurativa: Advances in Diagnosis and Treatment, JAMA, 318(20): 2019-2032.

Scala E, S Cacciapuoti, N Garzorz-Stark, M Megna, C Marasca, P Seiringer, T Volz, K Eyerich, and G Fabbrocini, 2021, Hidradenitis Suppurativa: Where We Are and Where We Are Going, Cells ,10 (2094): 1-19.

19.2. Financial Disclosure

In compliance with 21 CFR Part 54, the Applicant provided Certification/Disclosure Forms from clinical investigators and sub-investigators who participated in covered clinical trials for bimekizumab. Prior to trial initiation, the investigators certified the absence of certain financial interests or arrangements or disclosed, as required, those financial interests or arrangements as delineated in 21 CFR 54.4(a)(3)(i-iv).

The “covered clinical studies” as defined in 21 CFR 54.I) were, phase 3 Trials HS0003 and HS0004, which provided the primary data to establish effectiveness and safety of this product. Refer to Section 8.1.1 for the trial designs.

A total of two investigators from Trial HS0003, and one investigator from Trial HS0004 had disclosable financial interests and arrangements and are listed in the table below.

The Applicant adequately disclosed financial interests involving clinical investigators. To mitigate potential bias related to financial payments, the Applicant ensured site monitoring and/or audits for investigators who reported financial interests above the allowed limits,

reviewed and analyzed data for outlier points, and blinded assessments. In addition, the number of investigators with financial disclosures was limited. As such, the strategies employed by the Applicant to minimize potential bias arising from investigator financial interests/arrangements appear reasonable.

Table 42: Investigators with Financial Disclosure Forms 3455 for Trials HS0003 and HS0004

Investigator	Trial/Site	Country	# Subjects Randomized	Description of Disclosure
James Q. Del Rosso, DO	HS0003/50208	USA	(b) (6)	(b) (4)
Joslyn Sciacca Kirby, MD	HS0003/50147	USA		
Abel D. Jarell, MD	HS0004/50259	USA		

Source: Compiled by Reviewer from Applicant's submission

Covered Clinical Study: HS0003

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 86		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 2 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial	Yes ☒	No ☐ (Request details from Applicant)

interests/arrangements:		
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

Covered Clinical Study: HS0004

Was a list of clinical investigators provided:	Yes ☒	No ☐ (Request list from Applicant)
Total number of investigators identified: 90		
Number of investigators who are Sponsor employees (including both full-time and part-time employees): 0		
Number of investigators with disclosable financial interests/arrangements (Form FDA 3455): 2		
If there are investigators with disclosable financial interests/arrangements, identify the number of investigators with interests/arrangements in each category (as defined in 21 CFR 54.2(a), (b), (c) and (f)): Compensation to the investigator for conducting the study where the value could be influenced by the outcome of the study: 0 Significant payments of other sorts: 1 Proprietary interest in the product tested held by investigator: 0 Significant equity interest held by investigator in Sponsor of covered study: 0		
Is an attachment provided with details of the disclosable financial interests/arrangements:	Yes ☒	No ☐ (Request details from Applicant)
Is a description of the steps taken to minimize potential bias provided:	Yes ☒	No ☐ (Request information from Applicant)
Number of investigators with certification of due diligence (Form FDA 3454, box 3) 0		
Is an attachment provided with the reason: N/A	Yes ☐	No ☐ (Request explanation from Applicant)

19.3. Nonclinical Pharmacology/Toxicology

This section is not applicable.

19.4. OCP Appendices (Technical documents supporting OCP recommendations)

19.4.1. Bioanalytical Method Validation and Method Performance

Bioanalytical methods (PK method #2 and #3) used to analyze PK concentrations in HS studies were previously submitted with the original BLA. Both methods were reviewed as a part of the original BLA review. However, the validation summary of PK method #2 was only included in the original BLA review dated 05/11/2022. Hence, PK method #3 validation summary has been included in this review along with its in-study method performance. PK method #3 was used to measure plasma concentrations of bimekizumab derived from the pivotal HS studies.

The PK method #3 is identical to PK method #2 and was transferred to a different contract research organization (CRO) analytical lab (PPD). The method performance of PK method #3 as summarized in Table 7 is comparable with that of method #2.

All validation parameters of PK method #3 provided the accuracy (percent of analyte recovery) and precision (% coefficient of variation [%CV]) that are within acceptance criteria, supporting the adequacy (robustness, selectivity, reproducibility) of the bioanalytical method. Hence, the bioanalytical method validation is acceptable.

Table 43: Summary of validation parameters of PK method #3

Validation Parameters	Results
Calibration Range	0.25-20 µg/mL
Accuracy (LLOQ - ULOQ)	-3.98% to 3.31%
Precision (LLOQ - ULOQ)	≤3.78%
Selectivity	Selectivity determined in 10 individual plasma samples of HS patients at 250 ng/mL and 15,000 ng/mL level. 100% of the spiked samples were within 25% (250 ng/mL) and 20% (15,000 ng/mL) RE. Range of observed bias: 250 ng/mL drug: -3.99% to 4.30% RE; 15,000ng/mL drug: -6.61% to 3.28% RE.
Interference and specificity	Interference of IL-17A and IL-17F was tested at target levels of 4 and 8 ng/mL in combination with 250 ng/mL and 20,000 ng/mL drug. Target interference observed at 4 and 8 ng/mL target at the 250 ng/mL level (bias: -30.0% [4 ng/mL target] and -42.6% [8 ng/mL target]). No interference observed at the 20,000 ng/mL level (bias: -16.5% [4ng/mL target] and -13.9% [8ng/mL target]).
Hemolysis effect	The effect of hemolysis was determined in 5 individual healthy subject plasma samples prepared at 3% hemolyzed plasma and spiked at drug levels of 250 ng/mL (LLOQ) and 15,000 ng/mL. 100% of the spiked samples were within 25% (250 ng/mL) and 20% (15,000 ng/mL) RE. Range of observed bias:

	250ng/mL drug: -7.74% to -1.28% RE; 15,000 ng/mL drug: -8.55% to -5.97% RE.
Lipemic effect	The effect of hyperlipemia was determined in 5 individual healthy subject plasma samples containing approximately 400 mg/dL of triglycerides and spiked at drug levels of 250 ng/mL (LLOQ) and 15,000 ng/mL. 80% of the samples spiked with 250 ng/mL were within 25%, and 100% of the samples spiked with 15,000 ng/mL were within 20% RE. Range of observed bias: 250 ng/mL drug: -44.7% to -7.73% RE; 15,000 ng/mL drug: -11% to -7.62% RE.
Dilution linearity and hook effect	Dilution linearity: Demonstrated using a starting dilution of 250 µg/mL. Samples were diluted up to a factor of 400. The observed range of bias observed at the 20, 80, and 400 dilution level ranged from - 12.9% to -6.35% RE. Hook effect (prozone): No hook effect observed at concentrations up to 250 µg/mL drug.
Stability	Bench-top: 72 hours Six freeze/thaw cycles at -25° and -80°C. Long term stability: -25°C and -80°C up to 1098 days

RE: Relative Error

The bioanalytical method described in Table 43 was used to measure bimekizumab concentrations in plasma samples from studies HS0003 and HS0004. The in-study method performance for these studies is described in Table 44 below and is acceptable.

Table 44: Method performance summary – determination of human plasma concentrations of bimekizumab

Parameters	Results	
	HS0003	HS0004
Assay passing rate	98.3% (174 runs out of 177 passed)	97.3% (183 runs out of 188 passed)
Standard curve performance	Cumulative bias range observed: -3.22 to 3.33% RE; Cumulative precision observed: ≤4.03% CV	Cumulative bias range observed: -3.07 to 3.22% RE; Cumulative precision observed: ≤3.67% CV
QC performance QC levels: 18, 80, and 300 ng/mL	Cumulative bias range observed: 0.0643 to 6.15% RE; Cumulative precision observed: ≤17.2% CV; Cumulative %TE observed: ≤23.3% TE	Cumulative bias range observed: 0.0693 to 5.39% RE; Cumulative precision observed: ≤8.39% CV; Cumulative %TE observed: ≤11.2%
Method reproducibility (ISR)	Incurred sample reanalysis (ISR) was performed in 10% of study samples and 99.0% of samples met the pre-specified criteria.	Incurred sample reanalysis was performed in 11.6% of study samples and 99.7% of samples met the pre-specified criteria.
Study sample analysis/stability	All samples fell within established stability.	All samples fell within established stability.

RE: Relative error; TE: Total error; CV: Coefficient of variation.

In-study performance of PK method #2 for determination of plasma concentrations of bimekizumab derived from the study HS0001 was also found adequate.

19.4.2. Applicant's Population Pharmacokinetic Analysis

The Applicant conducted population pharmacokinetics (PopPK) modeling and simulations followed by exposure-response (E-R) analysis to support the proposed dosing regimen. A previously developed 1-compartment PopPK model was used as the starting model to describe the data derived from three HS clinical studies. The final PopPK model was also a 1-compartment model with first order absorption and linear elimination that adequately described the bimekizumab concentration-time profiles in subjects with HS. The PopPK model was combined with the E-R model to allow for E-R analysis. The final E-R model was a proportional odds model that adequately described the dose/exposure-response relationship with respect to the endpoints of HiSCR50/75/90/100. The key points of PopPK and E-R analysis are summarized below:

- Body weight, prior use of biologics, and disease severity were identified as significant covariates impacting the bimekizumab exposures. However, there were no clinically meaningful impact of these covariates in terms of efficacy outcomes. Hence, no dose adjustment is necessary based on any covariates.
- CL/F and V/F were 31% and 18% higher, respectively, in HS subjects compared to other indications (e.g., PsO, PsA, and axSpA) for a 90 kg subject. The t½ for a 90 kg individual was 20 days in subjects with HS.
- For a typical 95 kg HS subject, the estimated CL/F and V/F were 0.512 L/day and 14.5 L, respectively, which translates to a t1/2 of 19.7 days.
- CL/F was predicted to be 56% higher for a subject weighing 142 kg and 38% lower for a subject weighing 62 kg, compared to a typical subject weighing 95 kg. Consistently, exposures were decreased with increasing body weight.
- Bimekizumab exposures ($AUC_{\tau,ss}$, $C_{max,ss}$, and $C_{min,ss}$) were decreased by 30-40% for a HS subject of 142 kg (95th percentile) and increased by 50-70% for 62 kg (5th percentile of observed body weight distribution) compared to a reference HS subject (weighing 95 kg, not having prior biologics use and being Hurley stage II).
- There was no clear dose-response relationship found in E-R analysis as response rate versus time curves for all tested dosing regimens were overlapped. Simulations further suggest that the proposed dosing regimen (320 mg Q2W/Q4W) can provide ~3% higher response at Week 16 over Q4W (lowest dosing regimen) for HiSCR50. However, this benefit is diminished at Week 48 (at the end of maintenance treatment period) as the response rates are almost the same between these regimens.
- In E-R model, smoking status and baseline AN counts were found statistically significant. For example, non-smokers had 10% higher response rates compared with smokers/previous smokers. Subjects with high baseline AN counts (>20) had also 5-10% higher response rates than those with lower AN counts. However, the effect of these covariates was not clinically meaningful.

- No model-based exposure-safety analysis was conducted. Descriptive analysis indicates that the TEAEs are comparable across the tested dosing regimens and different quartiles of concentrations resulting from Q4W regimen.
- Overall, notwithstanding the proposed 320 mg Q2W/Q4W did not show a clear benefit over Q4W, the totality of evidence suggests its substantial effectiveness with a favorable benefit-risk ratio, hence recommended for the treatment of adults with moderate and severe HS. Despite body weight showed the most influential covariate impacting the bimekizumab exposures, no apparent dose/exposure response for efficacy was observed. Predicted response rates were similar across different body weight deciles at Weeks 16 and 48. Hence, flat dosing regimen across different body weight subgroups were considered acceptable.

Table 45: Summary of PopPK analyses

General Information	
Objectives of PopPK analysis	• To describe the population PK characteristics of bimekizumab, including associated interindividual variability (IIV) and residual unexplained variability (RUV) in patients with HS • To evaluate the impact of selected covariates on bimekizumab apparent clearance (CL/F) • To derive individual bimekizumab PK parameter estimates that can be used to compute individual specific PK exposures
Study and population included	The PopPK analysis dataset contained data collected from 3 clinical studies (HS0001, HS0003, and HS0004). Refer to section 8.1.1 for detailed study design.
Dose(s) included	Study HS0001: 620 mg (LD) at baseline, then 320 mg at Weeks 2, 4, 6, 8, and 10, subcutaneously. Studies HS0003 and HS0004: 320 mg Q2W from Weeks 0 – 48; 320 mg Q4W from Weeks 0 – 48; 320 mg Q2W to Week 16 (Initial treatment period, last dose at Week 14) then 320 mg Q4W from Weeks 16 -48 (maintenance treatment period); Placebo to Week 16, then 320 mg Q2W from Weeks 16 to 48. Dose was administered subcutaneously in all arms.
PopPK analysis dataset	This dataset contained a total of 8891 post-baseline PK observations. PK samples were collected at Weeks 2, 4, 8, 12 in study HS0001 and Weeks 1, 2, 4, 8, 12, 16, 18, 20, 24, 36, 48 in studies HS0003 and HS0004. See Figure 11 that represents a spaghetti plot describing individual concentration-time profiles with smooth splines.
No. of patients, PK samples, and BLQ	Adult patients with moderate to severe HS: 1035 Total PK samples post-baseline: 9051 Total BLQs after baseline: 160, which were ignored in PopPK analysis. Note that plasma concentrations that are below limit of quantitation (BLQ) were retained in the PopPK dataset, with the values set to LLOQ/2. However, the number of BLQs relative to the total number of plasma observation records was low, hence excluded from PopPK analysis as no alternative modelling approaches for handling these observations were deemed necessary.
Population Characteristics	Age (years): Median (min – max): 35 (18 – 78) Mean ± SD: 36.6 ± 12 Body weight (kg): Median (min – max): 95 (48 – 196), Mean ± SD: 97.2 ± 24.4 Sex: 447 (43%) Males and 588 (57%) Females

	Race: 826 White; 116 Black/African American; 42 Multiple/Other; 29 Japanese, 12 Asian (excluding Japanese), 5 Unknown/Not reported; 3 American Indian/Alaska Native; 2 Native Hawaiian/Pacific Islander Disease severity: 613 (59%) with Hurley stage II and 422 (41%) with Hurley stage III Prior biologics use: 190 (18%) used biologics before, 845 (82%) did not ADA and NAb status: 575 (56%) were ADA positive; 330 (32%) were both ADA and NAb positive.	
Final Model	Summary	Acceptability [FDA's Comments]
Software and version	• Nonlinear mixed effects modeling (NONMEM) (Version 7.5) • Perl-speaks-NONMEM (PsN), version 5.2.6 • R statistical software (version 3.5.3) was used for data tabulation/ visualization/ simulation activities.	Acceptable
Model Structure	The starting model was an existing bimekizumab population PK model developed from data in patients with psoriasis, psoriatic arthritis, and axial spondyloarthritis, which was reviewed as part of original BLA[10] and supplements 6 and 7.[11] The final bimekizumab PK model is a 1 compartment model with first-order absorption without lag time and first-order elimination from the central compartment. IIV terms are included on relative bioavailability (Frel), V/F and CL/F. In addition, the proportional plus additive RUV model with an exponential IIV term was found to provide a better description of the data.	Acceptable
Base Model Parameters	Body weight was included as a covariate on CL and V parameters in base model to adequately characterize the PK of bimekizumab in HS subjects See Table 46 for final parameter estimates All parameters were estimated with good precision (%RSE <25%).	Acceptable
Covariate Model	An assessment of covariate effects was conducted using the Stepwise Covariate Model (SCM) building procedure. As noted above, the BW was included as a mechanistic covariate in base model. Additional potential covariate-parameter relationships were evaluated on CL/F using the SCM procedure with adaptive scope reduction (ASR). The evaluated covariates include ADAb and NAb status as a combined covariate, prior use of biologics, disease severity (Hurley stage II and III), age, sex, race, and geographical region. Baseline values were used for all covariates except anti-drug-antibodies (ADAb) titers and the combined ADAb/neutralizing anti-drug-antibody (NAb) covariate. ADAb titers was treated as a time-varying covariate and last observation carried forward (LOCF) method was used to fill in titer values throughout and between adjacent visits.	Acceptable
Final Model Parameters	See Table 46 for parameter estimates. The pre-final model identified BW, Hurley stage III, prior biologics use, and Black/African American as significant covariates based on SCM	Acceptable

[10] REV-SUMMARY-13 (Unireview) DARRTS: 05/11/2022, Page 238.
[11] REV-SUMMARY-13 (Unireview) DARRTS: 09/20/2024, Page 181.

	procedure for which the forward and backward elimination with p-values of 0.01 and 0.001, respectively, were prespecified. Further, covariate model was refined based on influences of covariates on the secondary bimekizumab PK parameters AUCτ,ss, Cmax,ss, Cmin,ss, and t1/2, following dosing of bimekizumab Q4W or Q2W. Based on the estimated covariate effect and associated 90% CI generated in the Forest plots (Figure 12), Black/African American was excluded from the final model due to its negligible influence on the secondary PK parameters. The final model includes the following covariate parameter relationships: Baseline WT, prior use of biologics and disease severity (Hurley stage III) on CL/F, as well as baseline WT on V/F.	
GOF, VPC plots	The goodness-of-fit plots and VPC (visual predictive check) plots of the final population PK model are shown in Figure 13 and Figure 14, respectively.	**Acceptable**
Effect of Covariates	Only body weight, prior use of biologics, and disease severity (Hurley stage III) were found to be significant determinants of CL/F and body weight of V/F, although none of these covariates were concluded to be clinically relevant in terms of HiSCR outcomes and did not require any changes to bimekizumab dosing in HS.	Acceptable

CL/F: Apparent linear clearance from central compartment; V/F: Apparent central volume of distribution

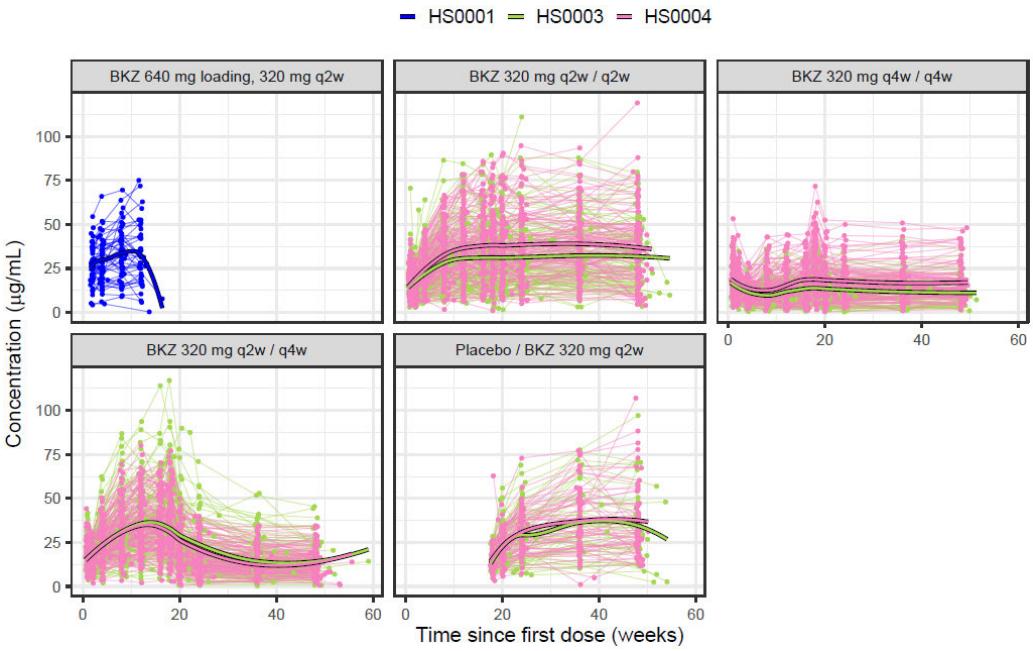
Table 46: Pharmacokinetic and Covariate Parameters in Final Population PK Model.

Model Parameter (Unit)	Population Estimate	RSE (%)	Shrinkage (%)
CL/F[a] (L/day)	0.512	1.47	-
V/F[b] (L)	14.5	1.18	-
ka (1/day)	0.499	4.04	-
Covariates effects)			
WT on CL/F[a]	1.12	3.96	-
Prior biologics on CL/F[c]	0.121	23.9	-
Hurley stage III on CL/F[c]	0.182	13.0	-
WT on V/F[b]	0.782	5.17	-
Inter-individual Variability (IIV)			
IIV CL/F (CV)	0.239	4.33	20.1
IIV V/F (CV)	0.192	7.72	32.6
IIV F_{rel} (CV)	0.274	4.06	14.8
IIV RUV (CV)	0.317	7.07	11.6
Residual Unexplained Variability (RUV)			
Proportional RUV (CV)	0.111	2.86	4.96
Additive RUV (SD, µg/mL)	0.871	10.3	4.96

The RSE for IIV and RUV parameters are reported on the approximate SD scale. ka: first order absorption rate constant.
[a]Parameter estimate is for a subject weighing 95 kg (updated to the median of WT in the PK analysis data set) with no prior biologics use and in Hurley stage II. The equation for the typical values of CL/F with respect to WT is $CL/F = 0.512 * (WT/95)^{1.12}$.
[b]Parameter estimate is for a subject weighing 95 kg (updated to the median of WT in the PK analysis data set).
The equation for the typical values of V/F is $V/F = 14.5 * (WT/95)^{0.782}$.
[c]The effects of disease severity (Hurley stage III) and Prior biologics use on CL/F are calculated as a proportional change (1+ final model value), compared to the corresponding reference categories.

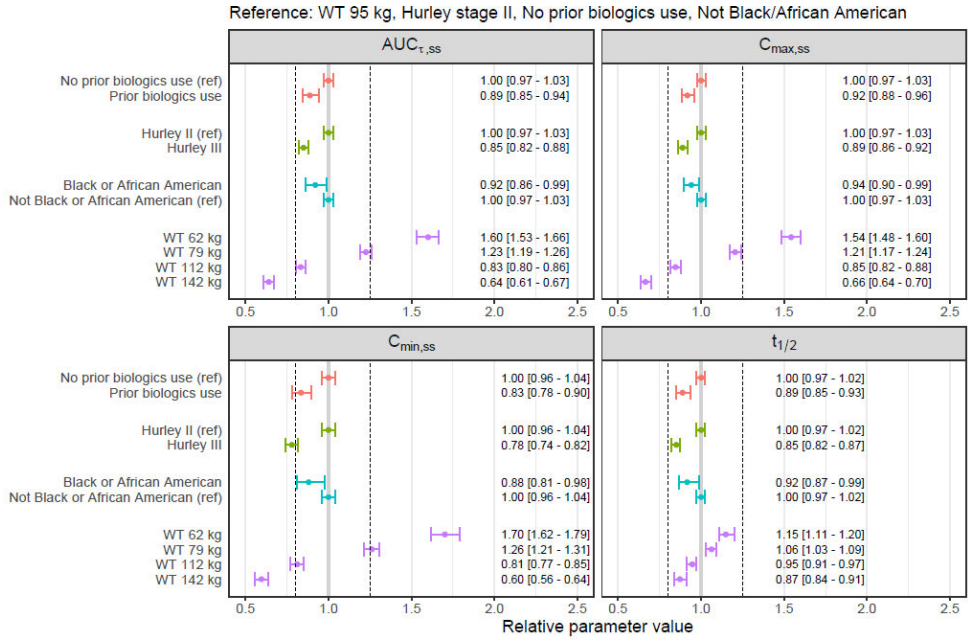
Source: Adapted from population pharmacokinetic analysis report (CL0561, table 15) available at m5.3.3.5-seq0116. Reviewer's independent analysis provides the similar estimates for all model parameters.

Figure 11: A spaghetti plot illustrating bimekizumab concentration-time profiles of individual subjects in HS clinical studies



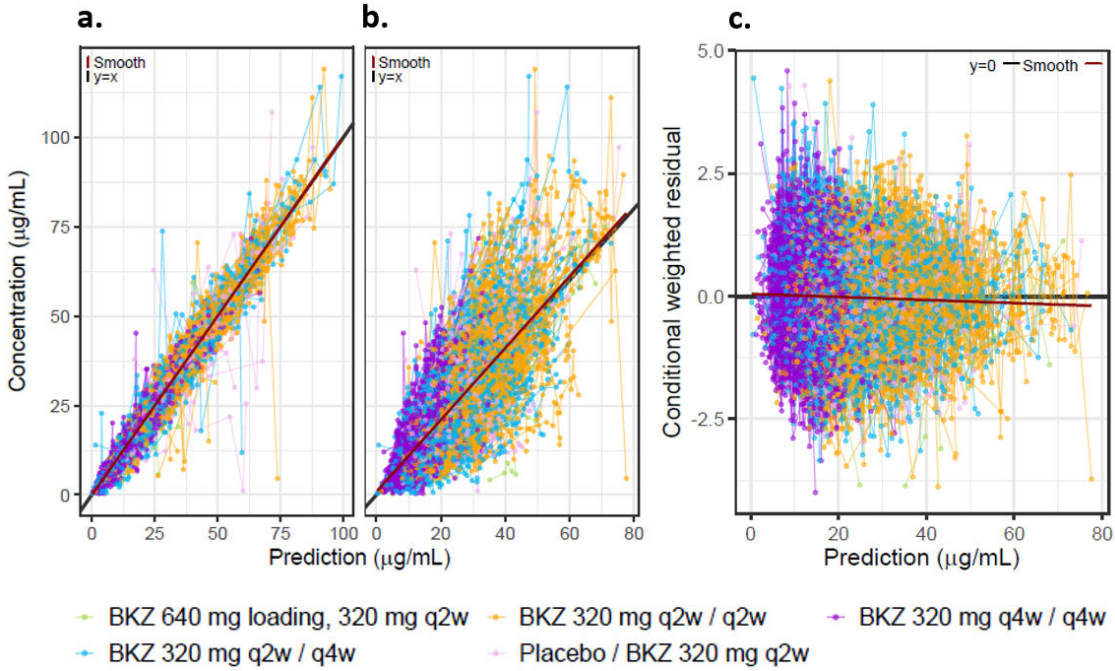
Note: Data are stratified by treatment and colored by study and presented on linear scale. The solid lines are smooths. Source: m5.3.3.5 – CL0561: Applicant's PopPK report, page 34.

Figure 12: Forrest plots illustrating the influences of various covariates on **AUCτ,ss,** Cmax,ss, Cmin,ss, and t1/2 for Q4W dosing regimen.



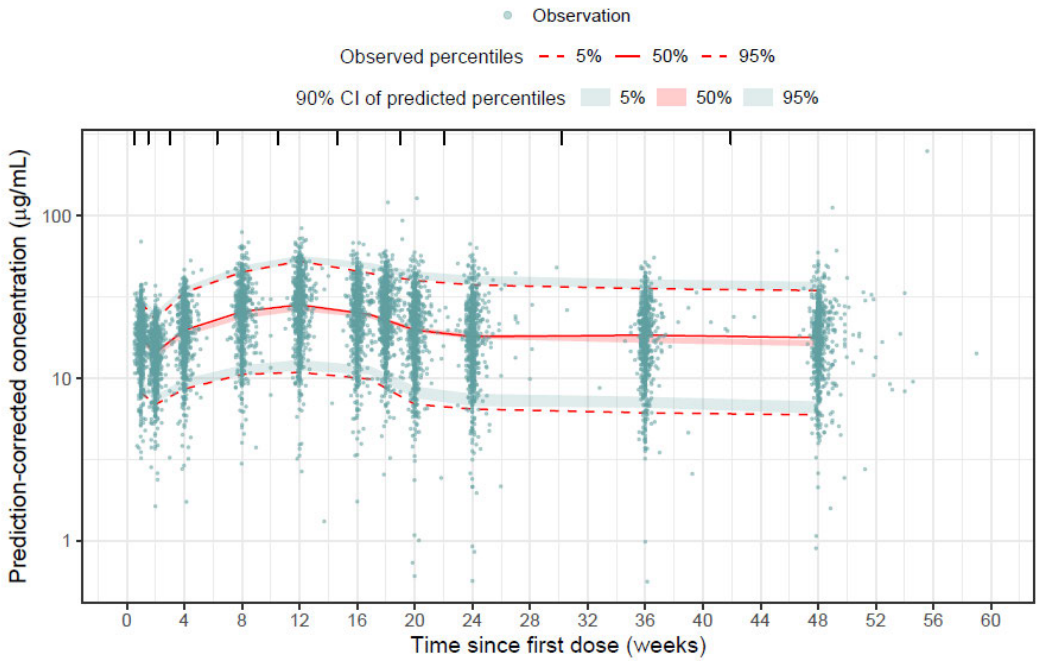
Notes: Closed dots and error bars, together with their specific values, represent the median of the predicted relative change from the reference subject and its associated 90% CIs; these values are calculated based on 200 sampled parameter vectors from the variance-covariance matrix obtained from NONMEM. The parameter values for a reference subject (for whom covariate characteristics are provided above the plot) are shown by the solid vertical lines with the associated 90% CIs reflecting uncertainty in the estimated PK parameters; the dashed vertical lines indicate the 80%-125% margins relative to the reference subject. For categorical covariates, the impact of each category is shown, compared to the reference group. For WT, the impact at the 5%, 25%, 75% and 95% percentiles is shown, compared to the median of the covariate. Source: m5.3.3.5 – CL0561: Applicant's PopPK report, page 71.

Figure 13:Goodness-of-fit plots from the final PopPK model in subjects with HS



Notes: a. Observed versus individual predicted concentrations; b. Observed versus population predicted concentrations; c. Conditional weighted residuals (CWRES) versus population predicted concentrations. Plots are based on the final bimekizumab PK model (run 129). Data are presented on linear scale. Lines connect data points from the same subject. Source: m5.3.3.5 – CL0561: Applicant's PopPK report, pages 179-81.

Figure 14: Visual predictive checks for the final PopPK model in subjects with HS



Note: Data are presented on a semi-logarithmic scale. Time points associated with BLQ observations were included in the VPC. Green dots: observations; The solid red line depicts median observed data, while pink shaded areas define the 95% prediction intervals around the median of the simulated data. Red dashed lines represent the 5th and 95th percentiles of observed data, while green shaded areas represent the simulated 95% prediction interval of 5th and 95th percentiles.
Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R analysis report, pages 74.

Applicant's Summary of Pharmacokinetic Analyses

The final is a one-compartment model with first-order absorption and first-order elimination to characterize the PK profile of bimekizumab in HS subjects. The model was found to have adequate and predictive performance for bimekizumab plasma concentrations as indicated by GOF and VPC plots.

Though body weight, prior use of biologics, and disease severity (Hurley stage III) were identified as significant covariates, these were not concluded to have clinically meaningful impact in terms of HiSCR outcomes. Therefore, no dose adjustment is needed based on any covariates or sub-population.

The significant covariates were identified based on both SCM procedure (based on objective function reduction with associated p-values of 0.01 for forward selection and 0.001 for backward elimination) and influence of a covariate on the secondary PK parameters. Despite Black/African American was statistically significant covariate in SCM analysis, it was excluded from the final PopPK model. Because forest plots illustrating the impact of covariates indicate that this covariate-mediated predicted change in PK exposures from the reference subject and associated 90% CIs fell within the no effect boundary of 80 – 125% for each secondary PK parameters. Conversely, body weight had a greater influence on the PK exposures as the 90%

CIs for lower and higher body weight bands either completely or partially fell out of 80 – 125% limit (Figure 12).

Summary results of bimekizumab PopPK analysis:

- For a reference HS subject weighing 95 kg, being in Hurley stage II and not having prior biologics use, CL/F was estimated to 0.512 L/day, V/F to 14.5 L. This results in a half-life (t1/2) of 19.7 days.
- As stated above, the largest covariate impact was demonstrated by body weight. CL/F was predicted to be 56% higher for a subject weighing 142 kg and 38% lower for a subject weighing 62 kg, compared to a typical subject weighing 95 kg (see Table 46). Note that when compared to other indications such as PsO, PsA, axSpA, CL/F and V/F in HS were 31% and 18% higher, respectively, for an individual weighing 90 kg. Consequently, the median steady state concentration at a dose of 320 mg Q4W was approximately 40% lower in HS compared to other indications.
- Simulations based on the final PopPK model suggest that increased in body weight decreases bimekizumab exposures (Table 47). For example, the bimekizumab exposures in terms of AUCτ,ss, Cmax,ss, and Cmin,ss were decreased by 30-40% for a HS subject of 142 kg (95th percentile) and increased by 50-70% for 62 kg (5th percentile of observed body weight distribution) compared to a reference HS subject (weighing 95 kg, not having prior biologics use and being Hurley stage II). The predicted t1/2 values were 13% lower in 142 kg subject and 15% higher in 62 kg subject.

Table 47: Simulated steady-state bimekizumab PK, stratified by body weight for a 320 mg Q4W dosing regimen.

Body weight percentile	Body weight[a] (kg)	n[b]	$AUC_{\tau,ss}$[c] (µg*day/mL)	$C_{max,ss}$[c] (µg/mL)	$C_{min,ss}$[c] (µg/mL)	$t_{½}$[c] (day)
<10th	62.0 [48.0 - 69.0]	97	951 [555 - 1900]	44.1 [27.5 - 83.7]	22.5 [11.4 - 53.1]	22.3 [12.3 - 42.4]
10th to 25th	74.5 [69.4 - 78.8]	152	727 [371 - 1410]	35.9 [18.2 - 67.9]	16.1 [5.53 - 37.3]	18.1 [9.65 - 35.6]
25th to 50th	86.8 [79.0 - 96.5]	251	637 [296 - 1270]	31.6 [15.6 - 61.9]	13.9 [5.14 - 31.8]	18.9 [9.97 - 33.8]
50th to 75th	104 [96.6 - 115]	248	512 [266 - 1020]	25.9 [13.3 - 48.2]	10.1 [3.73 - 24.7]	16.6 [8.86 - 32.4]
75th to 90th	123 [115 - 131]	152	382 [208 - 960]	19.7 [11.5 - 44.5]	7.41 [2.58 - 21.7]	16.0 [8.48 - 29.5]
≥90th	142 [132 - 184]	100	361 [156 - 849]	19.5 [9.31 - 40.9]	6.99 [1.62 - 17.3]	14.6 [7.26 - 26.0]

$AUC_{\tau, ss}$=steady-state area under the curve; $C_{max,ss}$=maximum concentration at steady state; $C_{min,ss}$=minimum concentration at steady state; $t_{½}$= half-life
[a] Median [minimum-maximum] weight in category.
[b] n corresponds to the number of study participants in the analysis data set.
[c] Median [2.5th-97.5th percentiles]

Source: m2.7.2-seq0116: Summary of Clinical Pharmacology Studies – HS, page 24.

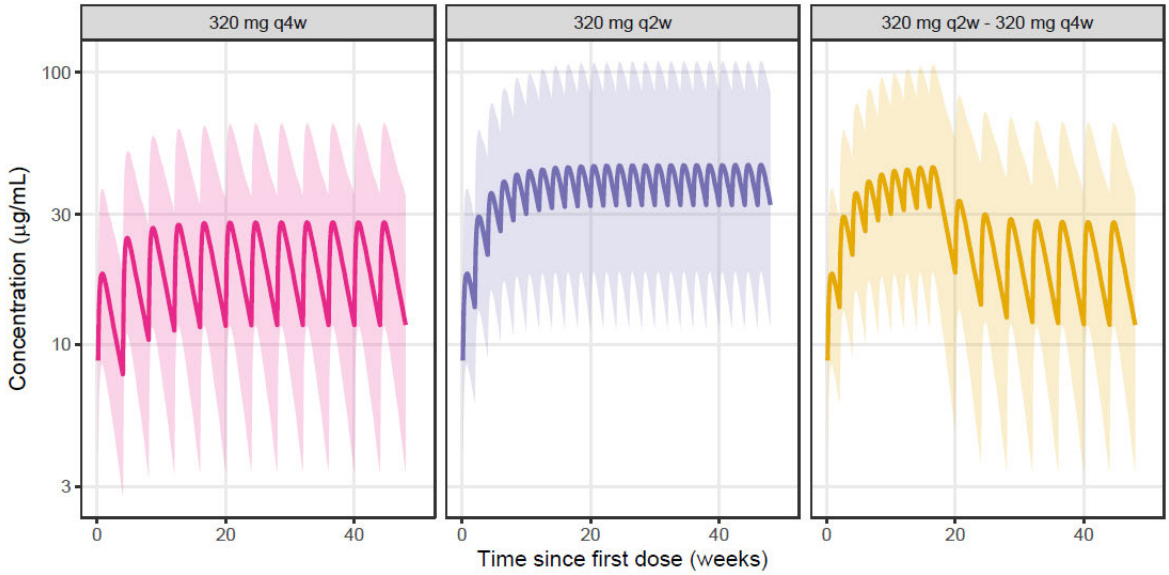
- Further, simulations imply that the bimekizumab concentrations increased in an approximate dose-proportional manner. Steady state was attained by Week 8 irrespective of dosing regimen. The predicted median (95% prediction interval) half-life was 17.3 (9.14 – 34.1) days with a median Tmax of approximately 4 days in HS subjects (See Table 48, Figure 15).

Table 48: Simulated PK parameters resulting from 320 mg Q4W and Q2W dosing regimens.

Dosing regimen	$AUC_{\tau,ss}$[a,b] (μg · day/mL)	$C_{max,ss}$[a] (μg/mL)	$C_{min,ss}$[a] (μg/mL)	t_{max}[a] (days)	$t_{1/2}$[a] (days)	AR[a]
320 mg q4w	569 [218 - 1390]	28.2 [11.7 - 64.9]	11.8 [3.39 - 35.0]	4.64 [4.15 - 4.94]	17.3 [9.14 - 34.1]	1.48 [1.14 - 2.30]
320 mg q2w	569 [218 - 1390]	45.7 [18.5 - 110]	32.6 [11.5 - 84.7]	3.66 [3.45 - 3.77]	17.3 [9.14 - 34.1]	2.33 [1.53 - 4.04]

[a]: Median [2.5th-97.5th percentiles]
[b]: $AUC_{\tau,ss}$ corresponds to area under the concentration-time curve (AUC) over the dosing interval.
Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R analysis report, pages 80.

Figure 15: Individual predictions of bimekizumab plasma concentrations versus time since first dose (TSFD) for the subjects in the simulation dataset.



Note: Data are stratified by dose, colored by dose and body weight category and presented on semi-logarithmic scale. The solid lines represent the median and the shaded areas represent the 95% prediction interval, representing variability between subjects.
Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R analysis report, pages 78

The reviewer's independent analysis of the final PopPK model provided similar parameter estimates with similar precision as reported by the Applicant. The adequacy and predictability of the Applicant's PopPK model is supported by the reviewer's independent analysis. The summary results of the final PopPK model were provided in Table 45. The reviewer agrees with the Applicant's overall conclusion of PopPK analysis of bimekizumab for HS subjects stated above.

Exposure-Response Analyses

Table 49: Summary of Exposure-Response (E-R) modeling

General Information		
Objectives of Exposure-Response (E-R) analysis	• To describe the ER for HiSCR outcomes. • To evaluate the impact of selected covariates on bimekizumab ER parameters. • To support dosing recommendations in the label by simulations from the developed PK and E-R models.	
Study and population included	The E-R analysis dataset contained data from 2 HS studies: HS0003, HS0004. There are 997 subjects with 11942 observations included for E-R analysis.	
Dose(s) included	Dosing regimens evaluated in HS0003 and HS0004 were only included. See Table 45.	
Endpoints/response variables*	Hidradenitis Suppurativa Clinical Response 50%, 75%, 90%, and 100% (HiSCR50, HiSCR75, HiSCR90, and HiSCR100). E-R response for each of HiSCR endpoints were evaluated at pre-dose and at Weeks 2, 4, 8, 12, 16, 20, 24, 28, 32, 36, 40, 44, 48. See section 8.xx (statistical review) for response rates on each HiSCR endpoints.	
Population characteristics at baseline	Age (years): Median (min – max): 36.5 (18 – 78), Mean ± SD: 36.5 ± 12.2. Body weight (kg): Median (min – max): 94.3 (48 – 196), Mean ± SD: 97.1 ± 24.4. Sex: 433 (43%) Males and 564 (57%) Females Race: 796 White; 106 Black/African American; 43 Multiple/Other; 29 Japanese, 13 Asian (excluding Japanese), 5 Unknown/Not reported; 3 American Indian/Alaska Native; 2 Native Hawaiian/Pacific Islander Disease severity: 595 (60%) with Hurley stage II and 402 (40%) with Hurley stage III Prior biologics use: 191 (19%) used biologics before, 806 (81%) did not Abscess and inflammatory nodule counts: Median (min – max): 11.0 (1.00 – 272), Mean ± SD: 16.2 ± 16.0 High-sensitivity C-reactive protein (mg/L): Median (min – max): 8.92 (0.120 – 204), Mean ± SD: 17.4 ± 24.9 Smoking Status: 382 (38%) non-smokers, 456 (46%) current smokers, and 149 (15%) previous smokers with 10 (1%) missing observations ADA and NAb status: 577 (58%) were ADA positive; 331 (33%) were both ADA and NAb positive.	
Final Model	Summary	Acceptability [FDA's Comments]
Software and version	See Table 45.	Acceptable
Base Model	The base model had the following characteristics: Placebo: Probabilities increasing log-linearly with time (fixed placebo parameter) Drug model: Probabilities dependent of longitudinal bimekizumab concentrations in an Emax relationship. Covariate model: None Markov elements: Probabilities dependent on the previous observation: separate Markov elements for placebo data (fixed) and for bimekizumab treatment data IIV model: IIV on the overall probability and Emax	**Acceptable**
Covariate Model	The influence of structural and exploratory covariates on model parameters was tested and statistically significant covariate-parameter relationships were added to the model the using SCM procedure. The covariate-parameter relationships that were evaluated in the HiSCR model are listed in Table 50. The significant covariates identified in this stage was included in the final E-R model.	

Final E-R model and parameter estimates	The final E-R model (run 213) was a proportional odds model with the following characteristics: Placebo: Probabilities increasing log-linearly with time (fixed placebo parameter) Drug model: Probabilities dependent of longitudinal bimekizumab concentrations in an Emax relationship. Covariate model: Baseline AN counts and smoking status on the probability parameters. Markov elements: Probabilities dependent on the previous observation: separate Markov elements for placebo data (fixed Markov elements) and for bimekizumab treatment data. IIV model: IIV on the overall probability and Emax The final model parameter estimates are presented in Table 51.	Acceptable
Diagnostic plots	The visual predictive check (VPC) plots did not show any model misspecification as illustrated in the Figure 16.	Acceptable

*HiSCR50/75/90/100 corresponds to 50%/75%/90%/100% improvement from baseline in hidradenitis suppurativa clinical response (HiSCR). The HiSCRxx is defined as at least a xx% reduction from baseline in the total abscess and inflammatory nodule (AN) counts, with no increase from baseline in abscess or draining tunnel counts.

Table 50: Covariate-parameter relationships evaluated in the ER HiSCR model development.

Parameter	Type	Covariate
Base probability parameters	Mechanistic	None
	Structural	body weight, smoking status, duration of disease, disease severity, baseline AN counts, prior use of biologics, antibiotic use at baseline entry
	Exploratory	BMI, age, sex, race, geographical region, hs-CRP
E_{max}	Mechanistic	None
	Structural	body weight, ADAb and NAb status[a]
	Exploratory	BMI

[a]Tested as a unique combined covariate with three categories: the reference level *ADAb negative*, and two levels for *ADAb positive* group: ADAb positive/NAb negative and ADAb positive/NAb positive. ADAb positive/NAb missing was combined with ADAb positiveNAb positive.

Table 51: Parameter estimates of the final HiSCR response model.

	Unit	Value	RSE (%)	SHR (%)
BL_{50} (θ_1)		-30.0	(FIX)	
DBL_{75} (θ_2)		-1.54	2.10	
DBL_{90} (θ_3)		-1.54	2.21	
DBL_{100} (θ_4)		-0.702	3.61	
Placebo slope	1/day	8.45E+04	(FIX)	
Drug EC_{50}	µg/mL	0.956	32.4	
Drug E_{max}		2.74	3.47	
Markov element,0-3 placebo ($\theta_{corr_{0,placebo}}$)		-1.06	(FIX)	
Markov element,0 (θ_{corr_0})		-2.53	3.29	
Markov element,1 (θ_{corr_1})		-1.61	5.27	
Markov element,2 (θ_{corr_2})		-1.04	7.83	
Markov element,3 (θ_{corr_3})		-0.552	18.5	
Baseline AN counts on overall probability		-0.0115	28.8	
Non-smoking on overall probability		0.498	20.7	
IIV overall probability	(SD)	1.23	5.94	20.0
IIV E_{max}	(CV)	0.914	12.3	49.9

BL_{50}, DBL_{75}, DBL_{90}, DBL_{100} probabilities are reported on the logit scale.
The RSE for IIV parameters are reported on the approximate SD scale.
The probabilities of response on the logit scale (LP) are calculated as followed:

$$LP_{50} = BL_{50} + \log(1 + \text{Placeboslope} \cdot 1000000) \cdot \text{time}) + \frac{E_{max} \cdot \text{concentration}}{\text{concentration} + EC_{50}} + \theta_{corr_{0,placebo}} + \text{Markov,drug} + \text{baselineANcounts} \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + \text{Non-smoking} & \text{if non-smoker} \end{cases} + IIV_{response}$$

$$LP_{75} = BL_{50} + DBL_{75} + \log(1 + \text{Placeboslope} \cdot 1000000) \cdot \text{time}) + \frac{E_{max} \cdot \text{concentration}}{\text{concentration} + EC_{50}} + \theta_{corr_{0,placebo}} + \text{Markov,drug} + \text{baselineANcounts} \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + \text{Non-smoking} & \text{if non-smoker} \end{cases} + IIV_{response}$$

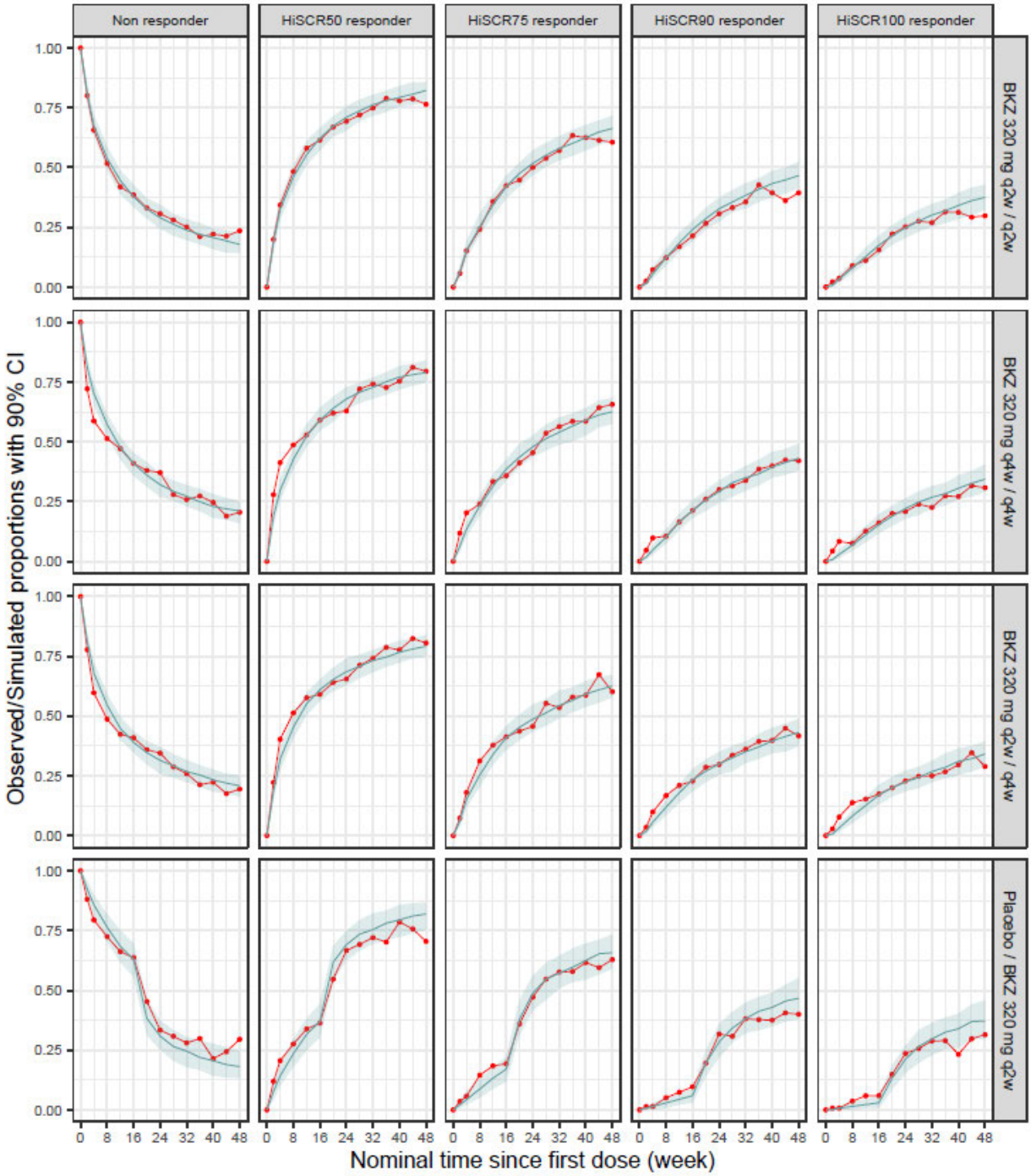
$$LP_{90} = BL_{50} + DBL_{75} + DBL_{90} + \log(1 + \text{Placeboslope} \cdot 1000000) \cdot \text{time}) + \frac{E_{max} \cdot \text{concentration}}{\text{concentration} + EC_{50}} + \theta_{corr_{0,placebo}} + \text{Markov,drug} + \text{baselineANcounts} \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + \text{Non-smoking} & \text{if non-smoker} \end{cases} + IIV_{response}$$

$$LP_{100} = BL_{50} + DBL_{75} + DBL_{90} + DBL_{100} + \log(1 + \text{Placeboslope} \cdot 1000000) \cdot \text{time}) + \frac{E_{max} \cdot \text{concentration}}{\text{concentration} + EC_{50}} + \theta_{corr_{0,placebo}} + \text{Markov,drug} + \text{baselineANcounts} \cdot (AN - 11) + \begin{cases} 1 & \text{if previous/current smoker} \\ 1 + \text{Non-smoking} & \text{if non-smoker} \end{cases} + IIV_{response}$$

Markov,drug was one of the parameters θ_{corr_0}, θ_{corr_1}, θ_{corr_2}, θ_{corr_3}, depending of the previous HiSCR observation.

Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R report, pages 93.

Figure 16: Visual predictive check for the proportion of non-responders and HiSCR50/75/90/100 responders versus nominal TSFD.



Plots are based on the final and drug HiSCR response model (run 213). The red points represent the observed proportion of study participants in the analysis data set, the red line connects the dots and the blue line and shaded areas represent the median and the 90% CI of model predictions. Observations at visits Weeks 10, 14, 18, 22, 26, 30, 34, 38, 42, 46 (visits not planned for HiSCR recording) are not included in this figure. Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R report, pages 94.

Summary Results of the Applicant's E-R analysis

- The final E-R HiSCR model was a proportional odds model and provided a good description of the E-R HiSCR response.

- The drug effect increased with increasing concentration and time. The concentration effect was adequately described by a Emax function with an estimated EC50 of 0.956 µg/mL.
- Of the covariates explored in the E-R model (body weight, disease duration, smoking status, baseline AN count, prior use of biologics, antibiotic use at baseline, BMI, sex, race, geographical region, hs-CRP, and ADAb/NAb status), only smoking status and baseline AN count were found to be influential.
- Simulations were performed for three dosing regimens: 320 mg Q2W/Q2W, Q2W/Q4W, and Q4W/Q4W. The simulated dose/exposure-response versus time curves for all dosing regimens are overlapped, implying that there is no dose-response relationship. Hence, there is no clinical benefit of the proposed dosing regimen (Q2W/Q4W) over the lower dosing regimen of Q4W/Q4W (See section 6-Clinical Pharmacology review, Figure 2)

Additionally, simulations were also conducted to quantitatively describe the response rates for HiSCR endpoints at Weeks 16 and 48 to allow for a comparison across the three dosing regimens.

- In the simulations, the median predicted (observed) proportion of HiSCR50 responders at Week 16 were 62% (61%) and 59% (59%) following dosing of 320 mg bimekizumab Q2W and Q4W, respectively. The corresponding proportions at Week 48 were 82% (77%) (q2w) and 81% (79%) (q4w). For HiSCR75 , the median predicted response rates were 41% and 38% at Week 16 for Q2W and Q4W, respectively. The corresponding rates at Week 48 were 66% and 64%. This implies a 3% higher response rate for Q2W over Q4W at Week 16, but the difference (1-2%) is further narrowed at Week 48 (Table 52).
- Similarly, the proposed dosing regimen (Q2W/Q4W) demonstrated a ~3% higher response rate over Q4W at only Week 16 for HiSCR50. However, at Week 48, the response rate is almost the same between Q2W/Q4W and Q4W, implying that the Q2W regimen during initial treatment period didn't provide treatment benefit over continuous Q4W regimen used for the entire treatment period (Table 52).

Table 52: Predicted HiSCR response rates at Weeks 16 and 48, stratified by dosing regimen

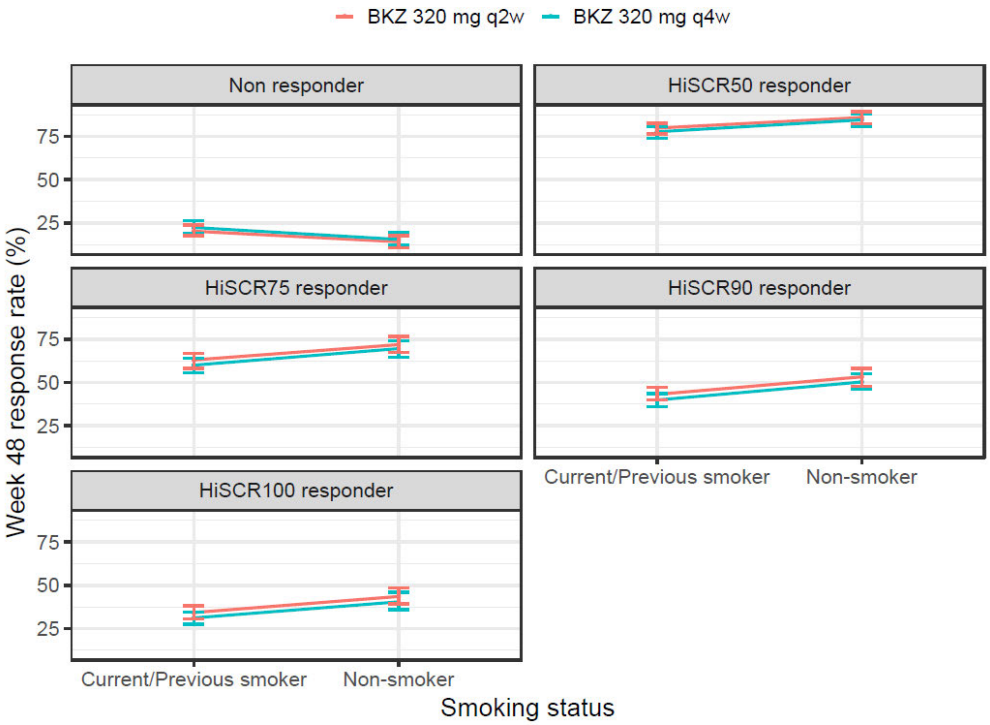
Dosing regimen	Time since first dose (week)	$HiSCR_{50}$ response rate [a] (%)	$HiSCR_{75}$ response rate [a] (%)	$HiSCR_{90}$ response rate [a] (%)	$HiSCR_{100}$ response rate [a] (%)
BKZ 320mg Q2W	16	61.8 [59.1 - 64.9]	41.3 [37.8 - 44.8]	23.6 [21.2 - 26.0]	17.1 [15.1 - 19.2]
BKZ 320mg Q2W/Q4W	16	61.8 [59.3 - 65.1]	41.3 [38.2 - 43.8]	23.6 [20.9 - 26.0]	17.2 [15.1 - 19.3]
BKZ 320mg Q4W	16	58.9 [55.9 - 62.1]	38.1 [35.5 - 40.9]	21.0 [18.7 - 23.2]	15.1 [12.8 - 17.0]
BKZ 320mg Q2W	48	82.1 [79.4 - 84.2]	66.3 [63.1 - 68.8]	47.0 [43.7 - 49.9]	37.7 [34.8 - 40.5]
BKZ 320mg Q2W/Q4W	48	80.0 [77.7 - 82.1]	63.4 [59.9 - 65.9]	43.8 [40.6 - 47.0]	34.7 [31.4 - 38.0]
BKZ 320mg Q4W	48	80.2 [77.7 - 82.8]	63.5 [60.5 - 66.4]	43.6 [40.9 - 46.6]	34.5 [32.0 - 37.6]

BKZ=bimekizumab; $HiSCR_{50, 75, 90, 100}$=Hidradenitis Suppurativa Clinical Response 50%, 75%, 90%, 100%; Q2W=every 2 weeks; Q4W=every 4 weeks
[a] Response rate: % median [2.5^{th} - 97.5^{th} percentile].

Source: m2.7.2-seq0116: Summary of Clinical Pharmacology Studies – HS, page 29.

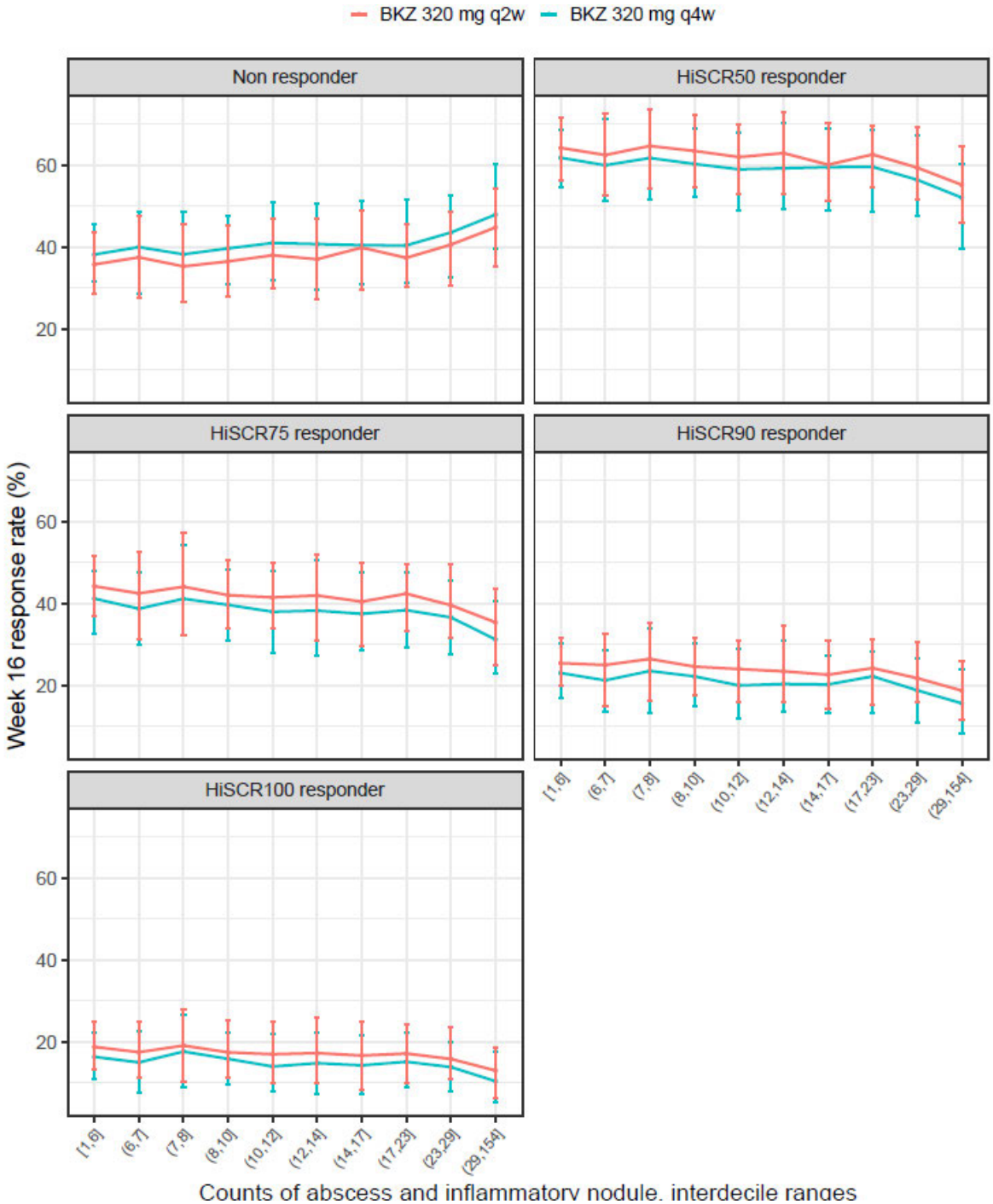
- Simulations suggested that non-smokers had an approximately 10% higher response rates compared with smokers/previous smokers. Subjects with high baseline AN counts (>20) had a lower probability to respond (~5% to 10% lower response rates). It is noted that the lower response in smokers/previous smokers and subjects with high baseline AN could not be meaningfully improved by treating with bimekizumab Q2W/Q2W (the highest dosing regimen) (Figure 17, Figure 18).
- Despite body weight showed the most influential covariate impacting the bimekizumab exposures, response rates were similar across different body weight deciles at Weeks 16 and 48 (Figure 19, Figure 20). Hence, no body weight-based subgroups were identified that may be benefitted from dose adjustments.
- Overall, E-R analysis indicated no specific sub-group (current/previous smoker, subjects with high baseline AN counts, subjects with high body WT, Hurley stage III subjects and subject with prior disease related biologics use) that would benefit from a different dosing regimen than the rest of the HS population.

Figure 17: Predicted response rates at Week 48 for HiSCR endpoints stratified by smoking status for bimekizumab 320 mg Q2W and Q4W.



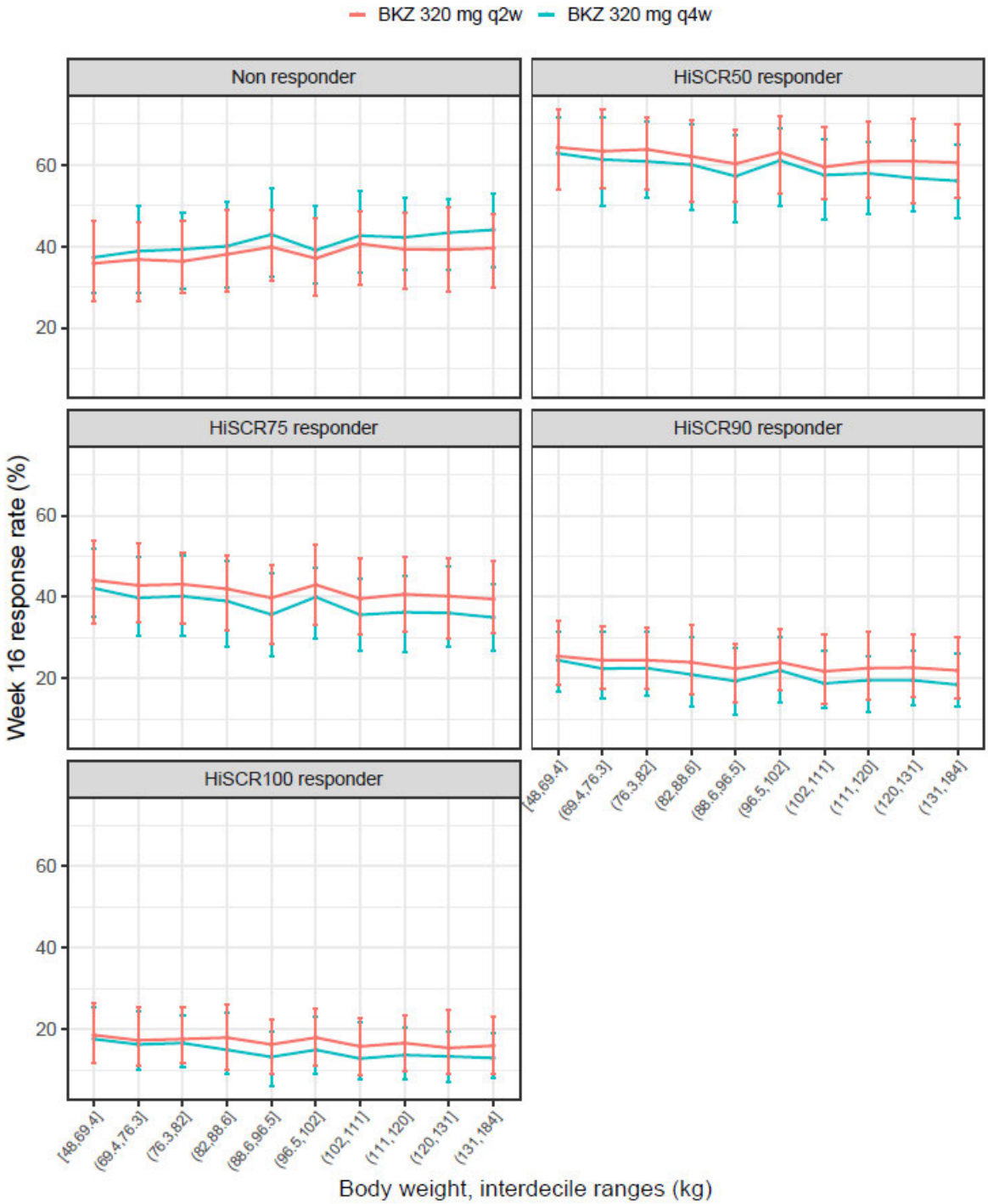
The lines and the error bars represent the median and 95% PI response rates, respectively.
Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R report, pages 101.

Figure 18: Predicted response rates at Week 48 for HiSCR endpoints versus baseline AN deciles for bimekizumab 320 mg Q2W and Q4W.



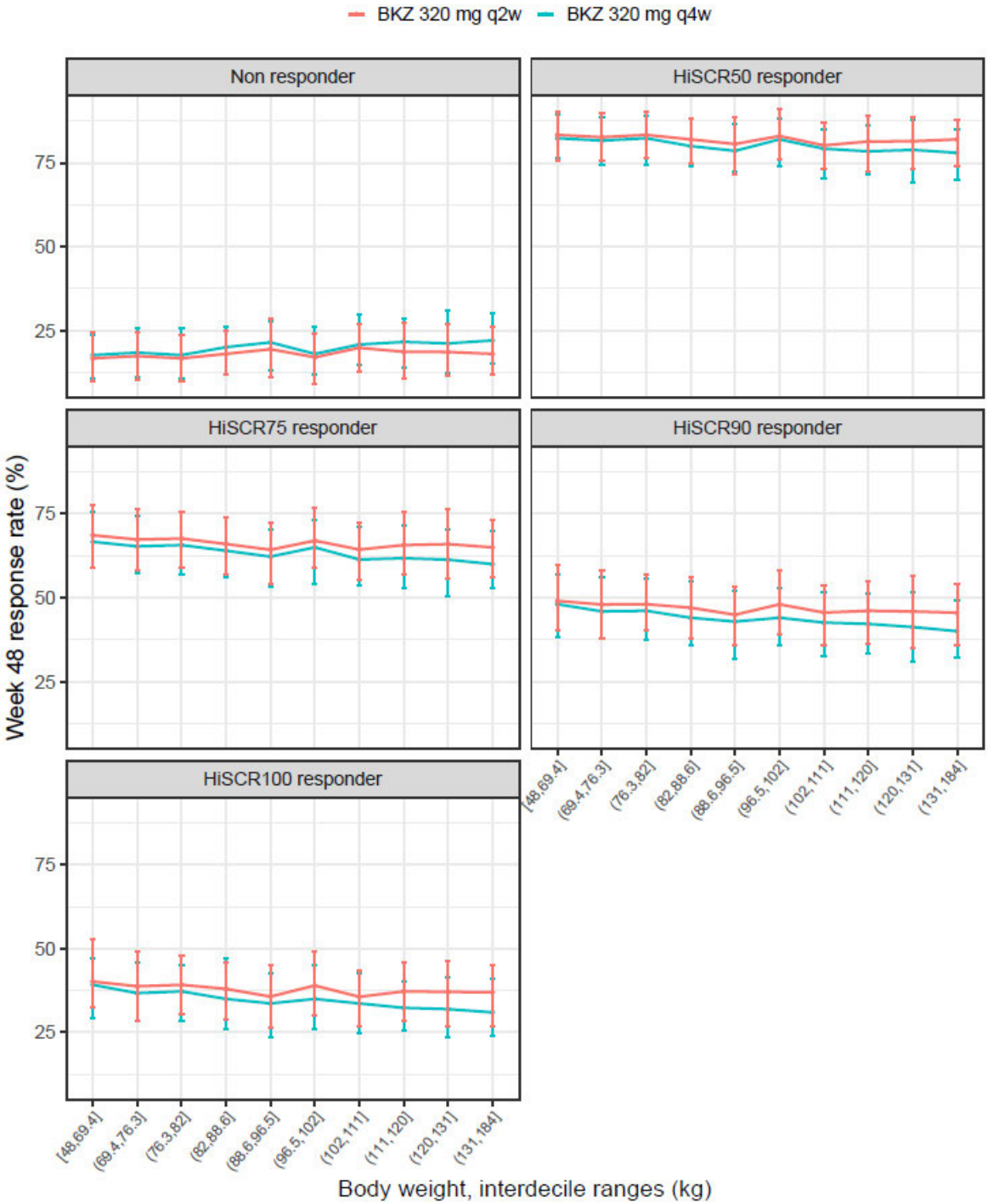
The lines and the error bars represent the median and 95% PI response rates, respectively. Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R report, pages 103.

Figure 19: Predicted response rates at Week 16 for HiSCR endpoints versus WT deciles for bimekizumab 320 mg Q2W and Q4W.



The lines and the error bars represent the median and 95% PI response rates, respectively. Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R report, pages 106.

Figure 20: Predicted response rates at Week 48 for HiSCR endpoints versus WT deciles for bimekizumab 320 mg Q2W and Q4W.



The lines and the error bars represent the median and 95% PI response rates, respectively. Source: m5.3.3.5 – CL0561: Applicant's PopPK and E-R report, pages 107.

19.5. Additional Clinical Outcome Assessment Analyses

[Add Text and Figures/Tables Here]

19.6. Additional Clinical Information

19.6.1. Additional AE tables

Table 53: SAEs by SOC and PT, Pool S2

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any SAE	23 (8.1)	8 (6.0)	13 (4.5)	20 (7.0)
Infections and infestations	7 (2.5)	2 (1.5)	4 (1.4)	3 (1.1)
Cellulitis	2 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Bartholinitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Groin infection	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Peritonitis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rash pustular	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Sepsis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Appendicitis	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Bronchitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Corona virus infection	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Gastroenteritis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Genital candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Oropharyngeal candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Periorbital cellulitis	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Tooth abscess	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Wound infection staphylococcal	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	6 (2.1)	1 (0.7)	3 (1.0)	5 (1.8)
Hidradenitis	4 (1.4)	1 (0.7)	2 (0.7)	4 (1.4)
Diabetic foot	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Diabetic ulcer	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Intertrigo	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pain of skin	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Gastrointestinal disorders	3 (1.1)	2 (1.5)	1 (0.3)	2 (0.7)
Anal fissure	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Anal fistula	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.4)	0 (0.0)	1 (0.3)	0 (0.0)
Irritable bowel syndrome	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Aphthous ulcer	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Crohn's disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Small intestinal obstruction	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any SAE	23 (8.1)	8 (6.0)	13 (4.5)	20 (7.0)
Hepatobiliary disorders	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)
Cholelithiasis	1 (0.4)	0 (0.0)	0 (0.0)	1 (0.4)
Drug-induced liver injury	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Vascular disorders	2 (0.7)	0 (0.0)	0 (0.0)	1 (0.4)
Deep vein thrombosis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Lymphoedema	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Cardiac disorders	1 (0.4)	1 (0.7)	1 (0.3)	0 (0.0)
Cardiac failure acute	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Acute coronary syndrome	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Atrial fibrillation	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Injury, poisoning and procedural complications	1 (0.4)	1 (0.7)	1 (0.3)	2 (0.7)
Meniscus injury	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Ankle fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Fibula fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Laceration	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Road traffic accident	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Tibia fracture	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Musculoskeletal and connective tissue disorders	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rhabdomyolysis	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	1 (0.7)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Intraductal proliferative breast lesion	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cerebral infarction	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (0.4)	1 (0.7)	1 (0.3)	2 (0.7)
Suicidal ideation	1 (0.4)	1 (0.7)	0 (0.0)	2 (0.7)
Depression	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Iron deficiency anaemia	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Ear and labyrinth disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Vertigo	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Eye disorders	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Keratitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	2 (0.7)	1 (0.4)
Abortion spontaneous	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any SAE	23 (8.1)	8 (6.0)	13 (4.5)	20 (7.0)
Pregnancy on contraceptive	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Renal and urinary disorders	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Nephrolithiasis	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Ureterolithiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Menorrhagia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Surgical and medical procedures	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Abortion induced	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S2" and TRTI1A = "BKZ 320mg Q2W/Q2W" (BKZ 320mg Q2W/Q2W); POOL = "S2" and TRTI1A = "Placebo/BKZ 320mg Q2W" (Placebo/BKZ 320mg Q2W); POOL = "S2" and TRTI1A = "BKZ 320mg Q2W/Q4W" (BKZ 320mg Q2W/Q4W); TRTI1A = "BKZ 320mg Q4W/Q4W" and POOL = "S2" (BKZ 320mg Q4W/Q4W); TRTEMFL = "Y" and ANL02FL = "Y" and AESER = "Y" (Adverse Events).

Table 54: SAEs by SOC and PT, Pool S3

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any SAE	57 (6.9)	39 (6.0)
Infections and infestations	13 (1.6)	9 (1.4)
Cellulitis	2 (0.2)	1 (0.2)
Appendicitis	1 (0.1)	0 (0.0)
Bartholinitis	1 (0.1)	0 (0.0)
Central nervous system infection	1 (0.1)	0 (0.0)
Corona virus infection	1 (0.1)	1 (0.2)
Diverticulitis	1 (0.1)	0 (0.0)
Groin infection	1 (0.1)	0 (0.0)
Periorbital cellulitis	1 (0.1)	0 (0.0)
Peritonitis	1 (0.1)	0 (0.0)
Rash pustular	1 (0.1)	0 (0.0)
Sepsis	1 (0.1)	0 (0.0)
Vulval abscess	1 (0.1)	0 (0.0)
Wound infection	1 (0.1)	0 (0.0)
Bronchitis	0 (0.0)	1 (0.2)
Gastroenteritis	0 (0.0)	1 (0.2)
Gastroenteritis viral	0 (0.0)	1 (0.2)
Genital candidiasis	0 (0.0)	1 (0.2)
Oropharyngeal candidiasis	0 (0.0)	1 (0.2)
Tooth abscess	0 (0.0)	1 (0.2)
Wound infection staphylococcal	0 (0.0)	1 (0.2)
Skin and subcutaneous tissue disorders	12 (1.5)	6 (0.9)
Hidradenitis	9 (1.1)	5 (0.8)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any SAE	57 (6.9)	39 (6.0)
Diabetic foot	1 (0.1)	0 (0.0)
Diabetic ulcer	1 (0.1)	0 (0.0)
Pain of skin	1 (0.1)	1 (0.2)
Intertrigo	0 (0.0)	1 (0.2)
Gastrointestinal disorders	7 (0.9)	3 (0.5)
Abdominal pain	1 (0.1)	0 (0.0)
Anal fissure	1 (0.1)	0 (0.0)
Anal fistula	1 (0.1)	0 (0.0)
Aphthous ulcer	1 (0.1)	0 (0.0)
Colitis	1 (0.1)	0 (0.0)
Colitis ulcerative	1 (0.1)	1 (0.2)
Irritable bowel syndrome	1 (0.1)	0 (0.0)
Pseudopolyposis	1 (0.1)	0 (0.0)
Crohn's disease	0 (0.0)	1 (0.2)
Small intestinal obstruction	0 (0.0)	1 (0.2)
Injury, poisoning and procedural complications	5 (0.6)	3 (0.5)
Meniscus injury	2 (0.2)	0 (0.0)
Laceration	1 (0.1)	0 (0.0)
Ligament injury	1 (0.1)	0 (0.0)
Road traffic accident	1 (0.1)	1 (0.2)
Spinal compression fracture	1 (0.1)	0 (0.0)
Ankle fracture	0 (0.0)	1 (0.2)
Fibula fracture	0 (0.0)	1 (0.2)
Tibia fracture	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	4 (0.5)	0 (0.0)
Extraskeletal ossification	1 (0.1)	0 (0.0)
Osteoarthritis	1 (0.1)	0 (0.0)
Rhabdomyolysis	1 (0.1)	0 (0.0)
Rotator cuff syndrome	1 (0.1)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	4 (0.5)	2 (0.3)
Breast cancer	1 (0.1)	0 (0.0)
Clear cell renal cell carcinoma	1 (0.1)	0 (0.0)
Intraductal proliferative breast lesion	1 (0.1)	0 (0.0)
Squamous cell carcinoma of the tongue	1 (0.1)	0 (0.0)
Hodgkin's disease	0 (0.0)	1 (0.2)
Papillary thyroid cancer	0 (0.0)	1 (0.2)
Nervous system disorders	4 (0.5)	1 (0.2)
Cerebral infarction	1 (0.1)	0 (0.0)
Migraine	1 (0.1)	0 (0.0)
Ruptured cerebral aneurysm	1 (0.1)	0 (0.0)
Transient ischaemic attack	1 (0.1)	0 (0.0)
Syncope	0 (0.0)	1 (0.2)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any SAE	57 (6.9)	39 (6.0)
Renal and urinary disorders	4 (0.5)	2 (0.3)
Nephrolithiasis	2 (0.2)	2 (0.3)
Renal impairment	1 (0.1)	0 (0.0)
Ureterolithiasis	1 (0.1)	1 (0.2)
Cardiac disorders	2 (0.2)	1 (0.2)
Atrial fibrillation	1 (0.1)	0 (0.0)
Cardiac failure acute	1 (0.1)	0 (0.0)
Cardiac failure congestive	1 (0.1)	0 (0.0)
Acute coronary syndrome	0 (0.0)	1 (0.2)
Hepatobiliary disorders	2 (0.2)	3 (0.5)
Cholelithiasis	1 (0.1)	1 (0.2)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Cholangitis	0 (0.0)	1 (0.2)
Cholecystitis	0 (0.0)	1 (0.2)
Cholecystitis acute	0 (0.0)	1 (0.2)
Hepatic haemorrhage	0 (0.0)	1 (0.2)
Psychiatric disorders	2 (0.2)	4 (0.6)
Suicidal ideation	2 (0.2)	3 (0.5)
Depression	0 (0.0)	2 (0.3)
Reproductive system and breast disorders	2 (0.2)	0 (0.0)
Menorrhagia	1 (0.1)	0 (0.0)
Prostatic dysplasia	1 (0.1)	0 (0.0)
Vascular disorders	2 (0.2)	2 (0.3)
Deep vein thrombosis	1 (0.1)	1 (0.2)
Lymphoedema	1 (0.1)	0 (0.0)
Thrombophlebitis superficial	0 (0.0)	1 (0.2)
Congenital, familial and genetic disorders	1 (0.1)	0 (0.0)
Familial periodic paralysis	1 (0.1)	0 (0.0)
General disorders and administration site conditions	1 (0.1)	1 (0.2)
Pyrexia	1 (0.1)	0 (0.0)
Non-cardiac chest pain	0 (0.0)	1 (0.2)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	2 (0.3)
Pregnancy on contraceptive	1 (0.1)	1 (0.2)
Abortion spontaneous	0 (0.0)	1 (0.2)
Blood and lymphatic system disorders	0 (0.0)	1 (0.2)
Iron deficiency anaemia	0 (0.0)	1 (0.2)
Ear and labyrinth disorders	0 (0.0)	1 (0.2)
Vertigo	0 (0.0)	1 (0.2)
Eye disorders	0 (0.0)	1 (0.2)
Keratitis	0 (0.0)	1 (0.2)
Metabolism and nutrition disorders	0 (0.0)	1 (0.2)
Diabetes mellitus	0 (0.0)	1 (0.2)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any SAE	57 (6.9)	39 (6.0)
Surgical and medical procedures	0 (0.0)	1 (0.2)
Abortion induced	0 (0.0)	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S3" and TRTNEW = "Phase 3 BKZ 320mg Q2W" (BKZ 320mg Q2W); POOL = "S3" and TRTNEW = "Phase 3 BKZ 320mg Q4W" (BKZ 320mg Q4W); TRTEMFL = "Y" and ANL03FL = "Y" and AESER = "Y" (Adverse Events).

Table 55: AEs Leading to Discontinuation by SOC and PT, Pool S2 (Weeks 0-48)

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any AE	17 (6.0)	9 (6.7)	20 (6.9)	21 (7.4)
Gastrointestinal disorders	5 (1.8)	1 (0.7)	3 (1.0)	5 (1.8)
Diarrhoea	2 (0.7)	1 (0.7)	1 (0.3)	3 (1.1)
Abdominal discomfort	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Gastrooesophageal reflux disease	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Abdominal pain upper	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Colitis microscopic	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Crohn's disease	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Salivary gland mass	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Skin and subcutaneous tissue disorders	5 (1.8)	4 (3.0)	7 (2.4)	5 (1.8)
Hidradenitis	3 (1.1)	3 (2.2)	4 (1.4)	3 (1.1)
Alopecia areata	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema nummular	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Eczema	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Night sweats	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Pain of skin	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Psoriasis	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Rash generalized	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Skin ulcer	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Infections and infestations	3 (1.1)	3 (2.2)	7 (2.4)	2 (0.7)
Conjunctivitis bacterial	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Groin infection	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Rash pustular	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Folliculitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Fungal skin infection	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Genital candidiasis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Herpangina	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Nasopharyngitis	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Esophageal candidiasis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Oral candidiasis	0 (0.0)	1 (0.7)	4 (1.4)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any AE	17 (6.0)	9 (6.7)	20 (6.9)	21 (7.4)
Periorbital cellulitis	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)
Sinusitis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Vulvovaginal candidiasis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Vulvovaginal mycotic infection	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Cardiac disorders	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Cardiac failure congestive	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (0.4)	0 (0.0)	2 (0.7)	0 (0.0)
Malaise	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Fatigue	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Injection site erythema	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Hepatobiliary disorders	1 (0.4)	0 (0.0)	0 (0.0)	2 (0.7)
Drug-induced liver injury	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Hepatic steatosis	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Hepatocellular injury	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Investigations	1 (0.4)	2 (1.5)	1 (0.3)	5 (1.8)
Psychiatric evaluation abnormal	1 (0.4)	2 (1.5)	1 (0.3)	4 (1.4)
Alanine aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Aspartate aminotransferase increased	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	1 (0.4)	0 (0.0)	1 (0.3)	4 (1.4)
Adjustment disorder	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)
Adjustment disorder with depressed mood	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Alcohol abuse	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Depression	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Suicidal ideation	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Eye disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Blepharitis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Arthralgia	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Nervous system disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Migraine	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Pregnancy on contraceptive	0 (0.0)	0 (0.0)	1 (0.3)	1 (0.4)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	2 (0.7)	0 (0.0)
Breast necrosis	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Vulvovaginal pruritus	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)
Vascular disorders	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W/Q2W N = 285 n (%)	Placebo/BKZ 320mg Q2W N = 134 n (%)	BKZ 320mg Q2W/Q4W N = 291 n (%)	BKZ 320mg Q4W/Q4W N = 285 n (%)
Any AE	17 (6.0)	9 (6.7)	20 (6.9)	21 (7.4)
Hot flush	0 (0.0)	0 (0.0)	1 (0.3)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S2" and TRTI1A = "BKZ 320mg Q2W/Q2W" (BKZ 320mg Q2W/Q2W); POOL = "S2" and TRTI1A = "Placebo/BKZ 320mg Q2W" (Placebo/BKZ 320mg Q2W); POOL = "S2" and TRTI1A = "BKZ 320mg Q2W/Q4W" (BKZ 320mg Q2W/Q4W); TRTI1A = "BKZ 320mg Q4W/Q4W" and POOL = "S2" (BKZ 320mg Q4W/Q4W); TRTEMFL = "Y" and ANL02FL = "Y" and AEDROP = "Y" (Adverse Events).

Table 56: AEs Leading to Discontinuation by SOC and PT, Pool S3

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any AE	53 (6.4)	35 (5.4)
Skin and subcutaneous tissue disorders	17 (2.1)	8 (1.2)
Hidradenitis	9 (1.1)	6 (0.9)
Psoriasis	2 (0.2)	1 (0.2)
Alopecia areata	1 (0.1)	0 (0.0)
Eczema nummular	1 (0.1)	0 (0.0)
Night sweats	1 (0.1)	0 (0.0)
Pain of skin	1 (0.1)	0 (0.0)
Papule	1 (0.1)	0 (0.0)
Rash generalized	1 (0.1)	0 (0.0)
Seborrhoeic dermatitis	1 (0.1)	0 (0.0)
Eczema	0 (0.0)	1 (0.2)
Skin ulcer	0 (0.0)	1 (0.2)
Infections and infestations	13 (1.6)	7 (1.1)
Oral candidiasis	3 (0.4)	2 (0.3)
Central nervous system infection	1 (0.1)	0 (0.0)
Conjunctivitis bacterial	1 (0.1)	0 (0.0)
Folliculitis	1 (0.1)	2 (0.3)
Genital candidiasis	1 (0.1)	0 (0.0)
Groin infection	1 (0.1)	0 (0.0)
Herpangina	1 (0.1)	0 (0.0)
Nasopharyngitis	1 (0.1)	1 (0.2)
Esophageal candidiasis	1 (0.1)	0 (0.0)
Periorbital cellulitis	1 (0.1)	0 (0.0)
Rash pustular	1 (0.1)	0 (0.0)
Wound infection	1 (0.1)	0 (0.0)
Fungal skin infection	0 (0.0)	1 (0.2)
Latent tuberculosis	0 (0.0)	1 (0.2)
Sinusitis	0 (0.0)	1 (0.2)
Vulvovaginal candidiasis	0 (0.0)	1 (0.2)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any AE	53 (6.4)	35 (5.4)
Vulvovaginal mycotic infection	0 (0.0)	1 (0.2)
Gastrointestinal disorders	10 (1.2)	7 (1.1)
Diarrhoea	4 (0.5)	4 (0.6)
Abdominal discomfort	1 (0.1)	0 (0.0)
Colitis microscopic	1 (0.1)	1 (0.2)
Colitis ulcerative	1 (0.1)	0 (0.0)
Crohn's disease	1 (0.1)	1 (0.2)
Gastrooesophageal reflux disease	1 (0.1)	0 (0.0)
Gingival pain	1 (0.1)	0 (0.0)
Salivary gland mass	1 (0.1)	0 (0.0)
Abdominal pain upper	0 (0.0)	1 (0.2)
Colitis	0 (0.0)	1 (0.2)
Investigations	6 (0.7)	6 (0.9)
Psychiatric evaluation abnormal	5 (0.6)	4 (0.6)
Liver function test increased	1 (0.1)	0 (0.0)
Alanine aminotransferase increased	0 (0.0)	1 (0.2)
Aspartate aminotransferase increased	0 (0.0)	1 (0.2)
Blood alkaline phosphatase increased	0 (0.0)	1 (0.2)
Gamma-glutamyl transferase increased	0 (0.0)	1 (0.2)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	3 (0.4)	2 (0.3)
Adrenal gland cancer	1 (0.1)	0 (0.0)
Breast cancer	1 (0.1)	0 (0.0)
Clear cell renal cell carcinoma	1 (0.1)	0 (0.0)
Hodgkin's disease	0 (0.0)	1 (0.2)
Papillary thyroid cancer	0 (0.0)	1 (0.2)
General disorders and administration site conditions	2 (0.2)	1 (0.2)
Injection site erythema	1 (0.1)	0 (0.0)
Malaise	1 (0.1)	0 (0.0)
Fatigue	0 (0.0)	1 (0.2)
Vascular disorders	2 (0.2)	0 (0.0)
Arteriosclerosis	1 (0.1)	0 (0.0)
Hot flush	1 (0.1)	0 (0.0)
Cardiac disorders	1 (0.1)	0 (0.0)
Cardiac failure congestive	1 (0.1)	0 (0.0)
Hepatobiliary disorders	1 (0.1)	2 (0.3)
Drug-induced liver injury	1 (0.1)	0 (0.0)
Hepatic steatosis	0 (0.0)	1 (0.2)
Hepatocellular injury	0 (0.0)	1 (0.2)
Musculoskeletal and connective tissue disorders	1 (0.1)	0 (0.0)
Arthralgia	1 (0.1)	0 (0.0)
Nervous system disorders	1 (0.1)	0 (0.0)
Migraine	1 (0.1)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 823 n (%)	BKZ 320mg Q4W N = 650 n (%)
Any AE	53 (6.4)	35 (5.4)
Pregnancy, puerperium and perinatal conditions	1 (0.1)	1 (0.2)
Pregnancy on contraceptive	1 (0.1)	1 (0.2)
Psychiatric disorders	1 (0.1)	6 (0.9)
Adjustment disorder	1 (0.1)	0 (0.0)
Adjustment disorder with depressed mood	0 (0.0)	1 (0.2)
Alcohol abuse	0 (0.0)	1 (0.2)
Depression	0 (0.0)	3 (0.5)
Suicidal ideation	0 (0.0)	2 (0.3)
Reproductive system and breast disorders	1 (0.1)	1 (0.2)
Vulvovaginal pruritus	1 (0.1)	0 (0.0)
Breast necrosis	0 (0.0)	1 (0.2)
Eye disorders	0 (0.0)	1 (0.2)
Blepharitis	0 (0.0)	1 (0.2)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S3" and TRTNEW = "Phase 3 BKZ 320mg Q2W" (BKZ 320mg Q2W); POOL = "S3" and TRTNEW = "Phase 3 BKZ 320mg Q4W" (BKZ 320mg Q4W); TRTEMFL = "Y" and ANL03FL = "Y" and AEDROP = "Y" (Adverse Events).

Table 57: TEAEs by SOC and PT, Pool S1

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Infections and infestations	193 (33.5)	91 (31.9)	30 (20.5)
Oral candidiasis	41 (7.1)	7 (2.5)	0 (0.0)
Nasopharyngitis	23 (4.0)	10 (3.5)	3 (2.1)
Corona virus infection	20 (3.5)	5 (1.8)	2 (1.4)
Folliculitis	16 (2.8)	8 (2.8)	0 (0.0)
Vulvovaginal mycotic infection	10 (1.7)	5 (1.8)	0 (0.0)
Otitis externa	9 (1.6)	2 (0.7)	1 (0.7)
Upper respiratory tract infection	9 (1.6)	0 (0.0)	1 (0.7)
Urinary tract infection	9 (1.6)	6 (2.1)	4 (2.7)
Pharyngitis	7 (1.2)	5 (1.8)	1 (0.7)
Tinea pedis	7 (1.2)	2 (0.7)	0 (0.0)
Vulvovaginal candidiasis	6 (1.0)	11 (3.9)	0 (0.0)
Bronchitis	5 (0.9)	0 (0.0)	1 (0.7)
Ear infection	5 (0.9)	1 (0.4)	0 (0.0)
Influenza	5 (0.9)	0 (0.0)	2 (1.4)
Paronychia	5 (0.9)	2 (0.7)	0 (0.0)
Rhinitis	5 (0.9)	1 (0.4)	1 (0.7)
Sinusitis	5 (0.9)	3 (1.1)	1 (0.7)
Tonsillitis	5 (0.9)	4 (1.4)	0 (0.0)
Hordeolum	4 (0.7)	3 (1.1)	1 (0.7)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Body tinea	3 (0.5)	0 (0.0)	0 (0.0)
Conjunctivitis	3 (0.5)	2 (0.7)	0 (0.0)
Conjunctivitis bacterial	3 (0.5)	1 (0.4)	1 (0.7)
Fungal skin infection	3 (0.5)	4 (1.4)	1 (0.7)
Gastroenteritis	3 (0.5)	1 (0.4)	1 (0.7)
Oral fungal infection	3 (0.5)	2 (0.7)	0 (0.0)
Oral herpes	3 (0.5)	1 (0.4)	0 (0.0)
Skin candida	3 (0.5)	3 (1.1)	0 (0.0)
Angular cheilitis	2 (0.3)	0 (0.0)	0 (0.0)
Bacterial vaginosis	2 (0.3)	2 (0.7)	2 (1.4)
Cellulitis	2 (0.3)	2 (0.7)	2 (1.4)
Dermatophytosis	2 (0.3)	0 (0.0)	0 (0.0)
Otitis media	2 (0.3)	1 (0.4)	0 (0.0)
Papilloma viral infection	2 (0.3)	0 (0.0)	0 (0.0)
Periodontitis	2 (0.3)	0 (0.0)	0 (0.0)
Pharyngitis streptococcal	2 (0.3)	1 (0.4)	0 (0.0)
Skin bacterial infection	2 (0.3)	2 (0.7)	0 (0.0)
Staphylococcal skin infection	2 (0.3)	0 (0.0)	0 (0.0)
Tinea capitis	2 (0.3)	0 (0.0)	0 (0.0)
Tooth abscess	2 (0.3)	0 (0.0)	1 (0.7)
Viral infection	2 (0.3)	0 (0.0)	1 (0.7)
Abscess limb	1 (0.2)	0 (0.0)	2 (1.4)
Acne pustular	1 (0.2)	0 (0.0)	1 (0.7)
Anal fungal infection	1 (0.2)	0 (0.0)	0 (0.0)
Asymptomatic bacteriuria	1 (0.2)	1 (0.4)	0 (0.0)
Bacterial disease carrier	1 (0.2)	0 (0.0)	0 (0.0)
Bacteriuria	1 (0.2)	2 (0.7)	2 (1.4)
Breast cellulitis	1 (0.2)	0 (0.0)	0 (0.0)
Bullous impetigo	1 (0.2)	0 (0.0)	0 (0.0)
Carbuncle	1 (0.2)	2 (0.7)	0 (0.0)
Cystitis	1 (0.2)	1 (0.4)	0 (0.0)
Cystitis bacterial	1 (0.2)	0 (0.0)	0 (0.0)
Diarrhoea infectious	1 (0.2)	0 (0.0)	0 (0.0)
Ear infection fungal	1 (0.2)	0 (0.0)	0 (0.0)
Erysipeloid	1 (0.2)	0 (0.0)	0 (0.0)
Escherichia urinary tract infection	1 (0.2)	0 (0.0)	0 (0.0)
Furuncle	1 (0.2)	1 (0.4)	0 (0.0)
Gastroenteritis salmonella	1 (0.2)	0 (0.0)	0 (0.0)
Gastroenteritis viral	1 (0.2)	0 (0.0)	2 (1.4)
Gastrointestinal infection	1 (0.2)	0 (0.0)	0 (0.0)
Genital candidiasis	1 (0.2)	2 (0.7)	0 (0.0)
Genital infection fungal	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Helicobacter gastritis	1 (0.2)	1 (0.4)	0 (0.0)
Kidney infection	1 (0.2)	0 (0.0)	0 (0.0)
Labyrinthitis	1 (0.2)	0 (0.0)	0 (0.0)
Laryngitis	1 (0.2)	0 (0.0)	0 (0.0)
Latent tuberculosis	1 (0.2)	0 (0.0)	0 (0.0)
Oesophageal candidiasis	1 (0.2)	1 (0.4)	0 (0.0)
Oesophageal infection	1 (0.2)	0 (0.0)	0 (0.0)
Orchitis	1 (0.2)	0 (0.0)	0 (0.0)
Parotitis	1 (0.2)	0 (0.0)	0 (0.0)
Pericoronitis	1 (0.2)	0 (0.0)	0 (0.0)
Pharyngeal abscess	1 (0.2)	0 (0.0)	0 (0.0)
Pharyngitis bacterial	1 (0.2)	0 (0.0)	0 (0.0)
Pyelonephritis	1 (0.2)	0 (0.0)	0 (0.0)
Tinea cruris	1 (0.2)	0 (0.0)	0 (0.0)
Tinea manuum	1 (0.2)	0 (0.0)	0 (0.0)
Tinea versicolour	1 (0.2)	1 (0.4)	0 (0.0)
Tooth infection	1 (0.2)	1 (0.4)	0 (0.0)
Vaginal infection	1 (0.2)	0 (0.0)	0 (0.0)
Vaginitis bacterial	1 (0.2)	0 (0.0)	0 (0.0)
Vaginitis gardnerella	1 (0.2)	0 (0.0)	0 (0.0)
Viral upper respiratory tract infection	1 (0.2)	0 (0.0)	0 (0.0)
Acarodermatitis	0 (0.0)	1 (0.4)	0 (0.0)
Acute sinusitis	0 (0.0)	1 (0.4)	0 (0.0)
Campylobacter colitis	0 (0.0)	1 (0.4)	0 (0.0)
Conjunctivitis viral	0 (0.0)	2 (0.7)	1 (0.7)
Demodicidosis	0 (0.0)	1 (0.4)	0 (0.0)
Fungal infection	0 (0.0)	1 (0.4)	0 (0.0)
Genital herpes	0 (0.0)	1 (0.4)	0 (0.0)
Giardiasis	0 (0.0)	1 (0.4)	0 (0.0)
Gingivitis	0 (0.0)	1 (0.4)	0 (0.0)
Infected cyst	0 (0.0)	0 (0.0)	1 (0.7)
Lower respiratory tract infection bacterial	0 (0.0)	0 (0.0)	1 (0.7)
Omphalitis	0 (0.0)	1 (0.4)	0 (0.0)
Oral infection	0 (0.0)	1 (0.4)	0 (0.0)
Oropharyngeal candidiasis	0 (0.0)	1 (0.4)	0 (0.0)
Pilonidal cyst	0 (0.0)	1 (0.4)	1 (0.7)
Pneumonia staphylococcal	0 (0.0)	1 (0.4)	0 (0.0)
Pulpitis dental	0 (0.0)	2 (0.7)	0 (0.0)
Staphylococcal infection	0 (0.0)	1 (0.4)	0 (0.0)
Skin and subcutaneous tissue disorders	148 (25.7)	67 (23.5)	26 (17.8)
Hidradenitis	44 (7.6)	25 (8.8)	15 (10.3)
Eczema	14 (2.4)	5 (1.8)	2 (1.4)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Pruritus	13 (2.3)	6 (2.1)	1 (0.7)
Dermatitis contact	12 (2.1)	4 (1.4)	0 (0.0)
Seborrhoeic dermatitis	11 (1.9)	7 (2.5)	0 (0.0)
Acne	9 (1.6)	3 (1.1)	0 (0.0)
Urticaria	8 (1.4)	1 (0.4)	0 (0.0)
Dermatitis psoriasiform	5 (0.9)	2 (0.7)	0 (0.0)
Dry skin	5 (0.9)	3 (1.1)	0 (0.0)
Dyshidrotic eczema	5 (0.9)	1 (0.4)	0 (0.0)
Intertrigo	5 (0.9)	8 (2.8)	2 (1.4)
Psoriasis	5 (0.9)	3 (1.1)	0 (0.0)
Dermatitis	4 (0.7)	4 (1.4)	0 (0.0)
Pruritus generalised	4 (0.7)	1 (0.4)	1 (0.7)
Dermatitis atopic	3 (0.5)	0 (0.0)	0 (0.0)
Alopecia	2 (0.3)	1 (0.4)	0 (0.0)
Blister	2 (0.3)	0 (0.0)	0 (0.0)
Dermal cyst	2 (0.3)	0 (0.0)	0 (0.0)
Eczema nummular	2 (0.3)	2 (0.7)	0 (0.0)
Night sweats	2 (0.3)	0 (0.0)	0 (0.0)
Rash	2 (0.3)	2 (0.7)	0 (0.0)
Skin odour abnormal	2 (0.3)	1 (0.4)	0 (0.0)
Acne cystic	1 (0.2)	0 (0.0)	0 (0.0)
Dermatitis allergic	1 (0.2)	0 (0.0)	2 (1.4)
Diffuse alopecia	1 (0.2)	0 (0.0)	0 (0.0)
Erythema	1 (0.2)	0 (0.0)	0 (0.0)
Hyperhidrosis	1 (0.2)	2 (0.7)	1 (0.7)
Hyperkeratosis	1 (0.2)	0 (0.0)	0 (0.0)
Hypertrichosis	1 (0.2)	0 (0.0)	0 (0.0)
Idiopathic urticaria	1 (0.2)	0 (0.0)	0 (0.0)
Keratosis pilaris	1 (0.2)	0 (0.0)	0 (0.0)
Milia	1 (0.2)	1 (0.4)	0 (0.0)
Nail bed bleeding	1 (0.2)	0 (0.0)	0 (0.0)
Pain of skin	1 (0.2)	0 (0.0)	1 (0.7)
Palmoplantar keratoderma	1 (0.2)	0 (0.0)	0 (0.0)
Pityriasis	1 (0.2)	0 (0.0)	0 (0.0)
Pustular psoriasis	1 (0.2)	1 (0.4)	0 (0.0)
Pyoderma gangrenosum	1 (0.2)	0 (0.0)	0 (0.0)
Rash maculo-papular	1 (0.2)	0 (0.0)	0 (0.0)
Rash pruritic	1 (0.2)	1 (0.4)	0 (0.0)
Skin erosion	1 (0.2)	0 (0.0)	0 (0.0)
Skin fissures	1 (0.2)	0 (0.0)	0 (0.0)
Skin ulcer	1 (0.2)	0 (0.0)	0 (0.0)
Uraemic pruritus	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Alopecia areata	0 (0.0)	2 (0.7)	1 (0.7)
Dermatitis acneiform	0 (0.0)	0 (0.0)	1 (0.7)
Ingrowing nail	0 (0.0)	0 (0.0)	1 (0.7)
Miliaria	0 (0.0)	1 (0.4)	0 (0.0)
Rash erythematous	0 (0.0)	1 (0.4)	0 (0.0)
Rosacea	0 (0.0)	1 (0.4)	0 (0.0)
Umbilical erythema	0 (0.0)	1 (0.4)	0 (0.0)
Gastrointestinal disorders	102 (17.7)	39 (13.7)	20 (13.7)
Diarrhoea	36 (6.3)	17 (6.0)	7 (4.8)
Abdominal pain	13 (2.3)	4 (1.4)	2 (1.4)
Constipation	10 (1.7)	1 (0.4)	0 (0.0)
Nausea	10 (1.7)	8 (2.8)	3 (2.1)
Abdominal pain upper	9 (1.6)	1 (0.4)	2 (1.4)
Gastrooesophageal reflux disease	7 (1.2)	2 (0.7)	2 (1.4)
Dyspepsia	6 (1.0)	1 (0.4)	0 (0.0)
Dry mouth	5 (0.9)	2 (0.7)	0 (0.0)
Vomiting	5 (0.9)	3 (1.1)	1 (0.7)
Flatulence	3 (0.5)	0 (0.0)	0 (0.0)
Stomatitis	3 (0.5)	1 (0.4)	0 (0.0)
Abdominal discomfort	2 (0.3)	0 (0.0)	1 (0.7)
Food poisoning	2 (0.3)	3 (1.1)	1 (0.7)
Gastritis	2 (0.3)	1 (0.4)	1 (0.7)
Haemorrhoids	2 (0.3)	3 (1.1)	1 (0.7)
Irritable bowel syndrome	2 (0.3)	0 (0.0)	0 (0.0)
Toothache	2 (0.3)	2 (0.7)	2 (1.4)
Abdominal distension	1 (0.2)	0 (0.0)	0 (0.0)
Abnormal faeces	1 (0.2)	0 (0.0)	0 (0.0)
Aphthous ulcer	1 (0.2)	1 (0.4)	1 (0.7)
Cheilitis	1 (0.2)	0 (0.0)	0 (0.0)
Colitis ulcerative	1 (0.2)	0 (0.0)	0 (0.0)
Crohn's disease	1 (0.2)	0 (0.0)	0 (0.0)
Dental caries	1 (0.2)	0 (0.0)	0 (0.0)
Diarrhoea haemorrhagic	1 (0.2)	0 (0.0)	0 (0.0)
Dysphagia	1 (0.2)	0 (0.0)	0 (0.0)
Faeces soft	1 (0.2)	0 (0.0)	0 (0.0)
Frequent bowel movements	1 (0.2)	0 (0.0)	0 (0.0)
Gastrointestinal disorder	1 (0.2)	0 (0.0)	0 (0.0)
Glossodynia	1 (0.2)	0 (0.0)	0 (0.0)
Haemorrhoidal haemorrhage	1 (0.2)	0 (0.0)	0 (0.0)
Large intestine polyp	1 (0.2)	0 (0.0)	0 (0.0)
Oesophagitis	1 (0.2)	1 (0.4)	0 (0.0)
Oral papule	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Proctitis	1 (0.2)	0 (0.0)	0 (0.0)
Salivary gland mass	1 (0.2)	0 (0.0)	0 (0.0)
Anal fissure	0 (0.0)	2 (0.7)	0 (0.0)
Colitis microscopic	0 (0.0)	1 (0.4)	0 (0.0)
Diverticulum	0 (0.0)	0 (0.0)	1 (0.7)
Mouth haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)
Odynophagia	0 (0.0)	1 (0.4)	0 (0.0)
Oral mucosa erosion	0 (0.0)	1 (0.4)	0 (0.0)
Small intestinal obstruction	0 (0.0)	1 (0.4)	0 (0.0)
General disorders and administration site conditions	90 (15.6)	38 (13.3)	13 (8.9)
Pyrexia	19 (3.3)	8 (2.8)	2 (1.4)
Fatigue	16 (2.8)	8 (2.8)	3 (2.1)
Injection site reaction	14 (2.4)	1 (0.4)	0 (0.0)
Asthenia	10 (1.7)	5 (1.8)	2 (1.4)
Injection site pain	9 (1.6)	8 (2.8)	1 (0.7)
Injection site erythema	7 (1.2)	1 (0.4)	0 (0.0)
Injection site pruritus	5 (0.9)	0 (0.0)	0 (0.0)
Chills	4 (0.7)	4 (1.4)	1 (0.7)
Influenza like illness	4 (0.7)	1 (0.4)	0 (0.0)
Malaise	4 (0.7)	1 (0.4)	1 (0.7)
Vaccination site pain	4 (0.7)	1 (0.4)	2 (1.4)
Injection site swelling	3 (0.5)	1 (0.4)	0 (0.0)
Injection site bruising	2 (0.3)	1 (0.4)	1 (0.7)
Injection site rash	2 (0.3)	0 (0.0)	0 (0.0)
Injection site urticaria	2 (0.3)	0 (0.0)	0 (0.0)
Oedema peripheral	2 (0.3)	2 (0.7)	1 (0.7)
Peripheral swelling	2 (0.3)	0 (0.0)	0 (0.0)
Axillary pain	1 (0.2)	1 (0.4)	0 (0.0)
Chest discomfort	1 (0.2)	0 (0.0)	1 (0.7)
Chest pain	1 (0.2)	1 (0.4)	1 (0.7)
Crying	1 (0.2)	0 (0.0)	0 (0.0)
Gait disturbance	1 (0.2)	0 (0.0)	0 (0.0)
Hangover	1 (0.2)	0 (0.0)	0 (0.0)
Injection site discolouration	1 (0.2)	0 (0.0)	0 (0.0)
Non-cardiac chest pain	1 (0.2)	0 (0.0)	0 (0.0)
Vaccination site reaction	1 (0.2)	0 (0.0)	0 (0.0)
Injection site haemorrhage	0 (0.0)	1 (0.4)	0 (0.0)
Pain	0 (0.0)	2 (0.7)	0 (0.0)
Vaccination site erythema	0 (0.0)	0 (0.0)	1 (0.7)
Nervous system disorders	54 (9.4)	25 (8.8)	13 (8.9)
Headache	40 (6.9)	15 (5.3)	10 (6.8)
Dizziness	5 (0.9)	2 (0.7)	1 (0.7)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Migraine	5 (0.9)	1 (0.4)	0 (0.0)
Presyncope	2 (0.3)	0 (0.0)	0 (0.0)
Syncope	2 (0.3)	0 (0.0)	0 (0.0)
Complex regional pain syndrome	1 (0.2)	0 (0.0)	0 (0.0)
Dysgeusia	1 (0.2)	2 (0.7)	0 (0.0)
Hypoaesthesia	1 (0.2)	1 (0.4)	0 (0.0)
Paraesthesia	1 (0.2)	0 (0.0)	1 (0.7)
Sciatica	1 (0.2)	0 (0.0)	0 (0.0)
Tension headache	1 (0.2)	1 (0.4)	0 (0.0)
Facial paralysis	0 (0.0)	1 (0.4)	0 (0.0)
Hyperreflexia	0 (0.0)	0 (0.0)	1 (0.7)
Lethargy	0 (0.0)	1 (0.4)	0 (0.0)
Neuropathy peripheral	0 (0.0)	1 (0.4)	0 (0.0)
Optic neuritis	0 (0.0)	0 (0.0)	1 (0.7)
Investigations	43 (7.5)	23 (8.1)	16 (11.0)
Psychiatric evaluation abnormal	7 (1.2)	7 (2.5)	2 (1.4)
Aspartate aminotransferase increased	5 (0.9)	2 (0.7)	1 (0.7)
Blood glucose increased	4 (0.7)	2 (0.7)	2 (1.4)
Gamma-glutamyl transferase increased	4 (0.7)	0 (0.0)	1 (0.7)
Alanine aminotransferase increased	3 (0.5)	2 (0.7)	0 (0.0)
Neutrophil count increased	3 (0.5)	0 (0.0)	1 (0.7)
White blood cell count increased	3 (0.5)	0 (0.0)	0 (0.0)
Blood bilirubin increased	2 (0.3)	0 (0.0)	0 (0.0)
Blood cholesterol increased	2 (0.3)	1 (0.4)	0 (0.0)
Blood urea increased	2 (0.3)	0 (0.0)	0 (0.0)
Blood uric acid increased	2 (0.3)	0 (0.0)	0 (0.0)
Monocyte count increased	2 (0.3)	1 (0.4)	0 (0.0)
Urine analysis abnormal	2 (0.3)	1 (0.4)	1 (0.7)
Blood lactate dehydrogenase increased	1 (0.2)	0 (0.0)	0 (0.0)
Blood pressure decreased	1 (0.2)	0 (0.0)	0 (0.0)
Body temperature increased	1 (0.2)	2 (0.7)	1 (0.7)
Coronavirus test positive	1 (0.2)	2 (0.7)	1 (0.7)
Electrocardiogram qt prolonged	1 (0.2)	1 (0.4)	0 (0.0)
Epstein-Barr virus test positive	1 (0.2)	0 (0.0)	0 (0.0)
Haematocrit decreased	1 (0.2)	1 (0.4)	1 (0.7)
Haemoglobin increased	1 (0.2)	0 (0.0)	0 (0.0)
Lymphocyte count increased	1 (0.2)	0 (0.0)	0 (0.0)
Monocyte percentage increased	1 (0.2)	1 (0.4)	0 (0.0)
Neutrophil percentage increased	1 (0.2)	0 (0.0)	0 (0.0)
Platelet count decreased	1 (0.2)	1 (0.4)	0 (0.0)
Platelet count increased	1 (0.2)	1 (0.4)	1 (0.7)
Smear cervix abnormal	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Sperm concentration decreased	1 (0.2)	0 (0.0)	0 (0.0)
Transaminases increased	1 (0.2)	1 (0.4)	0 (0.0)
Urinary sediment present	1 (0.2)	1 (0.4)	0 (0.0)
Vitamin d decreased	1 (0.2)	0 (0.0)	0 (0.0)
Weight decreased	1 (0.2)	0 (0.0)	0 (0.0)
Weight increased	1 (0.2)	0 (0.0)	0 (0.0)
Blood glucose abnormal	0 (0.0)	0 (0.0)	1 (0.7)
Blood urine present	0 (0.0)	2 (0.7)	0 (0.0)
Eosinophil count increased	0 (0.0)	1 (0.4)	0 (0.0)
False positive tuberculosis test	0 (0.0)	0 (0.0)	1 (0.7)
Haemoglobin decreased	0 (0.0)	2 (0.7)	1 (0.7)
Hepatic enzyme increased	0 (0.0)	1 (0.4)	1 (0.7)
Liver function test increased	0 (0.0)	0 (0.0)	1 (0.7)
Lymphocyte count decreased	0 (0.0)	1 (0.4)	0 (0.0)
Red blood cells urine positive	0 (0.0)	1 (0.4)	0 (0.0)
Specific gravity urine increased	0 (0.0)	1 (0.4)	0 (0.0)
Vitamin b12 decreased	0 (0.0)	0 (0.0)	1 (0.7)
White blood cells urine	0 (0.0)	1 (0.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	38 (6.6)	15 (5.3)	15 (10.3)
Arthralgia	8 (1.4)	2 (0.7)	2 (1.4)
Back pain	7 (1.2)	0 (0.0)	7 (4.8)
Myalgia	7 (1.2)	2 (0.7)	1 (0.7)
Pain in extremity	5 (0.9)	2 (0.7)	2 (1.4)
Musculoskeletal pain	2 (0.3)	3 (1.1)	0 (0.0)
Rotator cuff syndrome	2 (0.3)	0 (0.0)	0 (0.0)
Costochondritis	1 (0.2)	0 (0.0)	1 (0.7)
Flank pain	1 (0.2)	0 (0.0)	0 (0.0)
Hypermobility syndrome	1 (0.2)	0 (0.0)	0 (0.0)
Joint contracture	1 (0.2)	0 (0.0)	0 (0.0)
Musculoskeletal chest pain	1 (0.2)	0 (0.0)	0 (0.0)
Neck pain	1 (0.2)	2 (0.7)	1 (0.7)
Osteoarthritis	1 (0.2)	1 (0.4)	1 (0.7)
Plantar fasciitis	1 (0.2)	0 (0.0)	1 (0.7)
Rhabdomyolysis	1 (0.2)	0 (0.0)	0 (0.0)
Spinal pain	1 (0.2)	0 (0.0)	0 (0.0)
Arthritis reactive	0 (0.0)	0 (0.0)	1 (0.7)
Muscle spasms	0 (0.0)	3 (1.1)	0 (0.0)
Muscular weakness	0 (0.0)	1 (0.4)	0 (0.0)
Torticollis	0 (0.0)	1 (0.4)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	31 (5.4)	19 (6.7)	5 (3.4)
Oropharyngeal pain	15 (2.6)	4 (1.4)	2 (1.4)
Cough	6 (1.0)	5 (1.8)	1 (0.7)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Rhinitis allergic	3 (0.5)	2 (0.7)	0 (0.0)
Asthma	1 (0.2)	0 (0.0)	0 (0.0)
Catarrh	1 (0.2)	0 (0.0)	0 (0.0)
Dyspnoea	1 (0.2)	1 (0.4)	0 (0.0)
Dyspnoea exertional	1 (0.2)	0 (0.0)	0 (0.0)
Nasal congestion	1 (0.2)	4 (1.4)	0 (0.0)
Nasal dryness	1 (0.2)	0 (0.0)	0 (0.0)
Respiratory tract congestion	1 (0.2)	0 (0.0)	0 (0.0)
Rhinorrhoea	1 (0.2)	2 (0.7)	0 (0.0)
Sneezing	1 (0.2)	1 (0.4)	0 (0.0)
Tonsillar inflammation	1 (0.2)	0 (0.0)	0 (0.0)
Epistaxis	0 (0.0)	2 (0.7)	1 (0.7)
Productive cough	0 (0.0)	0 (0.0)	1 (0.7)
Sinus congestion	0 (0.0)	1 (0.4)	0 (0.0)
Injury, poisoning and procedural complications	25 (4.3)	13 (4.6)	7 (4.8)
Ligament sprain	4 (0.7)	2 (0.7)	1 (0.7)
Procedural pain	3 (0.5)	0 (0.0)	0 (0.0)
Contusion	2 (0.3)	0 (0.0)	1 (0.7)
Laceration	2 (0.3)	2 (0.7)	0 (0.0)
Meniscus injury	2 (0.3)	0 (0.0)	0 (0.0)
Thermal burn	2 (0.3)	0 (0.0)	0 (0.0)
Excoriation	1 (0.2)	0 (0.0)	0 (0.0)
Foot fracture	1 (0.2)	1 (0.4)	0 (0.0)
Ligament injury	1 (0.2)	1 (0.4)	0 (0.0)
Limb injury	1 (0.2)	0 (0.0)	1 (0.7)
Maternal exposure during pregnancy	1 (0.2)	0 (0.0)	0 (0.0)
Muscle strain	1 (0.2)	0 (0.0)	0 (0.0)
Post procedural haematoma	1 (0.2)	0 (0.0)	0 (0.0)
Road traffic accident	1 (0.2)	1 (0.4)	1 (0.7)
Skin injury	1 (0.2)	0 (0.0)	0 (0.0)
Tooth fracture	1 (0.2)	0 (0.0)	0 (0.0)
Vaccination complication	1 (0.2)	0 (0.0)	0 (0.0)
Accident at home	0 (0.0)	0 (0.0)	1 (0.7)
Arthropod bite	0 (0.0)	0 (0.0)	2 (1.4)
Arthropod sting	0 (0.0)	1 (0.4)	0 (0.0)
Back injury	0 (0.0)	0 (0.0)	1 (0.7)
Burns second degree	0 (0.0)	1 (0.4)	0 (0.0)
Fall	0 (0.0)	2 (0.7)	1 (0.7)
Fibula fracture	0 (0.0)	1 (0.4)	0 (0.0)
Hand fracture	0 (0.0)	0 (0.0)	1 (0.7)
Joint dislocation	0 (0.0)	1 (0.4)	0 (0.0)
Joint injury	0 (0.0)	1 (0.4)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Tibia fracture	0 (0.0)	1 (0.4)	0 (0.0)
Psychiatric disorders	23 (4.0)	16 (5.6)	4 (2.7)
Anxiety	6 (1.0)	3 (1.1)	1 (0.7)
Depression	6 (1.0)	5 (1.8)	1 (0.7)
Depressed mood	3 (0.5)	0 (0.0)	1 (0.7)
Insomnia	3 (0.5)	2 (0.7)	1 (0.7)
Sleep disorder	2 (0.3)	1 (0.4)	0 (0.0)
Acute stress disorder	1 (0.2)	0 (0.0)	0 (0.0)
Adjustment disorder	1 (0.2)	0 (0.0)	0 (0.0)
Adjustment disorder with depressed mood	1 (0.2)	0 (0.0)	0 (0.0)
Confusional state	1 (0.2)	0 (0.0)	0 (0.0)
Emotional distress	1 (0.2)	0 (0.0)	0 (0.0)
Panic attack	1 (0.2)	0 (0.0)	0 (0.0)
Alcohol abuse	0 (0.0)	2 (0.7)	0 (0.0)
Irritability	0 (0.0)	1 (0.4)	0 (0.0)
Libido decreased	0 (0.0)	1 (0.4)	0 (0.0)
Nervousness	0 (0.0)	1 (0.4)	0 (0.0)
Suicidal ideation	0 (0.0)	1 (0.4)	0 (0.0)
Eye disorders	19 (3.3)	7 (2.5)	2 (1.4)
Blepharitis	4 (0.7)	3 (1.1)	1 (0.7)
Cataract	1 (0.2)	0 (0.0)	0 (0.0)
Conjunctivitis allergic	1 (0.2)	0 (0.0)	0 (0.0)
Eczema eyelids	1 (0.2)	0 (0.0)	0 (0.0)
Erythema of eyelid	1 (0.2)	0 (0.0)	0 (0.0)
Eye discharge	1 (0.2)	0 (0.0)	0 (0.0)
Eye irritation	1 (0.2)	0 (0.0)	0 (0.0)
Eye pain	1 (0.2)	0 (0.0)	0 (0.0)
Eye pruritus	1 (0.2)	0 (0.0)	0 (0.0)
Eye swelling	1 (0.2)	0 (0.0)	0 (0.0)
Eyelid oedema	1 (0.2)	1 (0.4)	0 (0.0)
Eyelid ptosis	1 (0.2)	0 (0.0)	0 (0.0)
Metamorphopsia	1 (0.2)	0 (0.0)	0 (0.0)
Noninfective conjunctivitis	1 (0.2)	1 (0.4)	0 (0.0)
Ocular hyperaemia	1 (0.2)	0 (0.0)	0 (0.0)
Periorbital oedema	1 (0.2)	0 (0.0)	0 (0.0)
Scleral disorder	1 (0.2)	0 (0.0)	0 (0.0)
Vision blurred	1 (0.2)	0 (0.0)	0 (0.0)
Keratitis	0 (0.0)	1 (0.4)	0 (0.0)
Ocular discomfort	0 (0.0)	0 (0.0)	1 (0.7)
Vitreous floaters	0 (0.0)	1 (0.4)	0 (0.0)
Metabolism and nutrition disorders	16 (2.8)	10 (3.5)	6 (4.1)
Hypercholesterolaemia	5 (0.9)	4 (1.4)	2 (1.4)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Diabetes mellitus	2 (0.3)	0 (0.0)	0 (0.0)
Hyperuricaemia	2 (0.3)	0 (0.0)	0 (0.0)
Decreased appetite	1 (0.2)	1 (0.4)	0 (0.0)
Gout	1 (0.2)	1 (0.4)	0 (0.0)
Hyperglycaemia	1 (0.2)	0 (0.0)	0 (0.0)
Hyperkalaemia	1 (0.2)	0 (0.0)	0 (0.0)
Hypoalbuminaemia	1 (0.2)	0 (0.0)	0 (0.0)
Hypokalaemia	1 (0.2)	0 (0.0)	1 (0.7)
Hypomagnesaemia	1 (0.2)	0 (0.0)	0 (0.0)
Hyponatraemia	1 (0.2)	0 (0.0)	1 (0.7)
Insulin resistance	1 (0.2)	0 (0.0)	0 (0.0)
Iron deficiency	1 (0.2)	0 (0.0)	0 (0.0)
Vitamin d deficiency	1 (0.2)	1 (0.4)	0 (0.0)
Glucose tolerance impaired	0 (0.0)	0 (0.0)	1 (0.7)
Hyperlipidaemia	0 (0.0)	1 (0.4)	0 (0.0)
Hypoglycaemia	0 (0.0)	1 (0.4)	0 (0.0)
Lactose intolerance	0 (0.0)	1 (0.4)	0 (0.0)
Type 2 diabetes mellitus	0 (0.0)	1 (0.4)	2 (1.4)
Reproductive system and breast disorders	16 (2.8)	7 (2.5)	2 (1.4)
Dysmenorrhoea	4 (0.7)	2 (0.7)	1 (0.7)
Amenorrhoea	2 (0.3)	0 (0.0)	0 (0.0)
Vulvovaginal pruritus	2 (0.3)	0 (0.0)	0 (0.0)
Gynaecomastia	1 (0.2)	0 (0.0)	0 (0.0)
Menorrhagia	1 (0.2)	2 (0.7)	0 (0.0)
Metrorrhagia	1 (0.2)	1 (0.4)	0 (0.0)
Ovarian cyst	1 (0.2)	0 (0.0)	0 (0.0)
Penile oedema	1 (0.2)	0 (0.0)	0 (0.0)
Pruritus genital	1 (0.2)	0 (0.0)	0 (0.0)
Scrotal oedema	1 (0.2)	0 (0.0)	0 (0.0)
Vaginal discharge	1 (0.2)	0 (0.0)	0 (0.0)
Vulval disorder	1 (0.2)	0 (0.0)	0 (0.0)
Vulvovaginal discomfort	1 (0.2)	0 (0.0)	0 (0.0)
Erectile dysfunction	0 (0.0)	1 (0.4)	0 (0.0)
Menstruation delayed	0 (0.0)	1 (0.4)	1 (0.7)
Oligomenorrhoea	0 (0.0)	1 (0.4)	0 (0.0)
Ear and labyrinth disorders	13 (2.3)	0 (0.0)	0 (0.0)
Vertigo	4 (0.7)	0 (0.0)	0 (0.0)
Ear pain	2 (0.3)	0 (0.0)	0 (0.0)
Tinnitus	2 (0.3)	0 (0.0)	0 (0.0)
Deafness unilateral	1 (0.2)	0 (0.0)	0 (0.0)
Excessive cerumen production	1 (0.2)	0 (0.0)	0 (0.0)
Hypoacusis	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Middle ear effusion	1 (0.2)	0 (0.0)	0 (0.0)
Otorrhoea	1 (0.2)	0 (0.0)	0 (0.0)
Vertigo positional	1 (0.2)	0 (0.0)	0 (0.0)
Renal and urinary disorders	11 (1.9)	5 (1.8)	3 (2.1)
Dysuria	2 (0.3)	0 (0.0)	0 (0.0)
Nephrolithiasis	2 (0.3)	2 (0.7)	1 (0.7)
Pollakiuria	2 (0.3)	0 (0.0)	0 (0.0)
Chromaturia	1 (0.2)	0 (0.0)	0 (0.0)
Crystalluria	1 (0.2)	0 (0.0)	0 (0.0)
Glycosuria	1 (0.2)	0 (0.0)	0 (0.0)
Urinary tract inflammation	1 (0.2)	0 (0.0)	0 (0.0)
Urine abnormality	1 (0.2)	0 (0.0)	0 (0.0)
Urine odour abnormal	1 (0.2)	0 (0.0)	0 (0.0)
Haematuria	0 (0.0)	2 (0.7)	0 (0.0)
Proteinuria	0 (0.0)	0 (0.0)	1 (0.7)
Renal colic	0 (0.0)	1 (0.4)	1 (0.7)
Blood and lymphatic system disorders	10 (1.7)	5 (1.8)	5 (3.4)
Iron deficiency anaemia	2 (0.3)	2 (0.7)	1 (0.7)
Lymphadenopathy	2 (0.3)	0 (0.0)	0 (0.0)
Anaemia folate deficiency	1 (0.2)	0 (0.0)	0 (0.0)
Eosinophilia	1 (0.2)	0 (0.0)	0 (0.0)
Haemorrhagic anaemia	1 (0.2)	1 (0.4)	0 (0.0)
Leukocytosis	1 (0.2)	0 (0.0)	0 (0.0)
Leukopenia	1 (0.2)	0 (0.0)	0 (0.0)
Macrocytosis	1 (0.2)	0 (0.0)	1 (0.7)
Thrombocytopenia	1 (0.2)	0 (0.0)	0 (0.0)
Anaemia	0 (0.0)	1 (0.4)	1 (0.7)
Anaemia of chronic disease	0 (0.0)	0 (0.0)	1 (0.7)
Haemoglobinaemia	0 (0.0)	1 (0.4)	0 (0.0)
Neutrophilia	0 (0.0)	0 (0.0)	2 (1.4)
Thrombocytosis	0 (0.0)	0 (0.0)	1 (0.7)
Vascular disorders	9 (1.6)	0 (0.0)	3 (2.1)
Hypertension	5 (0.9)	0 (0.0)	2 (1.4)
Peripheral venous disease	2 (0.3)	0 (0.0)	0 (0.0)
Deep vein thrombosis	1 (0.2)	0 (0.0)	0 (0.0)
Hot flush	1 (0.2)	0 (0.0)	1 (0.7)
Thrombophlebitis superficial	1 (0.2)	0 (0.0)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	7 (1.2)	3 (1.1)	0 (0.0)
Uterine leiomyoma	2 (0.3)	0 (0.0)	0 (0.0)
Anogenital warts	1 (0.2)	0 (0.0)	0 (0.0)
Breast cancer	1 (0.2)	0 (0.0)	0 (0.0)

System Organ Class Preferred Term	BKZ 320mg Q2W N = 576 n (%)	BKZ 320mg Q4W N = 285 n (%)	Placebo N = 146 n (%)
Any AE	379 (65.8)	167 (58.6)	90 (61.6)
Haemangioma	1 (0.2)	0 (0.0)	0 (0.0)
Haemangioma of skin	1 (0.2)	0 (0.0)	0 (0.0)
Tongue neoplasm benign	1 (0.2)	0 (0.0)	0 (0.0)
Fibroma	0 (0.0)	1 (0.4)	0 (0.0)
Leiomyoma	0 (0.0)	1 (0.4)	0 (0.0)
Melanocytic naevus	0 (0.0)	1 (0.4)	0 (0.0)
Hepatobiliary disorders	6 (1.0)	1 (0.4)	0 (0.0)
Cholelithiasis	2 (0.3)	1 (0.4)	0 (0.0)
Hepatic steatosis	2 (0.3)	0 (0.0)	0 (0.0)
Drug-induced liver injury	1 (0.2)	0 (0.0)	0 (0.0)
Hyperbilirubinaemia	1 (0.2)	0 (0.0)	0 (0.0)
Cholecystitis acute	0 (0.0)	1 (0.4)	0 (0.0)
Cardiac disorders	5 (0.9)	6 (2.1)	1 (0.7)
Atrioventricular block first degree	1 (0.2)	1 (0.4)	0 (0.0)
Bradycardia	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac failure	1 (0.2)	0 (0.0)	0 (0.0)
Cardiac failure acute	1 (0.2)	0 (0.0)	0 (0.0)
Diastolic dysfunction	1 (0.2)	0 (0.0)	0 (0.0)
Tachycardia	1 (0.2)	4 (1.4)	1 (0.7)
Bundle branch block left	0 (0.0)	1 (0.4)	0 (0.0)
Immune system disorders	3 (0.5)	0 (0.0)	0 (0.0)
Seasonal allergy	3 (0.5)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	1 (0.2)	1 (0.4)	0 (0.0)
Pregnancy on contraceptive	1 (0.2)	0 (0.0)	0 (0.0)
Complication of pregnancy	0 (0.0)	1 (0.4)	0 (0.0)
Surgical and medical procedures	0 (0.0)	1 (0.4)	0 (0.0)
Abortion induced	0 (0.0)	1 (0.4)	0 (0.0)

Source: OCS Analysis Studio, Safety Explorer.
Filters: POOL = "S1" and TRT01A = "BKZ 320mg Q2W" (BKZ 320mg Q2W); TRT01A = "BKZ 320mg Q4W" and POOL = "S1" (BKZ 320mg Q4W); TRT01A = "Placebo" and POOL = "S1" (Placebo); TRTEMFL = "Y" and ANL01FL = "Y" (Adverse Events).

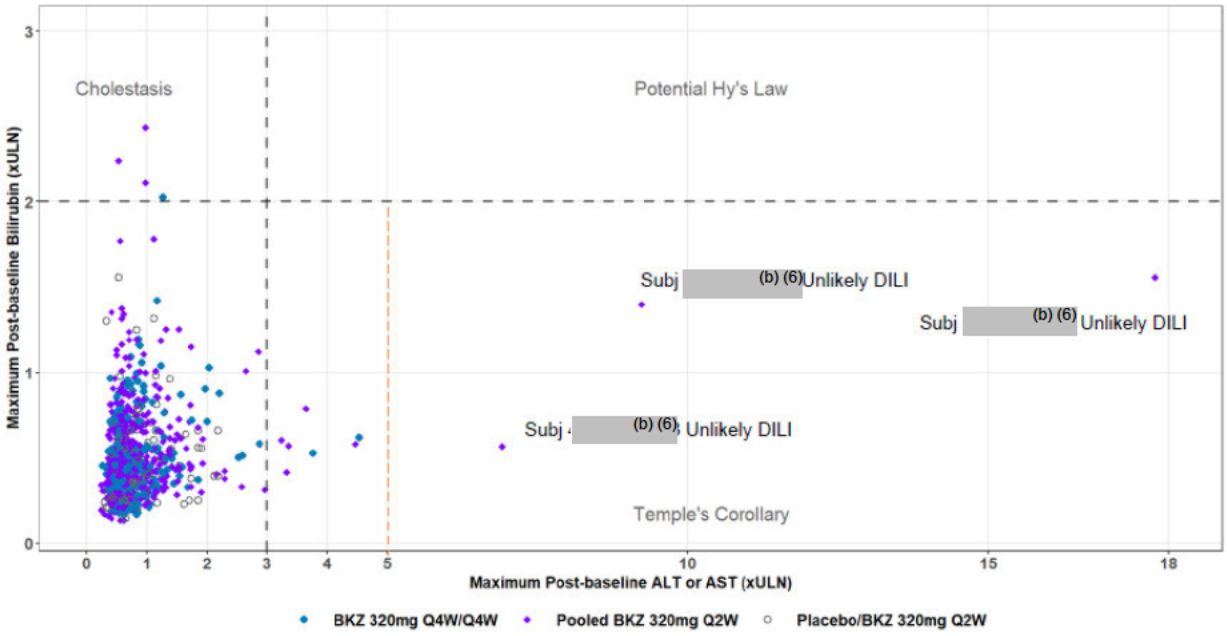
19.6.2. Additional Information from the DILI Team Consult Review

Pool S1

Pool S1 included data from the 16-week randomized, placebo-controlled trials (RPCT) of HS0003 and HS0004. Per the DILI team, “The hepatocellular DILI screening plot (eDISH) had no subjects in the potential Hy’s Law quadrant, but there were ten subjects on BKZ in Temple’s (corollary quadrant) and one on placebo (see figure below). The three with aminotransferase (AT) elevations >5x ULN met criteria for concerning for clinically important DILI, but we assessed all three as unlikely DILI due to BKZ. There were four subjects in the cholestasis

quadrant on BKZ and none on placebo (Figure not shown). None of these four moved to the right upper quadrant of the cholestatic DILI screening plot. Therefore, none of these four jaundiced subjects had ALP levels >2x ULN or AT >3x ULN making DILI unlikely in a non-cirrhotic population of subjects."

Figure 21: Hepatocellular DILI screening plot (eDISH) for Pool S1

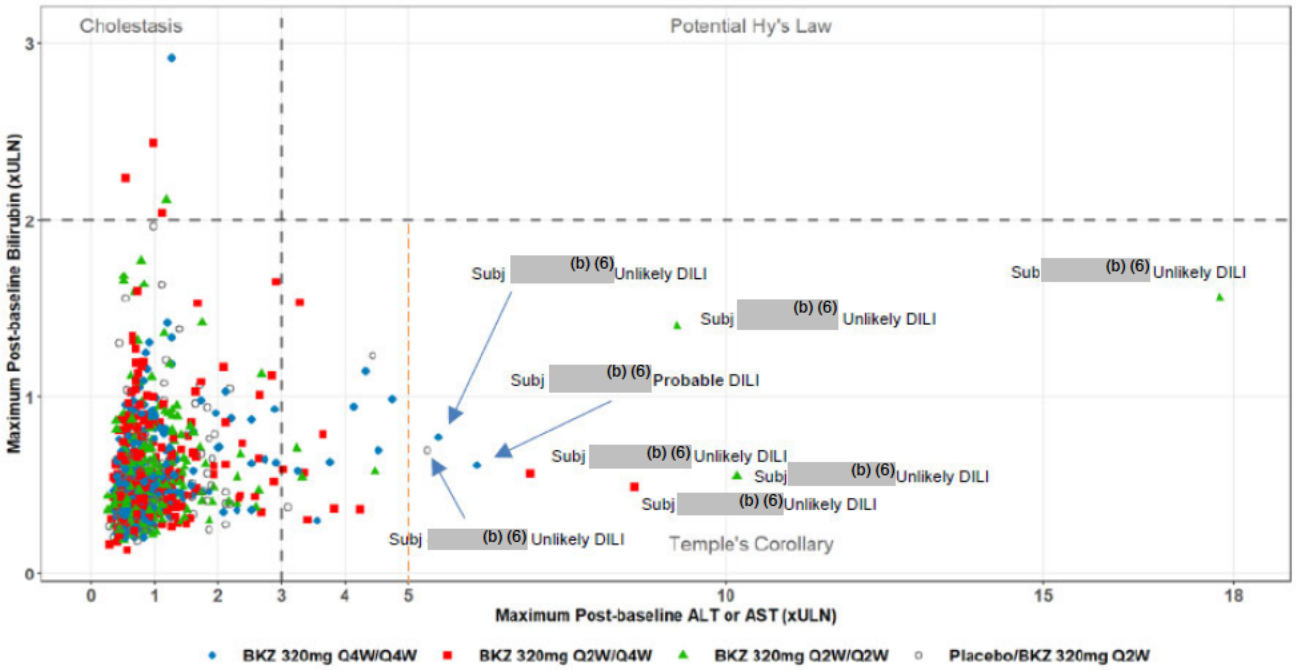


Source: DILI Team Consult Review dated May 31, 2024 (DARRTS Reference ID 5390131), Figure 5, p. 10

Pool S2

Pool S2 is comprised of the 16-week, placebo- controlled Initial Treatment Period and the Maintenance Treatment Period through Week 48. Per the DILI team, "In the maintenance (period) (i.e., after the first 16 weeks), the placebo arm is lost with all placebo subjects switching to BKZ treatment. The hepatocellular DILI screening plot (eDISH) had no subjects in the potential Hy's Law quadrant but 27 subjects in Temple's quadrant, eight of which had ATs >5x ULN (see figure below). Of these eight we assessed just one as probable DILI due to BKZ. Five subjects in the cholestasis quadrant (scatterplot not shown), did not move to the right upper quadrant in the cholestatic DILI scatterplot, suggesting no cholestatic DILI with jaundice occurred. Indeed, there were no cases in the right lower quadrant of the cholestatic screening plot either."

Figure 22:Hepatocellular DILI screening plot (eDISH) for Pool S2



Source: DILI Team Consult Review dated May 31, 2024 (DARRTS Reference ID 5390131), Figure 6, p. 12

Pool S3

Pool S3 is comprised of the combined Initial and maintenance Treatment Periods of Trials HS0003 and HS0004, as well as data from OLE Trial HS0005 through the data cutoff. Per the DILI team, "The analysis yielded one more case in Temple's (corollary quadrant) with ATs >5x ULN (Subject (b) (6). We assessed it as unlikely DILI due to a latency of 1.85 years, rapid resolution while still taking BKZ, and a competing diagnosis of mononucleosis with liver enzyme elevation. Cholestatic plots had two subjects on BKZ in the right lower quadrant (i.e., peak ALP>2x ULN). Both subjects were adjudicated as unlikely DILI. One subject was the same one identified in Temple's on eDISH discussed above (Subject (b) (6). The other subject (50190-16976) also had a long latency at 1.27 years and with resolution too quick for DILI (6 days) particularly if immune mediated.

Case level analyses: We assessed cases across the HS0001, HS0003, HS0004 and HS0005 with any of the following criterion:

- Sponsor identified potential Hy's law case
- ALT or AST >3x ULN with TB >2x ULN
- ALT or AST >5x ULN
- ALP> 2x ULN
- AEs under the Hepatic Failure Subgrouping in the Hepatobiliary System Organ Class.

Overall, we assessed 17 subjects for potential DILI. We considered one as probable DILI due to BKZ and three as possible. We assessed the rest as unlikely. There were no subjects with jaundice (TB >2x ULN) and thus no Hy's Law cases. We agreed with the sponsor that Subject 40286-18096 is the one probable case of DILI due BKZ. This subject is discussed in detail below. The three possible DILI cases had confounding alternative diagnoses as shown in the table below.

Table 58: Four subjects with at least possible DILI due to BKZ

#	ID	Causality Score*	Alternate diagnosis	Age (y)	Sex	Race	Latency from start drug (d)	Latency from stop drug (d)~	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	NA	24	F	White	129	[98]	243	82	104	0.41	7.15	2.41
2		4	Alcohol	41	F	Black	449	[13]	186	163	104	0.41	5.47	4.79
3		4	Cocaine/stone	18	F	White	448	0	325	166	NA	NA	NA	NA
4		4	Isoniazid	29	M	White	14	[76]	226	152	104	0.47	6.65	4.47
			Average	*28*			*[47]*	*[132]*	*245*	*141*	*104*	*0.43*	*6.4*	*3.9*
			Std dev	*8.46*			*41*	*149*	*51*	*34*	*0*	*0.03*	*0.7*	*1.1*
			Median	*26.5*			*[45]*	*[87]*	*235*	*158*	*104*	*0.41*	*6.6*	*4.5*
			Min	*18*			*[98]*	*[476]*	*186*	*82*	*104*	*0.41*	*5.5*	*2.4*
			Max	*41*			*0*	*14*	*325*	*166*	*104*	*0.47*	*7.1*	*4.8*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

~Bracketed [ ] day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

The unlikely cases are shown in the table below this paragraph. Overall, most of these injuries had long latencies and often resolved rapidly without stopping BKZ. Such an injury pattern would be inconsistent with DILI particularly because monoclonal antibodies are expected to have a substantial immune component to liver injury if it does occur. Such immune mediated DILI is expected to resolve more slowly. They were two subjects with probable myopathy along with several others we suspect had myopathy but did not have CK levels checked. These cases are noteworthy because they might explain some of the preponderance of AST elevations over ALT; AST is generally higher than ALT in myopathies. The subject with the highest AT values (Subject (b) (6)) had a history of widely fluctuating liver enzymes and her ALT had already increased 10-fold from her baseline on the day she started BKZ, making DILI unlikely, and autoimmune hepatitis (AIH) more likely. She also received COVID-19 vaccination just before the liver injury and rare cases of post-vaccination liver injury are reported.

Table 59: Thirteen subjects with unlikely DILI to BKZ

#	ID	Causality Score*	Alternate diagnosis	Age (y)	Sex	Race	Latency from start drug (d)	Latency from stop drug (d)~	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)	5	Myopathy	24	M	White	28	[476]	88	180	104	0.47	2.59	5.29
2		5	Myopathy	41	M	Black	393	[277]	59	177	104	1.05	1.74	5.21
3		5	?myopathy	21	F	Black	333	[114]	102	291	104	0.35	3.00	8.56
4		5	?myopathy	25	M	White	83	[277]	159	314	104	1.29	4.68	9.24
5		5	?myopathy	23	M	White	224	[14]	143	346	104	0.64	4.21	10.18
6		5	?myopathy	31	M	White	113	[117]	90	235	104	0.7	2.65	6.91
7		5	Alcohol	25	M	White	448	[224]	145	235	104	1.29	4.26	6.91
8		5	Alcohol	51	M	White	399	[401]	166	238	104	0.58	4.88	7.00
9		5	Fatty liver	40	F	White	126	14	239	167	104	0.53	7.03	4.91
10		5	AIH; Covid vaccine	18	F	White	0	[14]	978	514	104	1.17	28.76	15.12
11		5	Unknown	47	F	Black	448	0	NA	700	345	0.58	NA	6.21
12		5	Unknown	18	M	White	283	[27]	148	161	104	0.58	4.35	4.74
13		5	EBV	21	F	White	653	[75]	272	192	269	0.76	3.09	2.18

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

~Bracketed [ ] day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

Case of interest:

Subject (b) (6) (HS0004): probable DILI due to BKZ.

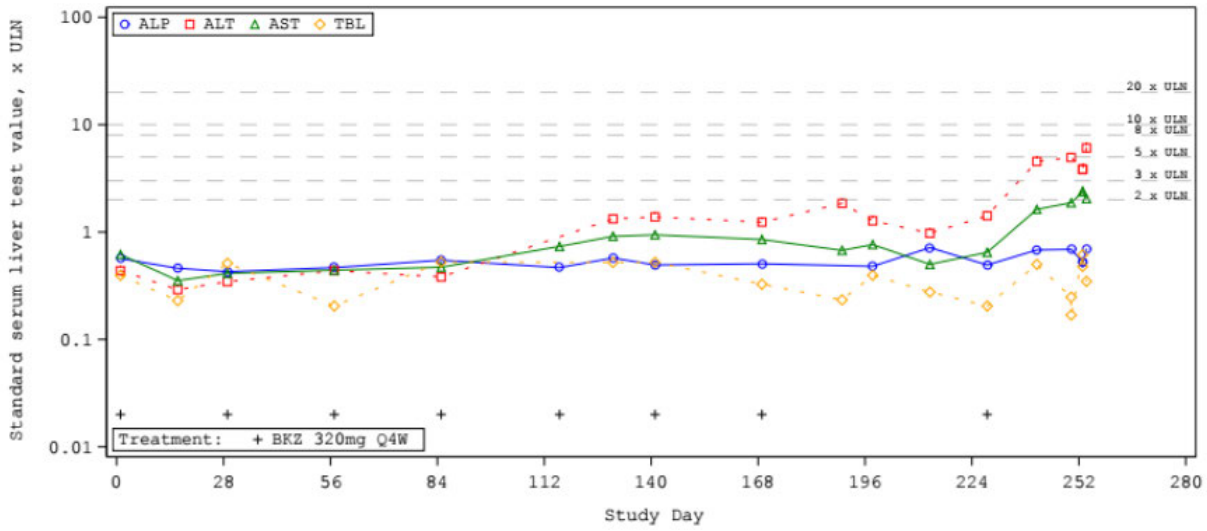
Summary: This is a 24-year-old female, white, with HS, who developed elevated aminotransferases approximately 129 days after starting BKZ. Initial dose was 320 mg SC q4 weeks.

At baseline, the subject's BMI was 32 kg/m^2. Relevant medical history, besides the target disease, included obesity, chronic diarrhea, chronic nausea and vomiting, and Cushing's syndrome. Alcohol history was described as "no alcohol intoxication." Concurrent medications relevant to DILI risk were ethinyl estradiol with levonorgestrel. The subject's ALT, AST, AP, and TB were 24 U/L, 21 U/L, 85 U/L, and 0.5 mg/dL, respectively.

The subject started BKZ at 320 mg subcutaneously (SC) q4 weeks on (b) (6) (Day 1). On (b) (6) (Day 129), ALT, AST, AP, and TB were 73 U/L, 31 U/L, 86 U/L and 0.6 mg/dL, respectively. The study drug continued without change. The subject had ongoing issues with diarrhea, nausea, and vomiting which were evaluated extensively during the trial. Thereafter, her ALT and AST gradually increased further (see figure below), and study drug was stopped with last dose on (b) (6) (Day 227). Liver enzymes continued rise to last documented (peak) levels on (b) (6) (Day 253), were ALT, AST, AP, and TB of 253 U/L, 81 U/L, 79 U/L and 0.76 mg/dL, respectively. No further lab values were provided, but the narrative says the "liver function tests were almost normal" by (b) (6) (Day 281). Evaluation testing results were not mentioned. Liver imaging by ultrasound was normal. However, the narrative states that "after discussion with the hepatologist, the Investigator

considered hepatic cytolysis as related to the study drug by the elimination of other plausible causes."

Figure 23: Liver analytes and BKZ dosing (+ signs) by study day for Subject (b) (6)



Assessment: We assessed this case as probable DILI due to BKZ. Latency is consistent; dechallenge washout (by narrative; not graphed) would also be consistent with a long acting drug and potential immune mediated liver injury. Evaluation testing was not well-documented, but the narrative suggests evaluation was done to the satisfaction of the on-site hepatologist such that the investigator implicated BKZ.

19.6.3. Additional Information from the DP Consult Review

Baseline Neuropsychiatric Characteristics

Table 60: Psychiatric Baseline Symptoms, Co-morbid History, and Concomitant Medications among Subjects Participating in the Initial Treatment Period (Pooled Trials HS0003 and HS0004)

Baseline Characteristics	Placebo (N=144)	BKZ 320 mg Q4W (N=285)	BZK 320 mg Q2W (N=576)	BKZ Total (N=861)
Baseline PHQ-9 Total Score, mean (SD)	3.7 (3.8)	3.6 (3.9)	3.1 (3.4)	3.2 (3.6)
total score < 5	96 (66)	196 (69)	441 (77)	637 (74)
total score ≥5 and ≤ 9	36 (25)	58 (20)	101 (18)	159 (19)
total score ≥10 and ≤ 14	12 (8.2)	25 (8.8)	28 (4.9)	53 (6.2)
Lifetime history of SI/B based on the C-SSRS, n (%)	18 (12)	44 (15)	71 (12)	115 (13)
Co-morbid Psychiatric Conditions, n (%)[1]	34 (23)	70 (25)	139 (24)	209 (24)
Anxiety	17 (12)	37 (13)	64 (11)	101 (12)
ADHD	2 (1.4)	4 (1.4)	10 (1.7)	14 (1.6)
Depression	23 (16)	43 (15)	78 (14)	121 (14)
Sleep disorder	4 (2.7)	11 (3.9)	28 (4.9)	39 (4.5)
Stress disorder	1 (0.7)	4 (1.4)	5 (0.9)	9 (1.0)
Substance-related disorders	2 (1.4)	1 (0.4)	10 (1.7)	11 (1.3)
SI/B and self-injury	1 (0.7)	4 (1.4)	7 (1.2)	11 (1.3)
Concomitant Medications				
Antidepressants	16 (11)	33 (12)	65 (11)	98 (11)
Antiepileptics	2 (1.4)	2 (0.7)	7 (1.2)	9 (1.0)
Antipsychotics	3 (2.1)	7 (2.5)	13 (2.3)	20 (2.3)
Anxiolytics	8 (5.5)	17 (6.0)	36 (6.3)	53 (6.2)
Hypnotics/sedatives	3 (2.1)	5 (1.8)	16 (2.8)	21 (2.4)
Pain management	7 (4.8)	9 (3.2)	18 (3.1)	27 (3.1)
Psychostimulants	2 (1.4)	4 (1.4)	8 (1.4)	12 (1.4)

[1]Occuring in at least 1% of patients
Note: Anxiolytics include antidepressants and benzodiazepines

DP Reviewer's Comment: *In general, the treatment arms from Studies HS0003 and HS0004 were well-balanced with respect to psychiatric co-morbidities and concomitant psychotropic medication use and reflect the overall population of patients with HS. Given Study HS0001's conservative SI/B eligibility criteria (i.e., exclusion of subjects with lifetime history of SB, SI within the past 6 months, and severe anxiety), the lower background rate of anxiety and SI/B history relative to Studies HS0003 and HS0004 is expected. Although psychiatric-relevant eligibility criteria for Studies HS0003 and HS0004 were identical relative to phase 3 studies supporting the PsO development program, differences in the proportion of subjects with a history of SI/B, depression, and anxiety are likely due to differences in background risk between patients with HS and PsO.*

Neuropsychiatric AEs

Table 61: Incidence of Psychiatric Adverse Events during the Initial Treatment Period (Pooled Trials HS0003 and HS0004)

Adverse events, n (%)	Placebo (N=144)	BKZ 320 mg Q4W (N=285)	BZK 320 mg Q2W (N=576)	BKZ Total (N=861)
Subjects with at least one Psychiatric AE	4 (2.7)	16 (5.6)	23 (4.0)	39 (4.5)
Adjustment disorder	-	-	2 (0.3)	2 (0.2)
Alcohol abuse	-	2 (0.7)	-	2 (0.2)
Anxiety	1 (0.7)	4 (1.4)	6 (1.0)	10 (1.2)
Confusion	-	-	1 (0.2)	1 (0.2)
Depression	2 (1.4)	5 (1.8)	9 (1.6)	14 (1.6)
Insomnia	1 (0.7)	2 (0.7)	3 (0.5)	5 (0.6)
Irritability	-	1 (0.4)	1 (0.2)	2 (0.2)
Panic attacks	-	-	1 (0.2)	1 (0.2)
Sleep disorder	-	1 (0.4)	2 (0.3)	3 (0.3)
Stress disorder	-	-	1 (0.2)	1 (0.1)
Suicidal ideation	-	1 (0.4)	-	1 (0.1)

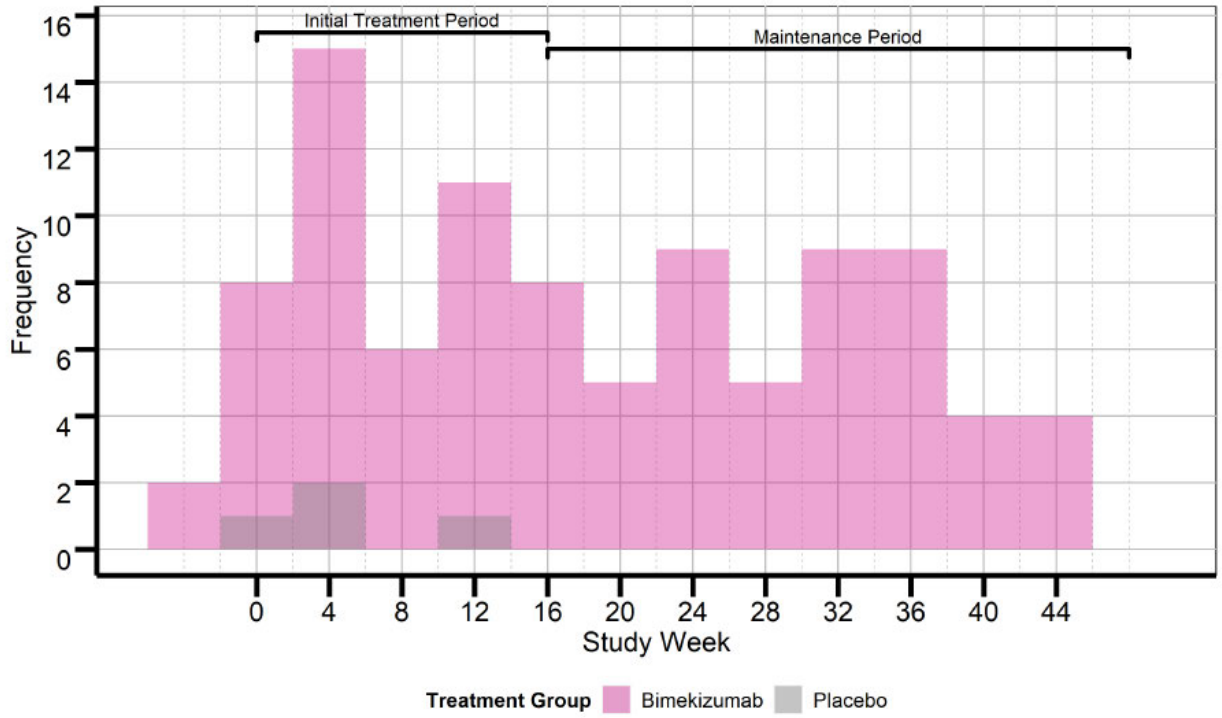
Source: Reviewer-created using iss adae.xpt dataset
Abbreviations: BKZ = bimekizumab
Notes: Adjustment disorder includes preferred terms for adjustment disorder and adjustment disorder with depressed mood; Anxiety includes preferred terms of anxiety and nervousness; Irritability includes preferred terms of irritability and emotional distress; Depression includes preferred terms of depression and depressed mood

Table 62: Incidence of Psychiatric Adverse Events during the Initial and Maintenance Treatment Period (Pooled Trials HS0003 and HS0004)

Adverse events, n (%)	Placebo (N=144)	BKZ 320 mg Q4W (N=285)	BZK 320 mg Q2W (N=576)	BKZ Total (N=861)
Subjects with at least one Psychiatric AE	4 (2.7)	16 (5.6)	23 (4.0)	39 (4.5)
Adjustment disorder	-	-	2 (0.3)	2 (0.2)
Alcohol abuse	-	2 (0.7)	-	2 (0.2)
Anxiety	1 (0.7)	4 (1.4)	6 (1.0)	10 (1.2)
Confusion	-	-	1 (0.2)	1 (0.2)
Depression	2 (1.4)	5 (1.8)	9 (1.6)	14 (1.6)
Insomnia	1 (0.7)	2 (0.7)	3 (0.5)	5 (0.6)
Irritability	-	1 (0.4)	1 (0.2)	2 (0.2)
Panic attacks	-	-	1 (0.2)	1 (0.2)
Sleep disorder	-	1 (0.4)	2 (0.3)	3 (0.3)
Stress disorder	-	-	1 (0.2)	1 (0.1)
Suicidal ideation	-	1 (0.4)	-	1 (0.1)

Source: Reviewer-created using iss adae.xpt dataset
Abbreviations: BKZ = bimekizumab
Notes: Adjustment disorder includes preferred terms for adjustment disorder and adjustment disorder with depressed mood; Anxiety includes preferred terms of anxiety, nervousness, stress, and tension; Irritability includes preferred terms of irritability and emotional distress; Depression includes preferred terms of depression and depressed mood

Figure 24: Frequency of Psychiatric Adverse Events by Treatment Arm and Study Visit across the Initial and Maintenance Treatment Periods (Pooled Trials HS0003 and HS0004)



Source: Reviewer-created using iss adae.xpt dataset

DP Reviewer's Comment: *In double-blind, placebo-controlled trials evaluating subjects with PsO, 12 out of 670 subjects (1.8%) receiving placebo and 0 out of 83 subjects receiving placebo experienced psychiatric AEs (most common AEs included anxiety and depression). Although the absolute risk differences for psychiatric AEs in the PsO (1.8%) and HS (1.6%) development program were similar, the percentage of subjects receiving bimekizumab and experiencing a psychiatric AE was three-fold higher in the HS development program. Because the incidence of psychiatric AEs in the placebo group was also higher in subjects with HS vs. PsO (2.7% vs. 0%), greater AE reporting in HS subject could be attributed to the higher background rates of co-morbid psychiatric conditions in subjects with HS.*

Given that the Applicant did not identify any new psychiatric AEs and the relatively low overall occurrence (<2%) of AEs related to depression and anxiety, DP does not recommend any additional descriptions of psychiatric AEs in product labeling.

Suicidal Ideation and Behavior (SI/B) Events per C-SSRS

"Pooled analysis of C-SSRS data from the 16-week initial treatment period of Studies HS0003 and HS0004 indicated that 1.9% bimekizumab-treated subjects and 0.7% placebo-treated subjects reported SI/B with an estimated relative risk of 2.70 (95% CI: 0.36, 20.12). Most of the subjects (12 out of 17) reported passive SI; all five cases of active SI during the initial

treatment period occurred in the bimekizumab treatment group. There were no cases of SB. When restricted to only new-onset positive C-SSRS events, the incidence for any positive SI/B response was 0% (0/146) for the placebo group and 0.9% (8/861) for the bimekizumab treatment group with a relative risk of 2.90 (95% CI: 0.17, 49.96). Among the eight bimekizumab-treated subjects who had new-onset SI/B during the first 16 weeks, only one subject had a positive response more than once throughout the treatment period.

Among subjects participating in the maintenance treatment period, seven subjects reported an SI/B event. Six subjects reported passive SI and one subject endorsed active SI with intent. None of the subjects that switched from placebo to bimekizumab reported a positive response to the C- SSRS. The Applicant also noted that there were also two serious AEs of SI (one that occurred during a follow-up period after study discontinuation) that were adjudicated as suicide attempts (Subject IDs: (b) (6) (b) (6). Both subjects appeared to endorse SI approximately 300 days after receiving their first dose and denied endorsing any SB. Based on the case summaries (see below), the Neuropsychiatric Adjudication Committee (NAC) adjudicated these event conservatively as a suicide attempt.

During the open-label treatment period, 11 subjects experienced SI (Wish to be dead = 6; nonspecific thoughts = 2; some intent to act, no plan = 3). Five out of the 11 subjects reported SI during initial and maintenance treatment periods. Two subjects reported SB; one subject ((b) (6) reported an actual attempt on Day 701 (Week 52 visit) and one subject ((b) (6) reported an interrupted/aborted attempt on Day 655 (Week 44 visit). The Applicant also reported no positive cases of SI/B in subjects participating in Study HS0001."

DP Reviewer's Comment: *Because of the low sample size in the placebo arm and the biased 6:1 randomization ratio between bimekizumab and placebo treatment arms, the estimated relative risk may not represent the true underlying risk in the population. Given that the Applicant excluded subjects with a lifetime history of SB and SI occurring within 6 months of study enrollment (more conservative criteria relative to Studies HS0003 and HS0004), it is also not surprising to see zero SI/B events in Study HS0001.*

Pooled analysis of C-SSRS data from two 16-week placebo-controlled studies in subjects with PsO indicated that 12/670 (1.8%) bimekizumab-treated subjects and 1/169 (0.6%) placebo-treated subjects reported SI. The estimated relative risk for SI/B in the PsO development program was 3.0 (95% CI: 0.39, 22.74). Similar to the HS development program, there were no cases of SB reported during the initial treatment period.

Evaluation of the case narratives (summarized below) suggest that several cases were confounded by background psychiatric history and external psychosocial stressors. It is also important to note that the three SB cases (not including the one suspected case during the follow- up period after treatment discontinuation) also occurred 1 to 2 years after treatment

initiation and that the majority of events were passive SI that did not lead to SB. It may be the case that a drug effect on SI/B is to make SI/B more likely when an individual experiences an unstable or worsening mental state due to an external psychosocial stressor.

Although a causal association between treatment with bimekizumab and increased risk for SI/B cannot be definitively established, the consistent signal between the PsO and HS development programs does support communicating the risk to prescribers and patients. The Applicant's proposal to communicate the risk as a Warning and Precaution statement in the product label (similar to C-SSRS data described for the PsO studies) is acceptable.

Table 63: Case Narratives for Psychiatric Events Occurring in Trials HS0003, HS0004, and HS0005

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZinjection	Summary	Causality Assessment
HS0003-(b) (6)	28/F/White	Depression/ Study discontinuation	BKZ 320 mg Q4W	225/1	Subject reported a PHQ-9 total score = 25 and AE of mild depression after having a bad week due to worsening underlying disease (HS flare). The subject had no medical history of depression or psychiatric illness. The subject was also not using any relevant concomitant medications at the time of AE. After psychology referral, the Applicant withdrew subject from the study. At the early termination visit, PHQ-9 total score decreased to 5.	Unclear, due to worsening underlying disease that is a known risk factor
HS0003-(b) (6)	58/M/White	Suicidal ideation/ SAE leading to study discontinuation	BKZ 329 mg Q4W	35/8	Subject reported that he grew up in a fairly strict environment and had several problems within his family (primary provider). Subject's father died of suicide and subject received psychological treatment (focusing on trauma) in 2014. After first administration, subject became irritated more quickly. Subject developed severe SI (urge to jump out of window) and anxiety. After transport to hospital, staff also suspected alcohol intoxication. Psychological assessment indicated that the combination of sudden diverse symptoms of agitation, motor restlessness, suspicion (partner cheating), and disorganization (no florid delusions or hallucinations) was most appropriate for a delirious condition in response to study drug.	Possible, due to timing of event relative drug administration and resolution of symptoms. However, assessment confounded by prior medical history and possible alcohol intoxication.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0003-(b) (6)	21/F/White	Suicidal ideation/SAE[1]	BKZ 320 mg Q2W	196/126	Subject reported an ongoing medical history of mild anxiety and depression (treated with duloxetine) and social history of stressful student life. Subject's parents were diagnosed with cancer and living in another country. The subject withdrew consent due to study burden; however, at the safety follow-up visit, the subject reported SI (2 weeks prior to visit) and indicated SB on the C-SSRS. During discussion with the Investigator, the subject denied SB. The event also resolved the same day.	Unlikely, due to having discontinued BKZ for several months before event, pre-existing psychiatric condition, and external social stressors.
HS0003-(b) (6)	33/F/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg QW	85/16	Subject reported no prior psychiatric history. The Investigator referred subject for further psychiatric evaluation after reporting a PHQ-9 total score of 21. Subject stated that she was "not in a good mood" when completing the PHQ-9 questionnaire and that her elevated score reflected frustrations with the status of her painful lesions in her genital areas. During the early termination visit, her PHQ-9 total score was 3 and she expressed disappointment for leaving the study.	Unclear, due to worsening underlying disease.
HS0003-(b) (6)	30/F/Black	Depression/ Study discontinuation	BKZ 320 mg Q4W	35/35	Subject's medical history includes depression and substance abuse. During the study, subject reported that she just moved, was having difficulty with work and with family, and recently terminated a relationship with her boyfriend. She was also stressed from going to the study site because of the distance. After experiencing a 9-point increase in the PHQ-9, she reported improvements in symptoms at the follow-up visit.	Unclear, due to pre-existing psychiatric condition and confounding external social stressors.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0003-(b) (6)	42/F/Black	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q2W	225/12	At the time of the abnormal psychiatric evaluation (PHQ-9 total score of 27), the subject was having a bad week due to worsening underlying disease. The subject reported trying to change her response to the PHQ-9 after realizing a potential data entry error. After medical referral, the psychologist noted the subject having mild depressive disorder and recommended professional psychological support would be necessary.	Unclear, due to possible data entry error and worsening underlying disease.
HS0003-(b) (6)	50/F/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q4W	168/27	Prior to the abnormal PHQ-9 total score of 20, the subject had an SAE for adjustment disorder with depressed mood. Concomitant medications included trazodone. Prior to the event, her sibling was murdered, and she had been feeling depressed.	Unlikely, due to extreme external psychological stress.
HS0003-(b) (6)	29/M/Black	Suicidal ideation/SAE	BKZ 320 mg Q2W	245/8	Subject had a medical and family history of depression and substance use. The subject also reported being a victim of sexual abuse in childhood. After being hospitalized for a diabetic foot ulcer that resulted in a toe amputation, the subject visited the emergency department for psychiatric evaluation due to suicidal ideation (plans to overdose on pills) and homicidal ideations (wanting to harm family). He reported that he had a stressful event in his life that triggered these feelings, but they resolved quickly without recurrence.	Unclear, due to pre-existing psychiatric condition, family history, worsening of comorbid diabetes and confounding external social stressors.
HS0003-(b) (6)	25/F/White	Suicidal ideation and abnormal psychiatric evaluation/SAE leading to study discontinuation[1]	BKZ 320 mg Q4W	313/33	Subject has a psychiatric history of depression, stimulant abuse, and post-traumatic stress disorder. Per the Investigator, the subject had been going through an unexpected personal issue lately, and her mental and emotional feelings were not normal. She was admitted to the psychiatric unit due to severe SI and was withdrawn from the study. Although the subject claimed to cut her leg 1 week earlier, she denied SB. Due to positive SB based on the C-SSRS	Unclear, due to pre-existing psychiatric condition and confounding external social stressors.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
					and a PHQ-9 score of 25, the subject met study withdrawal criteria.	
HS0003-(b) (6)	52/M/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q4W	198/31	Subject has a psychiatric history of depression and continues treatment with bupropion and venlafaxine. He reported that he had filled out several questions in PHQ-9 questionnaire in error (PHQ-9 total score was 16) because he did not have his glasses and was rushing to attend his therapist appointment afterwards. His regular therapist indicated that he had been attending outpatient therapy and medication management sessions since 2021. Previously unknown to the site was the information that he was diagnosed with narcissistic personality disorder. In consultation with the subject's therapist, the Investigator decided to not restart BKZ treatment and withdraw the subject.	Unclear, due to pre-existing psychiatric condition and potential data entry error.
HS0004-(b) (6)	57/M/White	Adjustment disorder/ Study discontinuation	BKZ 320 mg Q2W	29/1	Subject reported an ongoing psychiatric condition of adjustment disorder with depressed mood. The subject also reported taking cannabis and dexamethasone when experiencing worsening symptoms. The Investigator treated the subject with escitalopram.	Unlikely, due to worsening of pre-existing condition and confounding cannabis use.
HS0004-(b) (6)	31/F/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q4W	115/1	The Investigator referred the subject to a mental health professional after recording an elevated PHQ-9 score of 18. The event was not resolved at the time of study withdrawal.	Unassessable, due to insufficient information.
HS0004-(b) (6)	26/F/White	Depression/SAE	BKZ 320 mg Q4W	138/20	Subject had a psychiatric history of depression and attention deficient/hyperactivity disorder. After experiencing an SAE of worsening depression due to personal reasons ongoing in her life, investigators referred her for psychiatric follow-up. There were no abnormal ratings on the C-SSRS or PHQ-9. Symptoms of depression resolved after 82 days after onset.	Unclear, due to worsening of pre-existing condition and external psychosocial stressors.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0004-(b) (6)	23/F/Black	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q2W	40/1	The Investigator withdrew the subject from the study after the reporting a PHQ-9 total score ≥20. During her Week 4 visit, the subject reported passive SI on the C-SSRS. On follow-up, the subject stated that the questionnaire answers were inadvertent.	Unassessable, due to insufficient information and possible data entry error.
HS0005-(b) (6)	40/F/Black	Depression and suicidal ideation/SAE leading to study discontinuation	BKZ 320 mg Q4W	584/24	Subject had a psychiatric history of bipolar disorder, depression, and anxiety. One day after reporting an AE for back pain and SAEs for depression and SI, the subject was hospitalized and started treatment with olanzapine. Per the Investigator, the subject was withdrawn from the study due to depression and SI and not due to back pain. At the Week 36 follow-up visit, the subject discussed the hospitalization, prior history of mental issues, and she agreed to visit a mental health professional. Her PHQ-9 total score of 17 and endorsement of active SI on the C-SSRS corresponded to her SAEs and hospitalization.	Unclear, due to worsening of pre-existing condition.
HS0005-(b) (6)	30/F/Black	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q2W	435/15	After a reporting an elevated PHQ-9 score of 21, the Investigator referred the subject for mental health evaluation. Notes indicated that the subject had depressive symptoms for 7 years with no SI.	Unassessable, due to insufficient information and possibly unclear due to worsening underlying psychiatric condition.

Abbreviations: AE = adverse event; BKZ = bimekizumab; C-SSRS = Columbia Suicide Severity Rating Scale; F = female; M = male; PHQ-9 = Patient Health Questionnaire-9 items; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; SB = suicidal behavior; SI = suicidal ideation [1]Conservative adjudication as suicidal behavior, per the Neuropsychiatric Adjudication Committee

Note: The Applicant did not submit case narratives for Subjects (b) (6) (19-year-old white male) and (b) (6) (20-year-old while male). Both subjects endorsed suicidal behavior during the open-label extension period (> 600 days since first dose of study medication). Both cases were confounded by external psychosocial stressors (relationship problems with partner).

19.6.4. Additional Information from DCOA

Score Interpretability: skin pain
Background

The Applicant conducted anchor-based analyses supplemented with eCDF curves to evaluate clinically meaningful within-patient change in HSSDD worst skin pain item from baseline to Week 16 using the Patient Global Impression of Severity in Skin Pain (PGI-S-SP) and Patient Global Impression of Change of Severity in Skin Pain (PGI-C-SP) as anchor measures (Appendix B of the DCOA review dated October 11, 2024) and data collected from their phase 3 trials (HS0003 and HS0004). The Applicant identified a range of clinically meaningful within-patient change thresholds from baseline to Week 16 of a 3- to 4- point decrease, which corresponds to the mean and median decrease in the HSSDD Worst Skin Pain item for subjects who reported a 2-category improvement on the PGI-S-SP measure and the mean decrease in the HSSDD Worst Skin Pain for patients who reported "much better" on the PGI-C-SP measure.

In order to review the Applicant's anchor-based analyses, the review team issued an information request on July 31, 2024, for additional figures and tables for studies HS0003 and HS0004.

Assessment

The Applicant proposed a 2-category improvement from Baseline to Week 16 on the PGI-S-SP measure as the target anchor change category that constitutes a clinically meaningful within-patient change as the majority of subjects reported "Moderate" (n = 409 [43.8%]) or "Severe" (n = 287 [30.7%]) skin pain at Baseline and a 2-category improvement would imply "None" or "Mild" skin pain as measured by the PGI-S-SP measure at Week 16. Table 62 shows the change in HSSDD Worst Skin Pain scores from Baseline to Week 16 by change in the PGI-S-SP measure in Study HS0003. Patients who experienced a 2-point improvement in the PGI-S-SP measure had a mean change in HSSDD Worst Skin Pain score of -3.95 and a median change of -4.1. Table 63 shows the change in HSSDD Worst Skin Pain scores from Baseline to Week 16 by change in the PGI-S-SP measure in Study HS0004. Subjects who experienced a 2-point improvement in the PGI-S-SP measure had a mean change in HSSDD Worst Skin Pain score of -3.95 and a median change of -3.7.

Reviewer's comment(s): In general, the PGI-S-SP and PGI-C-SP measures appear to be reasonable for use as external anchors to interpret the HSSDD Worst Skin Pain item. The measurement concepts and recall period appear to align. While the PGI-S-SP includes a high number of response categories, collapse some of the response categories (e.g., Severe/Very severe) could help minimize poor distribution of responses across the categories for the anchor-based analyses.

Table 64: Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0003)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
PGI-S-SP Response at Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
3-point improvement	10 (2.0)	-5.27	2.053	-7.8	-1.7	-7.4	-6.7	-5.8	-3.9	-2.0	9 (1.8)
2-point improvement	38 (7.5)	-3.95	1.846	-7.5	0.2	-6.6	-5.0	-4.1	-2.4	-1.9	28 (5.5)
1-point improvement	108 (21.4)	-2.09	2.161	-7.3	2.2	-5.4	-3.2	-2.0	-0.7	0.5	54 (10.7)
No Change	86 (17.0)	-0.82	1.633	-5.0	4.0	-3.0	-2.0	-0.7	0.1	1.2	50 (9.9)
1-point worsening	22 (4.4)	0.91	1.795	-1.1	5.6	-0.6	-0.1	0.2	1.9	3.1	16 (3.2)
2-point worsening	4 (0.8)	2.18	1.885	0.6	4.8	0.6	0.9	1.7	3.5	4.8	4 (0.8)
4-point worsening	0										1 (0.2)
Missing	11 (2.2)	-1.83	3.161	-6.2	2.0	-5.7	-5.0	-2.0	1.6	1.9	64 (12.7)

Source: Applicant's IR Response Received August 6, 2024 (Table D3)
Abbreviations: PGI-S-SP, Patient Global Impression of Severity in Skin Pain; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

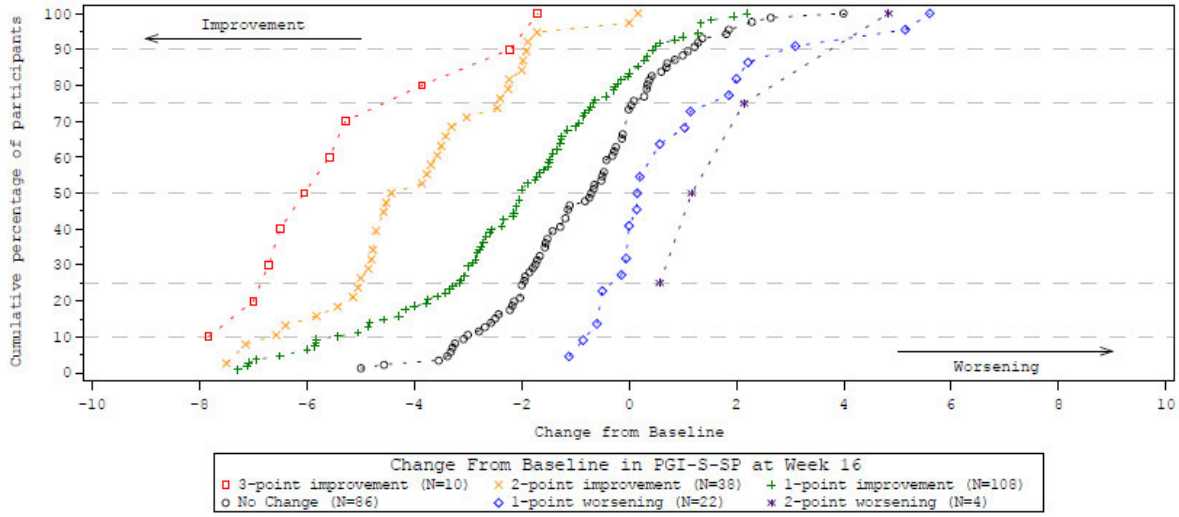
Table 65: Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0004)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
PGI-S-SP Response at Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
4-point improvement	0										1 (0.2)
3-point improvement	9 (1.8)	-4.78	2.425	-9.3	-0.7	-9.3	-5.6	-5.3	-4.0	-0.7	4 (0.8)
2-point improvement	49 (9.6)	-3.95	2.184	-8.4	0.0	-7.0	-5.6	-3.7	-2.3	-1.2	30 (5.9)
1-point improvement	115 (22.6)	-2.28	1.978	-7.6	6.0	-4.4	-3.5	-2.5	-1.0	0.0	48 (9.4)
No Change	118 (23.2)	-0.42	1.804	-4.6	4.7	-2.9	-1.7	-0.2	0.6	1.8	23 (4.5)
1-point worsening	35 (6.9)	0.72	1.486	-3.9	3.9	-1.2	0.0	0.9	1.6	2.5	20 (3.9)
2-point worsening	4 (0.8)	0.25	1.991	-2.2	2.4	-2.2	-1.3	0.4	1.8	2.4	1 (0.2)
Missing	8 (1.6)	-2.54	3.642	-5.8	4.6	-5.8	-5.4	-3.5	-0.6	4.6	44 (8.6)

Source: Applicant's IR Response Received August 6, 2024 (Table D4)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

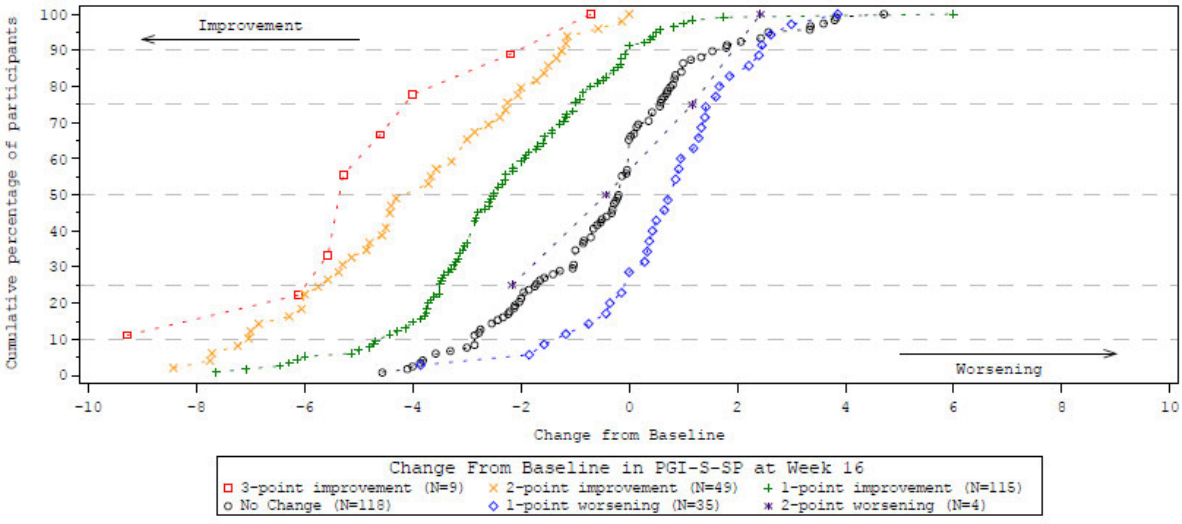
The Applicant additionally inspected the eCDF curves for change from baseline to Week 16 in HSSDD score by change in the PGI-S-SP measure in each trial (see Figure 26 and Figure 27; shown on next page) and found sufficient separation between the target anchor change category of a 2-point improvement in the PGI-S-SP measure and other anchor change categories, supporting their proposed anchor change category to define clinically meaningful within-patient change thresholds.

Figure 25: Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D1)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Figure 26: Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D2)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Additionally, the Applicant proposed "Much better" on the PGI-C-SP measure as the target anchor category on the supportive anchor. Subjects who reported "much better" skin pain at Week 16 had a mean change from Baseline to Week 16 in HSSDD Worst Skin Pain score of -3.17

and a median change of -2.8 in Study HS0003 (see Table 64). Subjects who reported "much better" skin pain at Week 16 had a mean change from Baseline to Week 16 in HSSDD Worst Skin Pain score of -3.32 and a median change of -3.3 in Study HS0004 (see Table 65; shown on next page). Based on these mean and median change scores of the HSSDD Worst Skin Pain item from Baseline to Week 16 for the target anchor change categories, the Applicant proposed a clinically meaningful within-patient change threshold range of a 3-point to 4-point improvement.

Table 66: Change from Baseline in HSSDD Worst Skin Pain Score at Week 16 by PGI-C-SP at Week 16 (HS0003)

		Change in HSSDD scores from Baseline to Week 16										
						Percentiles						
Change in PGI-C-SP from Baseline to Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$	(%)
Much Better	107 (21.2)	-3.17	2.291	-7.8	2.2	-6.5	-5.0	-2.8	-1.7	-0.3	62	(12.3)
A Little Better	100 (19.8)	-1.14	2.228	-7.1	5.6	-4.0	-2.5	-1.0	0.2	1.3	48	(9.5)
No Change	44 (8.7)	-0.65	2.055	-5.0	4.0	-3.4	-2.0	-0.4	0.5	1.9	35	(6.9)
A Little Worse	20 (4.0)	-0.61	1.649	-3.8	2.3	-3.4	-1.5	-0.5	0.6	1.4	13	(2.6)
Much Worse	6 (1.2)	0.86	1.814	-2.1	3.1	-2.1	-0.1	1.2	2.0	3.1	5	(1.0)
Missing	2 (0.4)	-0.35	2.377	-2.0	1.3	-2.0	-2.0	-0.3	1.3	1.3	63	(12.5)

Source: Applicant's IR Response Received August 6, 2024 (Table D5)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

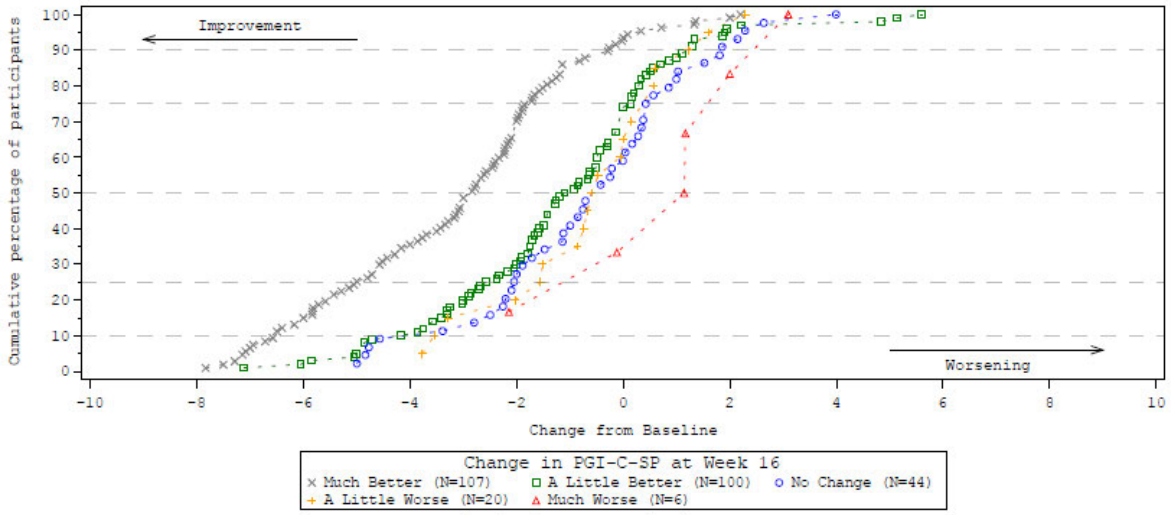
Table 67: Change from Baseline in HSSDD Worst Skin Pain Score at Week 16 by PGI-C-SP at Week 16 (HS0004)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
Change in PGI-C-SP from Baseline to Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
Much Better	114 (22.4)	-3.32	2.172	-9.3	3.0	-6.3	-4.6	-3.3	-1.9	-0.5	43 (8.4)
A Little Better	132 (25.9)	-1.17	2.071	-7.1	4.7	-3.7	-2.7	-1.0	0.1	0.9	51 (10.0)
No Change	64 (12.6)	-0.66	2.049	-6.0	3.6	-3.2	-2.0	-0.2	0.6	1.8	26 (5.1)
A Little Worse	18 (3.5)	1.17	1.782	-1.2	6.0	-0.4	-0.1	0.7	2.6	3.8	10 (2.0)
Much Worse	10 (2.0)	1.25	1.470	-1.2	3.9	-1.0	0.8	1.3	2.2	3.1	2 (0.4)
Missing	0										39 (7.7)

Source: Applicant's IR Response Received August 6, 2024 (Table D6)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

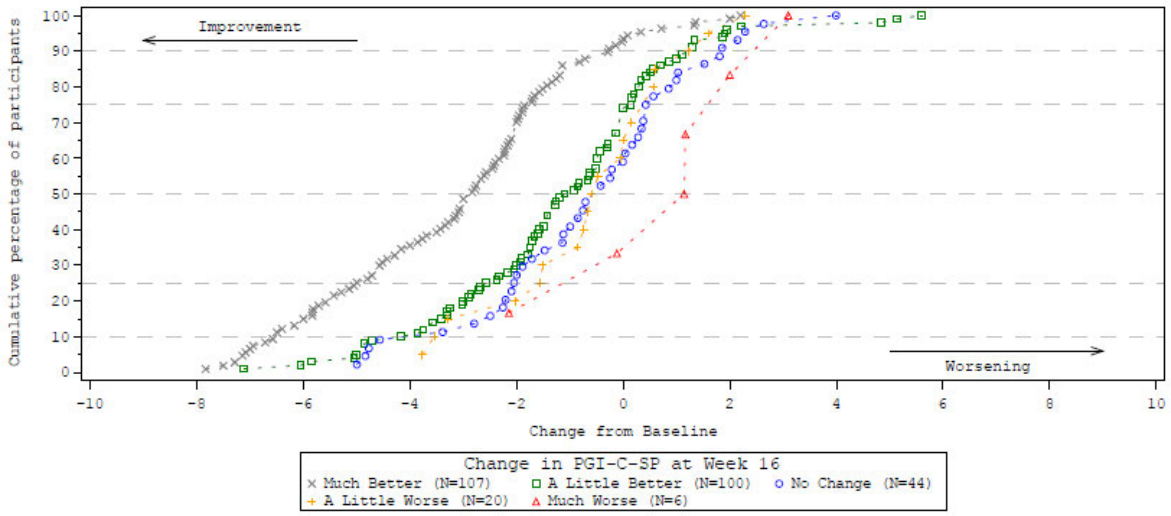
The Applicant inspected the eCDF curves for change from Baseline to Week 16 in HSSDD Worst Skin Pain score by the PGI-C-SP measure at Week 16 in each study (see Figure 28 and Figure 29; shown on next page) and found sufficient separation between the target anchor category of "Much better" and other anchor change categories, supporting their proposed anchor category to define clinically meaningful within-patient change thresholds.

Figure 27: Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-C-SP at Week 16 (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D3)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Figure 28: Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-C-SP at Week 16 (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D4)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Based on these analyses, the Applicant proposed a meaningful within-patient change threshold range of 3-point to 4-point improvement on HSSDD Worst Skin Pain score from Baseline to Week 16.

Reviewer comments: The Applicant's anchor-based analyses supplemented by eCDF curves is largely appropriate. Notably, while the Applicant did not explicitly discuss misclassification rates of subjects based on their threshold range, the observed misclassification rates of subjects who reported no change or worsening on the PGI-S-SP or PGI-C-SP measures at the meaningful within-patient change range of 3-point to 4-point improvement on HSSDD Worst Skin Pain item was below 20%, which is acceptable. However, what subjects consider to be clinically meaningful improvement may be impacted by the subject's baseline skin pain severity. Subject's baseline symptom severity should be considered when determining clinically meaningful within-patient change thresholds. Below is the Agency's evaluation of subject's baseline skin pain symptom severity on meaningful within-patient change thresholds.

Table 66 and Table 67 (shown on next page) show the distribution of change in HSSDD Worst Skin Pain scores from Baseline to Week 16 for subjects who achieved a 2-category improvement on the PGI-S-SP measure. The median change in the HSSDD Worst Skin Pain item is between -2.4 and -4.8 in Study HS0003 and between -3.0 and -4.4 in Study HS0004. The amount of change subjects consider meaningful tends to smaller the more severe skin pain they reported at Baseline. Based on the results of the anchor-based analyses supplemented by eCDF curves and the assessment of baseline symptom severity, the final clinically meaningful within-patient change range should be between -4.8 and -2.4, which includes the Applicant's proposed range (i.e., -3 to -4) so that, for subjects who achieved a 2-category improvement on the PGI-S-SP measure, at least 50% of subjects who reported moderate, severe, or very severe skin pain at Baseline are categorized as having experienced a meaningful improvement.

Table 68: Distribution of Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-S-SP at Baseline for Patients who Achieved a 2-category Improvement in PGI-S-SP at Week 16 (HS0003)

		HSSDD Change Score									
						Percentiles					
PGI-S-SP Response at Baseline	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
Moderate	9 (13.6)	-4.53	1.724	-7.1	-2.0	-7.1	-5.1	-4.8	-3.5	-2.0	7 (10.6)
Severe	22 (33.3)	-4.05	1.835	-7.5	0.2	-6.6	-5.1	-3.8	-3.0	-1.9	16 (24.2)
Very Severe	7 (10.6)	-2.88	1.847	-4.8	0.0	-4.8	-4.7	-2.4	-1.7	0.0	5 (7.6)

Source: Applicant's IR Response Received August 6, 2024 (Table D7)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

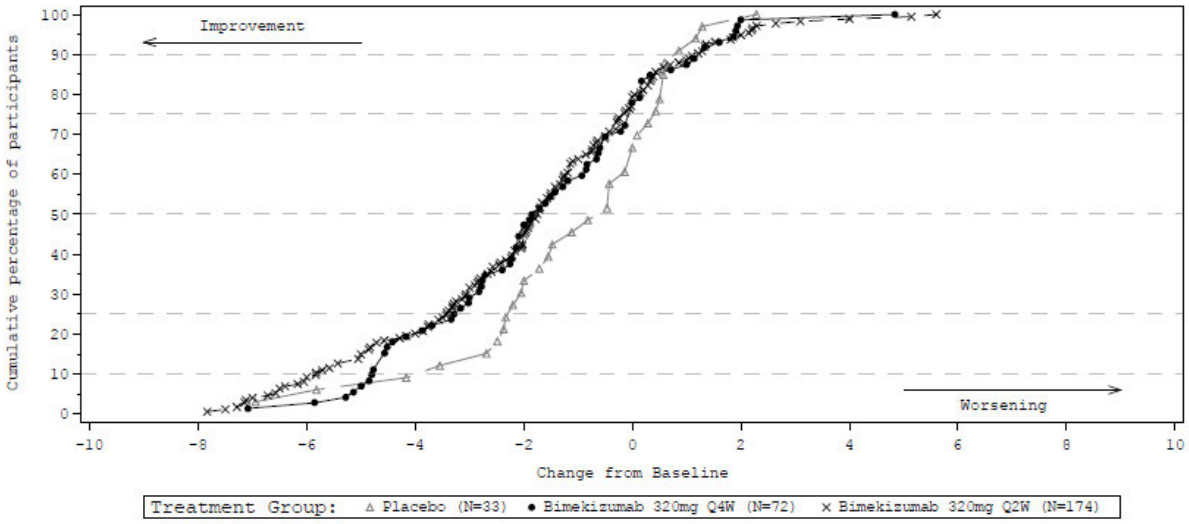
Table 69: Distribution of Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-S-SP at Baseline for Patients who Achieved a 2-category Improvement in PGI-S-SP at Week 16 (HS0004)

		HSSDD Change Score									
						Percentiles					
PGI-S-SP Response at Baseline	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
Moderate	15 (19.0)	-4.60	2.157	-8.4	-1.3	-7.8	-6.0	-4.4	-3.0	-2.1	12 (15.2)
Severe	29 (36.7)	-3.75	2.249	-7.2	0.0	-7.0	-5.6	-3.7	-1.7	-0.6	14 (17.7)
Very Severe	5 (6.3)	-3.16	1.706	-6.0	-1.5	-6.0	-3.0	-3.0	-2.3	-1.5	4 (5.1)

Source: Applicant's IR Response Received August 6, 2024 (Table D8)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

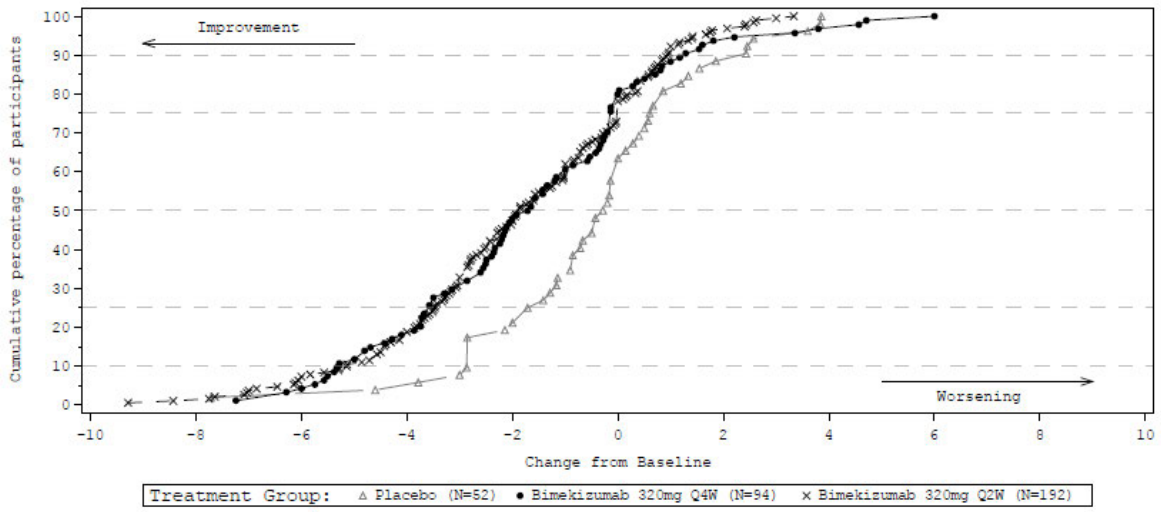
As seen in Figure 30 and Figure 31 (shown on next page), there is adequate separation between the eCDF curves for the placebo arm and the bimekizumab arms. The difference in proportion of subjects reported as experiencing a meaningful improvement between the placebo and bimekizumab treatment arms is between approximately 12% and 21% in Study HS0003 and between approximately 11% and 22% in Study HS0004 in the range patients consider meaningful (i.e., -4.8 and -2.4).

Figure 29: Empirical Cumulative Distribution Function Plot for Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Treatment Group (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D5)
Abbreviations: HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

Figure 30: Empirical Cumulative Distribution Function Plot for Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Treatment Group (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D6)
Abbreviations: HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

19.6.5. Additional Information from Biostatistics

Table 70 presents the number and percentage of subjects with missing data for the primary efficacy endpoint at Week 16 by treatment group and trial. The percentage of subjects with missing data in Trial HS0003 was slightly higher than Trial HS0004.

Table 70: Missing Data for the Primary Efficacy Endpoint at Week 16 (RS[1])

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
Subjects with Missing Data at Week 16, n (%)						
All Subjects	32 (11)	20 (14)	7 (10)	26 (9)	11 (8)	4 (5)
Excluding Subjects with a Preceding ICE	23 (8)	14 (10)	5 (7)	13 (4)	9 (6)	3 (4)

Source: Statistical Reviewer's Analysis (similar as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Randomized Set (RS) population: all randomized subjects.

Table 71 presents the results for the primary efficacy endpoint at Week 16 across the prespecified imputation methods. For both trials, the results were generally similar across the various methods except for the extreme case (i.e., worst case scenario). The Applicant's worst case scenario treated subjects with ICEs (e.g., rescue therapy) as missing data. As these analyses are to evaluate the robustness of the results due to the handling of missing data and not the handling of the ICEs, this reviewer conducted an addition worst case scenario where

subjects with ICEs are treated as non-responders. While not statistically significant, a positive treatment effect of bimekizumab over placebo was observed even under the statistical reviewer's worst case scenario.

Table 71: Results for the Primary Efficacy Endpoint at Week 16 with Different Approach for Handling Missing Data

	Bimekizumab 320 mg			Difference (P-value)[7]	
	Q2W	Q4W	Placebo	Q2W vs. Placebo	Q4W vs. Placebo
Trial HS0003	**N=289**	**N=144**	**N=72**		
MI-MCMC/Reg[1]	48%	45%	29%	18% (0.006)	15% (0.030)
NRI[2]	44%	41%	28%	16% (0.014)	13% (0.062)
MI-MCMC/Ref[3]	46%	44%	29%	17% (0.010)	15% (0.038)
Worst Case (Applicant)[4]	44%	41%	43%	1% (0.890)	-2% (0.753)
Worst Case (Reviewer)[5]	44%	41%	35%	9% (0.158)	6% (0.385)
OC[6]	59%	58%	39%	20% (0.009)	19% (0.029)
Trial HS0004	**N=291**	**N=144**	**N=74**		
MI-MCMC/Reg[1]	52%	54%	32%	20% (0.004)	21% (0.003)
NRI[2]	49%	50%	31%	18% (0.005)	18% (0.008)
MI-MCMC/Ref[3]	51%	53%	32%	19% (0.004)	20% (0.005)
Worst Case (Applicant)[4]	49%	50%	38%	12% (0.072)	12% (0.091)
Worst Case (Reviewer)[5]	49%	50%	35%	14% (0.027)	14% (0.039)
OC[6]	64%	62%	36%	28% (<0.001)	26% (<0.001)

Source: Statistical Reviewer's Analysis (similar as Applicant's Analysis); ADSL.xpt, ADFA.xpt
[1] Missing data was imputed using multiple imputation (MI) using the Markov-Chain Monte Carlo (MCMC) method to impute intermittent missing data, followed by the regression method for the monotone missing data. This was the primary method for handling missing data.
[2] Missing data was imputed using non-responder imputation (NRI).
[3] Missing data was imputed using multiple imputation (MI) using the MCMC method to impute intermittent missing data, followed by imputation model based on placebo (reference) data to impute the monotone missing data.
[4] Missing data in the bimekizumab groups was imputed as non-responders and missing data in the placebo was imputed as responders. The Applicant's worst case treated subjects with ICEs as missing data.
[5] Missing data in the bimekizumab groups was imputed as non-responders and missing data in the placebo was imputed as responders. The Reviewer's worst case treated subjects with ICEs as non-responders.
[6] Missing data was not imputed. Rates displayed are based on only observed cases (OCs). Subjects with ICEs are treated as missing.
[7] Difference and p-value were based on logistic regression with treatment, Hurley Stage at baseline, and baseline antibiotic use were used as fixed effects.

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

/s/

MELINDA L MCCORD
11/18/2024 11:34:19 AM

SELIM FAKHRUDDIN
11/18/2024 11:37:06 AM

CHINMAY SHUKLA
11/18/2024 11:40:03 AM

YOUWEI N BI
11/18/2024 11:47:45 AM

KEVIN L CLARK
11/18/2024 11:50:07 AM
Signing on behalf of myself and Jessica Nguyen, MD

MATTHEW W GUERRA
11/18/2024 11:50:59 AM

YASMIN A CHOUDHRY
11/18/2024 12:02:41 PM

SELENA R DANIELS
11/18/2024 12:06:21 PM

GORDANA DIGLISIC
11/18/2024 12:25:59 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2024047
BLA# (Reference IND#)	sBLA 761151 S-010 / IND 134700
Applicant:	UCB, Inc.
Established Name/Trade Name:	BIMZELX® (bimekizumab)
Indication:	Treatment of adult patients with moderate to severe hidradenitis suppurativa.
PDUFA Goal Date:	November 19, 2024
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer:	Kevin Clark, M.D.
Clinical Team Leader (TL)	Melinda McCord, M.D.
Regulatory Project Manager:	Strother Dixon
COA Reviewer:	Yasmin Choudhry, M.D.
COA Deputy Director:	Selena Daniels, PharmD., Ph.D.
COA Division Director:	David Reasner, Ph.D.
Patient-Focused Statistical Scientists (PFSS) Reviewer:	Monica Morell, Ph.D.
Instruments reviewed:	1. Hidradenitis Suppurativa Symptom Daily Diary ☒ Patient-reported outcome (PRO)
	2. Hidradenitis Suppurativa Quality of Life ☒ Patient-reported outcome (PRO)

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1. EXECUTIVE SUMMARY

In this submission, the Applicant is seeking to update the United States Prescribing Information (USPI) for BIMZELX® (bimekizumab) to include a new indication for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). The specific COA-related labeling claims are for improvement in worst skin pain and health-related quality of life (HRQoL) based on data from two identical, multi-center randomized, double-blind, placebo-controlled phase 3 studies (Studies HS0003 and HS0004).

The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to the concept of interest.

The secondary efficacy COA endpoints (adjusted for multiplicity) proposed for labeling are:

- Absolute change from Baseline in the Worst HS Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD)
- Pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16

The exploratory efficacy COA endpoint proposed for labeling is:

- Absolute change from Baseline in Hidradenitis Suppurativa Quality of Life (HiSQOL) domain scores (symptoms, psychosocial, activities, adaptations)

Data from Study HS0003 demonstrated that bimekizumab Q2W was not statistically superior to placebo for pain response (i.e., ≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16). Therefore, statistical superiority of bimekizumab Q4W over placebo cannot be claimed for any of the secondary efficacy endpoints per the multiplicity testing strategy. In Trial HS0004, both bimekizumab Q2W and bimekizumab Q4W were statistically superior to placebo on the 1st secondary endpoint (i.e., HiSCR75 at Week 16); however, both dose regimens of bimekizumab were not statistically significant to placebo (p-values ≥ 0.497) for the 2nd secondary endpoint (i.e., at least 1 flare by Week 16). Consequently, per the multiplicity testing procedure, statistical significance of the remaining secondary endpoints cannot be claimed in Trial HS0004 (which includes the Worst HS Skin Pain-based endpoints).

For both studies, the HisQOL-based endpoints were exploratory endpoints and, as such, there was no formal hypothesis testing.

From a COA perspective, the HSSDD Worst HS Skin Pain score could potentially support labeling claims, if supported by the clinical trial study design and statistical analysis. Given that

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the results for the HSSDD Worst HS Skin Pain-based endpoints were not statistically significant, DCOA ultimately defers to the Division whether a descriptive claim is acceptable. However, we recommend that the term "skin pain" should be further defined. The HiSQOL-based endpoints were collected for exploratory purposes, and therefore was not reviewed at the request of the Division.

2 REVIEW CONCLUSIONS

The Applicant submitted an evidence dossier for HSSDD. The HSSDD Worst HS Skin Pain item was reviewed for content validity and other measurement properties, as well as score interpretability (i.e., interpretation of meaningful within-patient score change).

Review Summary

- The HSSDD Worst HS Skin Pain item assesses an important aspect of HS (i.e., pain intensity).
- The HSSDD Worst HS Skin Pain item appears to be well-understood; however, patients did not use the term skin pain when characterizing their HS experience.
- The Applicant has generally established the other measurement properties for the HSSDD Worst HS Skin Pain item.
- Anchor-based analyses to assess meaningful within-patient change in the HSSDD Worst Skin Pain score between Baseline and Week 16 indicates patients consider a reduction of between 2.4 and 4.8 points to be meaningful. The observed treatment effect on the HSSDD Worst Skin Pain endpoint substantiated a clinically meaningful within-patient improvement in patients receiving bimekizumab compared to placebo.

Key Issues Identified

- Issue 1: Content Validity
    - While pain is a relevant and an important concept for the target population, based on the patient interview transcripts, the term "skin pain" was not used by patients when describing their HS experience. Participants described their HS-related pain generally using the following terms: sore, extreme pain, very painful, feeling like pinching/hurts, thumping sensation, and stabbing. All participants reported that the pain was related to the lesions, boils, and cysts.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, sponsors should consider the following:

- Qualitative studies should be designed to provide a complete understanding of the disease and/or treatment including presentation of symptoms and associated impacts (e.g., bother) in the target population, as well as establish the appropriateness (content relevance) and comprehensiveness of the assessment (e.g., conceptual coverage). Qualitative studies should generating in-depth information about the patient experience in

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their own words; this should help inform the wording of the measurement concept in the COA.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- There have been previous communications related to the sponsor's COA measurement strategy, which included the following (not an exhaustive list):

    - Advice/Information Request letter dated 16 Aug 2022 (IND 134700)
        - Communicated that the results of the interim analyses for the responder definition and clinically important difference in Skin Pain were inconclusive.
        - Requested a rationale and justification for the primary target anchor change category that represents a clinically meaningful change to patients on the Patient Global Impression of Severity (PGIS) measure.
        - Requested a rationale and justification for the target Patient Global Impression of Change (PGIC) response category that represents a clinically meaningful change to patients.

      Reviewer's comment(s): *The Applicant's results of the interim analyses dated 17 Feb 2022 were reviewed to evaluate the score interpretability of the HSSDD Worst Skin Pain score. Refer to the PFSS Review dated June 26, 2022 (DARRTS Reference ID: 5005358).*

    - Advice/Information Request letter dated 21 Jan 2020 (IND 134700)
        - Requested exact copies of the COAs and anchor measures that would be administered in Studies HS0003 and HS0004.
        - Commented on the power calculation assumptions for the COAs (i.e., based on a mean change from baseline value).
        - Agreed that a single item 11-point numeric rating scale, in principle, is fit-for-purpose to assess pain intensity at its worst.
        - Requested details on the scoring of the HSSDD Skin Pain item score.
        - Requested evidence of content relevancy of the Dermatology Life Quality Index (DLQI).
        - Identified limitations of the proposed anchor scales (e.g., indistinguishable response categories, recall period does not match target instrument).
        - Suggested exit interviews or surveys to cognitively interview patients.

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- Type B End-of-Phase 2 Meeting Minutes dated 01 Aug 2019
  - Agreed that the Patient Global Assessment (PGA) of skin pain may be an acceptable option to assess pain intensity.
  - Recommended assessing pain intensity at its worst for the secondary endpoint instead of 30% reduction in pain.
  - Recommended using anchor-based methods to determine meaningful change thresholds in the target COAs (using phase 2 data).

- Advice/Information Request letter dated 26 Sept 2017 (IND 134700)
  - Identified limitations of the DLQI (issues of content validity, multibarreled items etc.)

Disease Background:
Hidradenitis suppurativa is a chronic, inflammatory, and recurrent skin condition characterized by painful, deep-seated, and inflamed lesions typically located in the intertriginous areas of the body (e.g., axillae, inguinal, and anogenital regions). The inflamed nodules can progress to abscess formation and may rupture to form fistulas and subsequent scarring which can lead to contractures and limitations in limb mobility.

Investigational Product:
Bimekizumab is a humanized, full-length monoclonal antibody of immunoglobulin G1 subclass. Bimekizumab has a high affinity for human interleukin (IL)-17A and IL-17F which are key pro-inflammatory cytokines that play important roles in autoimmune and inflammatory diseases.

Materials reviewed:
The materials reviewed for this submission are summarized in Table 1.

Table 1. Materials reviewed

Document	SDN	eCTD #	Date Received
sBLA Submission including • Study protocols • Clinical study reports	165	0116	19 Jan 2024
• HS PRO Evidence Dossier HSSDD			
Response to 31 Jul 2024 Information Request			06 Aug 2024
• EVM-26511 HS CDUT Interviews transcripts			

• Studies HS0003 HS0004 anchor scales screenshots		
Communications and Reviews	**DARRTS Ref ID**	**Date**
Information Request (BLA 761151)	5422968	31 July 2024
Information Request/Advice letter	5030901	16 Aug 2022
Information Request/Advice letter	4549196	21 Jan 2020
Type B End-of-Phase 2 Meeting Minutes	4470936	01 Aug 2019
Advice/Information Request letter	4157109	26 Sept 2017
Statistical Review and Evaluation	5005358	27 Jun 2022
Advice Information Request letter	4549196	21 Jan 2020
Previous COA Review: C2022190_IND 134700_Choudhry	5020025	29 Jul 2022
Previous COA Review: C2019461_ IND 134700_Choudhry	4542990	07 Jan 2020
Previous COA review: C2019172_IND 134700_Choudhry	4534196	19 Dec 2019
Previous COA review: C2017191_IND 134700_Choudhry	4143194	15 Sept 2017

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies HS0003 and HS0004 were adults (≥18 years) with a diagnosis of HS[1]. Eligible participants must have had:

- HS lesions present in at least two distinct anatomic areas (e.g., left and right axilla), one of which must be at least Hurley Stage II or Hurley Stage III at both the Screening and Baseline visits.

[1] Based on clinical history and physical examination for at least 6 months prior to the Baseline visit; diagnosis must be verifiable through medical notes and documentation.

- Moderate to severe HS defined as a total of ≥5 inflammatory lesions (ie, number of abscesses plus number of inflammatory nodules) at both the Screening and Baseline visits.

A complete list of the inclusion and exclusion criteria is summarized in Section 5.1 of the clinical study protocol for Studies HS0003 and HS0004.

Reviewer's comment(s):
For Study HS0003, the randomized set consisted of 144 study participants in the bimekizumab 320mg Q4W group, 289 study participants in the bimekizumab 320mg Q2W group, and 72 study participants in the placebo group. The mean age of all study participants was 36.7 years, with a range of 18 to 78 years of age. More than half of the participants were female (63.0%), and the majority of study participants were White (77.8%), not of Hispanic or Latino ethnicity (92.3%), and in the nonJapanese ethnic subgroup (99.2%). The mean body weight and mean BMI overall were 98.42kg and 33.79kg/m^2, respectively. Study participants were most commonly enrolled in the following countries: United States (40.8%), Germany (10.3%), Greece (8.9%), and France (7.5%).

For Study HS0004, the randomized set consisted of 144 study participants in the bimekizumab 320mg Q4W group, 291 study participants in the bimekizumab 320mg Q2W group, and 74 study participants in the placebo group. The mean age of all study participants was 36.6 years of age, with a range of 18 to 75 years of age. Half of the participants were female (50.7%), and the majority of study participants were White (81.5%), not of Hispanic or Latino ethnicity (93.7%), and in the non-Japanese ethnic subgroup (94.1%). The mean body weight and mean BMI overall were 96.09kg and 32.34kg/m^2, respectively. Study participants were most commonly enrolled in the following countries: Poland (24.4%), the United States (22.2%), Bulgaria (12.0%), and France (10.2%).

Baseline demographics and disease characteristics (pooled; n=1014) were reflective of the study population with moderate to severe HS. The mean and median HSSDD worst skin pain scores were 5.47 and 5.7, respectively.

Clinical Trial Design

The Applicant conducted two identical randomized, double-blind, placebo-controlled, multicenter, phase 3 studies (Studies HS0003 and HS0004)[2] to evaluate the efficacy and safety of bimekizumab in study participants with moderate to severe HS.

The studies consisted of a:

- Screening Period of 14 days to up to 5 weeks;

[2] Note that some of the secondary endpoints differed across the two studies.

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- Double-blind, 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period; and
- 20-week Safety Follow-up Period following the final injection of investigational medicinal product if study participants did not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment.

Study participants were randomized in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 4 treatment sequences:

- Bimekizumab 320mg Q2W from Weeks 0 to 48
- Bimekizumab 320mg Q4W from Weeks 0 to 48
- Bimekizumab 320mg Q2W to Week 16, continuing on 320mg Q4W from Weeks 16 to 48
- Placebo to Week 16, continuing on bimekizumab 320mg Q2W from Weeks 16 to 48

5.2 Endpoint Position and Definition

The placement of the COAs in the endpoint hierarchy, including the endpoint definition Studies HS0003 and HS0004 is summarized below:

Primary efficacy endpoint

- Hidradenitis Suppurativa Clinical Response (HiSCR50), defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining tunnel count at Week 16.

Secondary efficacy endpoints (multiplicity adjusted)

- HiSCR50 at Week 16
- Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline) by Week 16 (Study HS0003 only)
- Absolute change from Baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 16
- Absolute change from Baseline in Skin Pain score at Week 16, as assessed by the Worst Skin Pain item (11-point numeric rating scale) in the HSSDD
- Pain response (defined as a decrease from Baseline in HSSDD weekly Worst Skin Pain score at or beyond the threshold for clinically meaningful change) at Week 16

Reviewer's comment(s): *For the key secondary endpoint, change from Baseline in worst skin pain score was defined as the average Week 16 HSSDD Worst Skin Pain score minus the Baseline worst skin pain score.*

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5.3 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant has proposed the following specific targeted COA-related labeling claims (in *blue italicized text*):

Reviewer's comment(s):
From a COA perspective, the HSSDD Worst HS Skin Pain score could potentially support labeling claims, if supported by the clinical trial study design and statistical analysis. Given that the results for the HSSDD Worst HS Skin Pain-based endpoints were not statistically significant, this reviewer defers to the Division whether a descriptive claim is acceptable. If a descriptive claim is given, this reviewer recommends that the term "skin pain" be qualified as lesion pain. Based on the review of the anchor-based analyses supplemented with empirical cumulative distribution function (eCDF) curves, a 3-4 point change in the HSSDD Worst Skin Pain score falls within the meaningful change threshold range of 2.4 to 4.8 and appears clinically meaningful.

Based on discussion with the Division, the HiSQOL-based endpoints will not be labeled as they were exploratory endpoints.

5.4 Clinical Outcome Assessment(s) Clinical Outcome Assessment Description(s)

5.4.1.1 Hidradenitis Suppurativa Symptom Daily Diary (HSSDD) Worst Skin Pain item

The HSSDD Worst Skin Pain item (Appendix A) is a single item within the HSSDD, a 5-item PRO instrument designed to assess HS signs/symptoms of HS. The Worst Skin Pain item is designed to assess skin pain intensity at its worst using an 11-point numeric rating scale (NRS) ranging from 0 ("No skin pain") to 10 ("Skin pain as bad as you can imagine"). The recall period is the previous 24 hours. The HSSDD Worst Skin Pain was administered electronically daily (at

the end of the day) from Screening through Week 16.

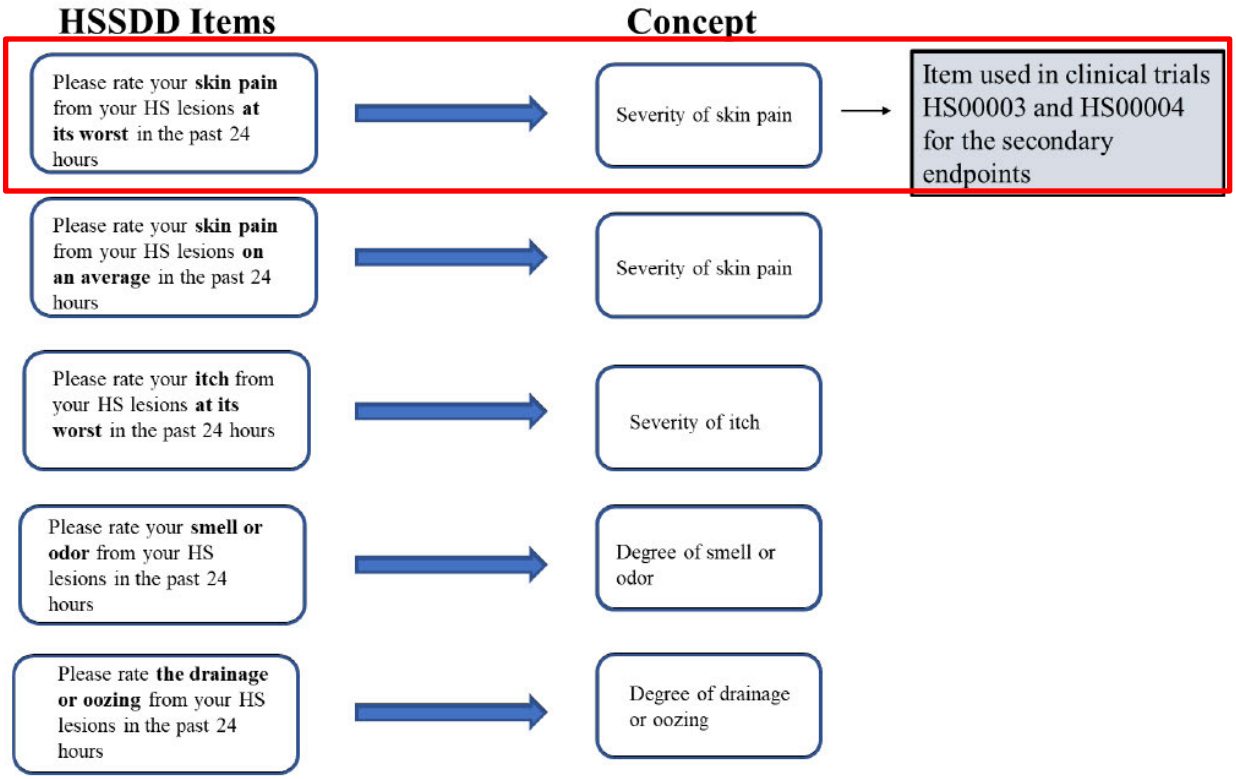
Reviewer's comment(s): *The copy of the HSSDD included in the BLA submission does not include the instructions to the participants. However, the Applicant developed instructions for the investigators/clinical site staff for use of the electronic patient-reported outcome (ePRO) device, including preparation of the device for participant use and the handling of device hardware components. Training materials were not specifically developed for participants. The ePRO device was handed out to the participants who were asked to complete the HSSDD daily in a quiet place.*

5.4.2 Conceptual Framework(s)

5.4.2.1 HSSDD Worst Skin Pain item

The conceptual framework of the HSSDD is shown in Figure 1. The HSSDD Worst Skin Pain item is outlined in a red box.

Figure 1. Conceptual framework of HSSDD



Abbreviations: HS = Hidradenitis Suppurativa; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary

Source:Applicant's PRO evidence dossier (Figure 4-1)

5.4.3 Scoring Algorithm

5.4.3.1 HSSDD Worst Skin Pain item

The HSSDD Worst Skin Pain item generates a single item score that ranges from 0 to 10, with a higher score indicating greater skin pain intensity.

Weekly averages were derived for the HSSDD Worst Skin Pain item for weeks matching the post-Baseline dosing weeks up to Week 16. A weekly average was calculated as the sum of the scored item over the course of the study week divided by the number of days on which the item was completed. The weekly averages were relative to the respective visit date except for Baseline, which was anchored to the first dose of study drug.

A weekly average was only calculated if at least four non-missing values (not necessarily consecutive) were available. Otherwise, the HSSDD weekly average score for the given question was set to missing. Baseline was computed as the average from the first seven consecutive day period in which there were at least four non-missing entries. That is, the first seven consecutive days prior to the Baseline visit were considered, but not including the Baseline visit day itself. If there were at least 4 non-missing values (not necessarily consecutive), then the Baseline average was calculated. If there were less than four values, the seven consecutive day period was moved one day earlier. If there were at least four non-missing values (not necessarily consecutive) in that period, then the Baseline average was calculated. This continued until there were at least four non-missing values in a seven consecutive day period in the 14 days prior to Baseline. If there was no period in which there were at least four non-missing entries, then the Baseline value was set to missing.

Reviewer's comment(s): *Missing data imputation was applied to the weekly averages and not to the individual daily PRO data. Refer to the Statistical Review for mode details regarding imputation methods.*

The Applicant conducted a simulation analysis to assess the appropriateness of the current weekly scoring rule (i.e., 4 out of 7 daily scores required for a given week) used to derive the weekly symptom item scores of the HSSDD.

The simulation analysis results showed that there were no significant differences in SDs of weekly symptom item scores observed when comparing the current scoring rule with the zero-day missing scenario across different timepoints (Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, and 16).

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5.4.4 Content Validity

5.4.4.1 HSSDD Worst Skin Pain Item

The Applicant completed the following instrument development activities to evaluate the content validity of the HSSDD Worst Skin Pain Item:

- Literature review and PRO Gap Analysis
- Expert input (interviews with key opinion leaders)
- Item generation
- Patient input (cognitive interviews and usability testing)

A summary of the results for each activity is described below. Refer to Section 5 and Appendix D of the Applicant's PRO evidence dossier ("Patient-Reported Outcome Dossier: Hidrdenitis Suppurativa Symptom Daily Diary (HSSDD) dated 05 May 2023 Version 1.0") for full details regarding the methodology and results of each activity.

5.4.4.1.1 Literature review and PRO Gap Analysis

Literature Review

A review of published literature was conducted to identify concepts of interest in HS to inform the development of the HSSDD. Three qualitative studies were identified along with 41 published studies from Medline/Embase and 12 ongoing trials from clinicaltrials.gov. The main concepts measured in all retrieved references were disease severity, HRQoL, and pain. Specifically, results from this review showed that HS is a chronic and painful skin condition presenting with inflammatory nodules and abscesses associated with pain, depression, anxiety, and disability.

The Applicant also conducted a post-hoc literature review to further understand, from the patient perspective, the experience of skin pain related to HS and other core HS symptoms (smell/odor, oozing/drainage from HS lesions, and itch), and to support the content validity of the preliminary HSSDD, an additional targeted literature review of both published and grey literature was performed. Searches were conducted using Ovid (Medline, Embase, and PsycINFO) databases, grey literature sources (Google Scholar), and clinical trial databases (clinicaltrial.gov, clinicaltrialsregister.eu). Searches combined condition-related terms with assessment-related terms using Boolean operators and were tailored to focus on literature which discussed skin pain, odor, oozing, and itch in relation to HS.

In total, 318 articles were reviewed for title/abstract, and 112 trials were reviewed for COAs, resulting in 430 total articles. From this 430, 69 publications and 64 trials were identified as eligible for full text review, and from these, a total of 10 articles were selected for the literature review. Pain was mentioned in all articles included in the literature review. Skin pain and odor were discussed in 4 (40%) articles, while itching and drainage were mentioned in 6 (60%). All articles reported the negative impact of HS symptoms on HRQoL for patients. A summary of

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each article's contents and relevant discussion points is presented in Table 5–2 of the Applicant's PRO evidence dossier.

PRO Gap Analysis

From a review of existing PRO measures in the published literature, the Dermatology Life Quality Indext (DLQI) was the most common instrument used in HS (23 of the 41 published studies and 3 of the 12 ongoing trials identified). In addition, the Skindex, Hidradenitis Suppurativa Impact Assessment, 36-item Short Form Health Survey (SF-36), Treatment Satisfaction Questionnaire for Medication, Hidradenitis Suppurativa Symptom Assessment, and EQ-5D were used to assess HRQoL in HS patients. Based on these findings, the Applicant identified strengths and weaknesses for each PRO measure. Although the DLQI was the most common PRO measure, the Applicant concluded that there was a lack of information on internal consistency reliability in HS, and further evidence was needed regarding its responsiveness in HS.

5.4.4.1.2 Expert Input

The Applicant conducted one-on-one telephone interviews with two key opinion leaders (KOLs). participated in a semi-structured, 1-on-1 telephone interview. The KOLs mentioned that the most important symptom that causes discomfort and complaints in their HS patients is pain. These experts indicated that the inflammatory lesions are very painful, and that they cause further discomfort when they drain.

Although both KOLs perceived that the DLQI was the most common tool for assessing HRQoL in HS, 1 KOL stated that the measure fails to capture problems specific to HS patients. The KOL added that a disease-specific questionnaire addressing pain and all factors that affect patients is needed. Other PRO tools mentioned by the KOLs included the EQ-5D, Health Assessment Questionnaire, Functional Assessment of Chronic Illness Therapy – Fatigue, and SF-36.

Reviewer's comment(s): *Per the Applicant, a formal report was not developed. However, the interview transcripts were provided as an appendix to the PRO evidence dossier (Appendix E).*

5.4.4.1.3 Item Generation

The HSSDD was developed based on the literature review and expert input. It included five items that measure HS sign/symptom severity in the previous 24 hours. The HSSDD items assess itch, smell/odor, and drainage/oozing due to HS.

Reviewer's comment(s): *The Applicant did not conduct concept elicitation interviews prior to generating the content of the HSSDD.*

5.4.4.1.4 Patient Input

The Applicant conducted 90-minute cognitive interviews using the web-based teleconference platform Zoom to:

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- Confirm the relevance of the sign/symptoms covered by the HSSDD for participants with HS
- Evaluate the comprehension of the content in the electronic versions of the HSSDD
- Evaluate the acceptability and usability of the electronic version of the HSSDD,

One-on-one video interviews were conducted with 20 US HS participants recruited from one academic medical center between September and November 2021. Participants had to have:

- a clinically confirmed diagnosis of HS* for at least six months prior to Screening.
- moderate-to-severe HS defined as a total of ≥ five inflammatory lesions (abscess and/or inflammatory nodules) at Screening
- HS lesions present in at least two distinct anatomic areas (e.g., left and right axilla), one of which must be at least Hurley Stage II or Hurley Stage III at Screening.

Reviewer's comment(s): *The inclusion criteria for the qualitative study appears to be comparable to those for the registration studies.*

The results from these interviews are summarized below.

- A total of 20 adult participants were interviewed. The majority of the participants were White (n=12/20, 60.0%), Non-Hispanic (n=17/20, 85.0%), females (n=16/20 , 80%) with a mean age of 40 years (standard deviation [SD]: 4.26; median: 41.5 years; range: 20.0 to 64.0) and at least some college education (n= 16/20, 80.0%).
- The majority of participants (n=15/20, 75.0%) reported living with an HS diagnosis for five years or longer. Slightly more than half (n=11/20, 55.0%) considered the severity of their HS as moderate, and rated their health as fair or poor (n=12/20, 60.0%).
- On average, participants were diagnosed with moderate HS based on the Hurley Stage grading system (n=15/20, 75%) for at least eight years (SD=8.95). Antibiotics (e.g., doxycycline), antiandrogenic medication (e.g., spironolactone), immunosuppressive drugs, and minor surgeries or procedures were common past and current therapies/procedures that participants used to manage their HS.
- Most participants used electronic devices such as tablets and iPads, smartphones, laptops with touch screens (n=11 to 18, 55.0% to 90.0%) in their daily lives. Many participants (n=15/20, 75.0%) reported being very or extremely familiar with touch screen devices, and being very or extremely comfortable using such devices (n=14/20, 70.0%). Difficulty reading or using electronic devices in general was not an issue for the majority of the interview sample (n=19/20, 95.0%).
- Thirteen participants (65.0%) reported the symptom that led them to the doctor was pain. Several participants (n=11/20, 55.0%) described draining or oozing as a symptom that led them to the doctor, while four (20%) reported odor or smell as one of the reasons. No participants reported itching as a symptom that led them to the doctor.

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- All participants (n=20/20, 100.0%) reported at least one other HS symptom that led them to visit the doctor. These included lesions or its variations (e.g., boils, lumps, abscesses, cysts, tumors, pockets, nodules, pustules, abnormal pimples, sores, and blackheads; n=19/20, 95.0%; infections, puss, or swelling (n=5/20, 25.0%); bleeding or wounds (n=4/20, 20.0%); and tunneling, tracts, or sinus canals (n=4/20, 20.0%).
- Several participants (n=5/20, 25.0%) reported triggers that exacerbated their HS symptoms. These included diet (e.g., increased sugar intake; n=5/5, 100.0%), stress (n=4/5, 80.0%), smoking and alcohol intake (n=1/5, 20.0%), sweating (n=1/5, 20.0%), touching the site of flare-up (n=1/5, 20.0%), shaving (n=1/5, 20.0%), constriction (e.g., wearing tight clothing or wrapping with bandages; n=1/5, 20.0%), menstruation (n=1/5, 20.0%), soaps (n=1/5, 20.0%), and delaying time to address flare-ups (n=1/5, 20.0%).
- All core HS symptoms (drainage/oozing, skin pain, itching, smell/odor) were highly reported by more than 90% of participants. Symptoms most commonly appeared in the underarm and groin. Most participants (n=15/20, 75%) reported other symptoms, such as boils, bleeding, cysts, swelling, and tunneling.
- Common body locations where HS symptoms were experienced included the back, breast, buttocks/anus, chest, face/neck, genitals, groin/bikini line, legs/thighs, stomach, and underarms armpits.
- Most participants (n=9/20, 45.0%) rated their HS as moderate because they were symptomatic with active HS widespread across the body, or experienced flare-ups. Three participants (33.0%) considered their condition moderate because they felt their HS was less severe compared to the past (e.g., in teenage years, prior to procedure).
- Of the nineteen participants asked, most (n=18/19, 94.7%) reported change in their symptoms since diagnosis. Half of participants (n=9/18, 50.0%) reported only improvement, while others (n=7/18, 38.9%) reported only worsening. Two participants (11.1%) reported aspects of their HS that both improved and worsened.
- Some participants (n=3/9, 33.0%) reported impacts on daily activities (e.g., unable to remain in hot places for extended periods of time) and emotional health (e.g., mental exhaustion). Other impacts mentioned were limp (n=1/20, 5.00%) and embarrassment (n=1/20, 5.00%).

- Regarding the HSSDD,
    - Participants (n=10/20, 50.0%) described it as “simple,” “easy,” and “self-explanatory.” Several participants (n=10/20, 50.0%) spontaneously mentioned that the questionnaire asked the “right” or “spot on” questions relevant to HS.
        - Other feedback from participants included that the questionnaire was limiting with a 24-hour recall period, since HS can vary based on flare-up frequency (n=4/20, 20.0%), and potentially be useful for disease tracking purposes (n=2/20, 10.0%).
        - Participants also liked that the questionnaire utilized a good recall period (n=2/20, 10.0%), was short (n=1/20, 5.0%), allowed them to select rather

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than input an answer (n=1/20, 5.0%), and was not personal or offensive (n=1/20, 5.0%).

- All participants (n=20/20, 100.0%) reflected on the 24-hour recall period when answering the HSSDD items, and felt they were accurately able to recall their HS experience during this timeframe. However, two participants (10.0%) also reflected on broader recall periods, such as "in general" or "bad days."
  - Of the 15 participants asked, all but one participant (n=14/15, 93.0%) considered both daytime and evening/nighttime hours. The other participant considered daytime hours only.
- All participants (n=20/20, 100.0%) shared that the HSSDD instructions were clear by restating so in their own words, including but not limited to reflecting on HS-related symptoms, thinking about the past 24 hours, selecting only one answer, or completing at the end of the day.
- Most participants (n=19/20, 95.0%) were able to differentiate between the 0 to 10 numerical response options to select their answer. Only one participant (5.0%) reported some difficulty differentiating response options for the average skin pain item.
- All but one participant (n=19/20, 95.0%) correctly interpreted the worst skin pain item. The participant who did not understand suggested the item was asking about change in pain severity, rather than an assessment of pain severity within a specific time period. Of those participants who understood, two did not explicitly mention or highlight that the item asked about worst skin pain.

- Regarding the electronic handheld device,
  - Most participants (n=13/20, 65.0%) mentioned that it was "fine," "clear," "easy," or "self-explanatory" with a "nice set-up." Some participants (n=4/20, 20.0%) also stated that they thought it would be a helpful tool for logging and tracking HS-related information for everyday use, measuring trends, and sharing with medical professionals. Other feedback mentioned by three participants each (15.0%) included the following: the handheld questionnaire was preferred and more convenient to paper, easy to navigate and select answers, and compact (e.g., similar to a cell phone).
  - All participants (n=20/20; 100.0%) reported no difficulty completing the questionnaire on the electronic symptom daily diary, navigating from screen to screen, or manually selecting an answer with their finger. Additionally, all participants (n=20/20; 100.0%) reported no problems with viewing the questions or response options, noting that the text could be clearly read and words appeared large enough. No participants suggested changing the way the questions appeared on the screen.
  - Of the sample, only five participants (25.0%) needed to change their answer, and did not report any problems doing so. An error message appeared for only one participant (5.0%). All participants (n=20/20, 100.0%) saw and understood the final verification screen that displayed "Select OK" and "Next."

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Reviewer's comment(s): *While the Applicant referred to these as cognitive interviews, there was some time carved out in the interviews to query the participants about their HS experience. Because there was not a defined concept elicitation portion, the qualitative study lacked certain key information related to the patient experience of HS symptoms. For example, it is unclear how the pain presents (sharp, burning, etc.) and origin (e.g., lesion), what attributes of pain are most important (e.g., severity, frequency), or how participants refer to their HS-related pain in their own words, etc. Therefore, an information request (IR) was sent to the Applicant on July 31, 2024 requesting patient interview transcripts for the cognitive interviews, as well as clarification on whether concept elicitation interviews were conducted in patients with HS.*

The Applicant confirmed that concept elicitation was included in the 1.5-hour long interviews described in the Cognitive Interviewing and Usability Testing of the Electronic HSSDD, HSSQ, and HiSQOL qualitative interview report (EVM-26511-00, Sections 3.4.1 and 4.5; Appendix D of the evidence dossier. The Applicant also submitted the patient interview transcripts.

Based on review of the patient interview transcripts, this reviewer notes the following:

- *Participants (n=20) described their pain using one or more of the following terms: Sore, extreme pain, very painful, feeling like pinching/hurts, thumping sensation, or stabbing etc.)*
    - *All participants reported that the pain was related to the lesions, boils, and cysts.*
    - *All participants reported that the big boils, cysts, bleeding and pain were the reasons to seek medical advice.*

- *None of the 20 participants interviewed spontaneously mentioned "skin pain."*

- *Every participant was asked directly about skin pain (e.g., "Do you experience skin pain currently?," "Where do you have your skin pain?," " Do you ever experience skin pain?" etc.)*

- *Of the 20 participants,*
    - *Three (15 %) participants (ID# 001-015, 001-019 and 001-020) stated that they were not experiencing any pain at the time of the interview.*
    - *One participant (ID# 001-009) did not understand the question as intended and therefore did not provide an answer.*
    - *The remaining 16 participants responded to the interviewer's question on skin pain by describing their pain in terms extreme pain, very painful etc.*
        - *Two of the 16 (12 %) participants reported that their pain was on the skin and also below the surface.*

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- *One participant (ID# 001-023) stated "…Please rate your skin from your HS lesions as worst—" My skin pain. Just basically the pain overall from my lesions over—at its worst over the last 24 hours.*

This reviewer believes that pain is a relevant symptom in the target patient population and suggests that the term "skin pain" either be labeled as "pain"or qualified in parentheses as "lesion pain." Based on the qualitative data, the HSSDD Worst Skin Pain item appears to be well-understood.

Overall, findings from the qualitative study generally appear to support the content validity of the HSSDD Worst Skin Pain item.

5.4.5 Other Measurement Properties

The Applicant used pooled blinded data from Studies HS0003 and HS0004 to evaluate the other measurement properties of the HSSDD Worst Skin Pain item.

The analysis population consisted of 934 participants (n=458 [49.0%] from Study HS0003 andn= 476 [51.0%] from Study HS0004).[3] The majority of participants were White (n=722/934, 77.3%), Non-Hispanic (n=832/934, 89.1%), females (n=525/934, 56.2%) with a mean (SD) age of 37 (12.2) years at Baseline. Overall, 56% of participants were Hurley Stage II at Baseline and 43% were Hurley Stage III, indicative of a moderate-to-severe HS.

At Baseline, the Patient Global Impression of Change in Severity of Skin Pain (PGI-S-SP) indicated that the majority of study participants initiated the study with moderate (43.8%) to severe (30.7%) skin pain. Study participants also reported moderate (45.7%) to severe (27.7%) HS on the Patient Global Impression of Hidradenitis Suppurativa Severity (PGI-S-HS) at Baseline.

Reviewer's comment(s): *Per the Applicant, demographics were generally similar between the HS0003 and HS0004 HSSDD Analysis Sets, except for gender, where there were more female participants in Study HS0003.*

Psychometric analyses were conducted on the blinded HSSDD analysis set, defined as all randomized study participants from both studies who had at least 1 non-missing weekly symptom item score of the HSSDD at any scheduled assessment visit. The analyses focused on Week 16 (prioritized) and Baseline.

A summary of the psychometric findings from Studies HS0003 and HS0004 is provided in the following subsections. For more details on the methodology and results of these analyses, refer to Section 6 and Appendix B of the PRO evidence dossier.

3 The analysis set was defined as all randomized study participants from both studies who had at least 1 non-missing weekly symptom item score of the HSSDD at any scheduled assessment visit.

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5.4.5.1 HSSDD Worst Skin Pain Item

5.4.5.1.1 Item descriptives and response distributions

- A total of 847 out of 934 study participants had non-missing Baseline HSSDD scores (9.3% missing).
- The mean (SD) and median HSSDD Worst Skin Pain item scores at Baseline was 5.5 (2.5) and 5.7, respectively. The mean (SD) and median HSSDD Worst Skin Pain item score at Week 16 was 3.8 (2.6) and 3.4, respectively.
- 1.5% of study participants endorsed a score of 0 at Baseline on the HSSDD Worst Skin Pain item. Less than 5% of the study participants endorsed a score of 10 at Baseline on the HSSDD Worst Skin Pain item.

Reviewer's comment(s):
There were no observed floor or ceiling effects.

5.4.5.1.2 Reliability

5.4.5.1.2.1 Test-Retest Reliability

Test-retest reliability assesses whether instrument scores are reasonably consistent over time within clinically stable patients. Test-retest reliability was assessed by estimating the intra-class correlation coefficient (ICC) for the HSSDD Worst Skin Pain score among stable study participants[4]. Based on this analysis, the ICC was 0.83.

Reviewer's comment(s): *In general, the ICC was within an acceptable and reasonable range for the analysis.*

5.4.5.1.3 Construct validity

5.4.5.1.3.1 Convergent validity

Convergent validity assesses how closely related two or more measures are that are intended to assess the same construct (concept). Convergent validity was assessed for the HSSDD Worst Skin Pain item using Spearman correlations with scores from reference measures at Baseline and Week 16. Specifically, at Baseline, the reference measures used were the International Hidradenitis Suppurativa Severity Score System (IHS4), DLQI, and HiSQOL. The strength of the correlation between two variables was interpreted as weak, moderate, strong, or very strong when the correlation coefficient was <0.3, ≥ 0.3 to <0.7, ≥ 0.7 to <0.9, or ≥ 0.9, respectively. All correlations were positive as hypothesized by the Applicant.

[4] A stable population was defined as participants with no change in the PGI-S-SP score between Baseline and Week 4.

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Based on the correlation analyses,

- The correlation (r) between the HSSDD Worst Skin Pain item and IHS4 at Baseline was 0.25. At Week 16, the correlation (r) was 0.38.

  Reviewer's comment(s): *The correlation between the HSSDD Worst Skin Pain item and IHS4 observed at Baseline was weak, whereas the correlation observed at Week 16 was moderate. Per the Applicant, the lower correlation coefficients at Baseline were likely due to inclusion criteria, which required that study participants had moderate-to-severe HS, defined as a total of ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules, which are both included in the IHS4 score calculation at both the Screening and Baseline visits. The Applicant further states that these lower correlations between the HSSDD and IHS4 are aligned with findings from the literature where divergence between clinician-reported outcomes and PROs in general have been widely reported across disease areas.*

  This reviewer notes that the IHS4 assesses HS severity which is based on the number of nodules, abscesses, and draining tunnels [fistulae/sinuses]. It is unknown whether there is a relationship between disease severity and symptom severity.

- Correlations (r) between the HSSDD Worst Skin Pain item and DLQI item and total scores at Baseline ranged from 0.27 to 0.60. At Week 16, correlations (r) ranged from 0.25 to 0.52.

  Reviewer's comment(s): *Most of the correlations observed between the HSSDD Worst Skin Pain item and DLQI item and total scores were moderate. However, there weak correlations observed between the HSSDD Worst Skin Pain item and DLQI items 7 ("Prevented Working/Studying"; Baseline and Week 16), 8 ("Partner, Close Friends, or Relatives"; Baseline), and 9 ("Sexual Difficulties"; Baseline).*

- Correlations (r) between the HSSDD Worst Skin Pain item and HiSQOL domain and total scores at Baseline ranged from 0.35 to 0.62. At Week 16, correlations (r) ranged from 0.40 to 0.66.

  Reviewer's comment(s): *All correlations observed between the HSSDD Worst Skin Pain item and HiSQOL domain and total scores were moderate. This reviewer notes that the HiSQOL is an HS-specific measure. As expected, the correlations are higher with the Symptom domain. The lower correlations were observed with the domains that measured more distal concepts (e.g., Psychosocial).*

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5.4.5.1.3.2 Known-groups validity

Known-groups validity assesses whether instrument scores can discriminate among groups of participants known to be clinically different. Descriptive statistics and boxplots were used to assess known-groups validity. Known-groups were defined by the Hurley Stage and PGI-S-HS.

- When defining known groups by Hurley Stage at Week 16,
  - TheHSSDD worst skin pain scores differed between each of the stages (I, II, and III).
  - The HSSDD Worst Skin Pain score in the Hurley Stage II group differed from the Hurley Stage I group by a mean (95% CI) of 0.49 (-0.31, 1.30).
  - The HSSDD Worst Skin ain score in the Hurley Stage III group differed from the Hurley Stage II group by a mean (95% CI) of (0.68, 1.51).

- When defining known groups by the PGI-S-HS at Week 16, due to the small sample size in the very severe group (n=7), the "Severe" and "Very severe" groups were combined.
  - The HSSDD Worst Skin Pain scores differed between each response level (None, Mild, Moderate, and Severe or Very severe).
  - The HSSDD Worst Skin Pain score in the group responding "Mild" on the PGI-S-HS differed from the group responding "None" on the PGI-S-HS by a mean (95% CI) of 1.22 (0.71, 1.74).
  - The HSSDD Worst Skin Pain score in the group responding "Moderate" on the PGI-S-HS group differed from the group responding "Mild" on the PGI-S-HS by a mean (95% CI) of 2.14 (1.79, 2.49).
  - The HSSDD Worst Skin Pain score in the group responding "Severe" or "Very severe" on the PGI-S-HS differed from the group responding "Moderate" on the PGI-S-HS by a mean (95% CI) of 2.50 (1.99, 3.00).

- When defining known groups by IHS4 score at Week 16,
  - The HSSDD Worst Skin Pain scores differed between each of the levels (Mild, Moderate, and Severe).
  - The HSSDD Worst Skin Pain score in the IHS4 "Moderate" group differed from the IHS4 "Mild" group by a mean (95% CI) of 1.17 (0.65, 1.70)
  - The HSSDD Worst Skin Pain score in the IHS4 "Severe" group differed from the IHS4 "Moderate" group by a mean (95% CI) of 1.12 (0.68, 1.57).

- When defining known groups by the HS Physician's Global Assessment (PGA) at Week 16,
  - The HSSDD Worst Skin Pain score in the "Minimal" HS PGA group differed from the "Clear" HS PGA group by a mean (95% CI) of 0.81 (-0.65, 2.27).
  - The HSSDD Worst Skin Pain score in the "Mild" HS PGA group differed from the "Minimal" HS PGA group by a mean (95% CI) of -0.33 (-1.30, 0.64), with the

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difference in the medians also being negative (2.14 vs. 2.86, respectively; a difference of -0.72).
- The HSSDD Worst Skin Pain score in the "Moderate" HS PGA group differed from the "Mild" HS PGA group by a mean (95% CI) of 1.18 (0.67, 1.68).
- The HSSDD Worst Skin Pain score in the "Severe" HS PGA group differed from the "Moderate" HS PGA group by a mean (95% CI) of 1.02 (0.05, 1.99).
- The HSSDD Worst Skin Pain score in the "Very severe" group differed from the "Severe" HS PGA group by a mean (95% CI) of 0.41 (-0.61, 1.42), with the difference in medians being negative (5.00 vs. 5.18, respectively; a difference of -0.18).

Reviewer's comment(s):
Overall, for most of the known-group analyses, the HSSDD Worst Skin Pain item appears to be able to distinguish among clinically distinct groups as evidenced by higher HSSDD Worst Skin Pain scores for groups with more severe Hurley Stage, PGIS-HS, and IHS4. The exception was the HS PGA. Per the Applicant, the differences going in the unexpected direction for the HS PGA (i.e., decreasing worst skin pain score with more severe HS PGA group) is likely due to the small sample sizes in the clear (n=32) and minimal (n=24) groups, leading to larger uncertainty around the sample mean and distribution in the minimal group, in particular, as seen by the distribution and the wide CI in the observed score for the "Minimal" group vs. the "Mild" group (mean [95% CI]: 2.88 [1.72, 4.04] vs. 2.55 [2.17, 2.93]). Additionally, the Applicant states that it may also be that the difference between the definitions of "Clear" and "Minimal" on the HS PGA, which is the presence of at least one non-inflammatory nodule, may not have a clear or direct impact on worst skin pain. Regarding, the smaller difference in the HSSDD Worst Skin Pain score between the "Very severe"and "Severe" HS PGA groups than in the other comparisons, the Applicant suggests that it is likely due to the small sample size in the "Severe" group (n=28). This reviewer questions the adequacy of the HS PGA as a reference measure due to potential overlap of the responses.

5.4.5.1.4 Responsiveness

Responsiveness assesses the ability of an instrument to measure any degree of change when a known change in the concept of interest has occurred. Responsiveness was evaluated by (1) examining correlation coefficients (Spearman, including p-values) between the change in HSSDD Worst Skin Pain item score at Week 16 from Baseline and the change in a given external anchor and (2) comparing the change score at Week 16 from Baseline in HSSDD Worst Skin Pain item score between groups defined by the level of change (e.g., Improvement, No change, Worsening) in a given external anchor. The PGI-S-SP and PGI-C-SP measures were considered as potential anchors for the HSSDD Worst Skin Pain item.

Based on these correlation analyses,

- Spearman correlation coefficients between the changes in the HSSDD Worst Skin Pain item and changes in the potential anchors from Baseline at Week 16 were:
  - PGI-S-SP: 0.63 ($p < 0.001$)

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- PGI-C-SP: 0.51 ($p < 0.001$)

- When using PGI-S-SP as an anchor,
  - The HSSDD Worst Skin Pain item LS mean change score (95% CI) in the 'No change 'category was below 0 (-0.78 [-1.11, -0.45); however, the effect size was small (-0.31 [-0.41, -0.22]), as hypothesized by the Applicant.
  - The response groups with 1, 2, and 3 levels of improvement on the PGI-S-SP had LS mean change scores (95% CI) of -2.09 (-2.39, -1,79), -3.61 (-4.05, -3.17), and -4.51 (-5.39, -3.63), respectively.

- When using PGI-C-SP as an anchor,
  - The HSSDD Worst Skin Pain item LS mean change score (95% CI) in the 'No change' category was below 0 (-0.70 [-1.10, -0.30); however, the effect size was small (-0.28 [-0.44, -0.13]) as hypothesized by the Applicant.
  - The response groups with 1 and 2 levels of improvement on the PGI-C-SP had LS mean change scores (95% CI) of -1.24 (-1.55, -0.93) and -3.22 (-3.53, -2.91).

Reviewer's comment(s):
The HSSDD Worst Skin Pain item score appears to be moving in the anticipated direction (i.e., an increase in score corresponds to worsening on the PGI-S-SP and PGI-C-SP); however, CIs for both levels of worsening included 0. The Applicant suggests that it is likely due to the small sample sizes (57 and 10, respectively) and/or relatively small effect sizes of change.

Overall, the HSSDD Worst Skin Pain item appears to be responsive to improvement in other measures assessing a similar construct in the target population. Per the Applicant, its responsiveness to worsening remains to be further verified. This reviewer agrees with this conclusion.

5.4.6 Interpretation of Meaningful Within-Patient Score Changes

The following section was authored by the Patient-Focused Statistical Scientists (PFSS) team.

Background

The Agency recommends the use of anchor-based methods to establish meaningful within-patient change in COA-based endpoint scores, although other methods (e.g., qualitative evidence) can be used (April 20235). The Applicant conducted anchor-based analyses supplemented with eCDF curves to evaluate clinically meaningful within-patient change in HSSDD worst skin pain item from baseline to week 16 using the PGI-S-SP and PGI-C-SP as anchor measures (Appendix B) and data collected from their Phase 3 studies (HS0003 and HS0004). The Applicant identified a range of clinically meaningful within-patient change

5 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-incorporating-clinical-outcome-assessments-endpoints-regulatory

Reference ID: 5461541

thresholds from baseline to week 16 of a 3- to 4- point decrease, which corresponds to the mean and median decrease in the HSSDD Worst Skin Pain item for patients who reported a 2-category improvement on the PGI-S-SP measure and the mean decrease in the HSSDD Worst Skin Pain for patients who reported "much better" on the PGI-C-SP measure.

In order to review the Applicant's anchor-based analyses, the review team issued an information request on July 31, 2024, for exactr copies of the anchor scales and additional figures and tables for studies HS0003 and HS0004.

Assessment

The Applicant proposed a 2-category improvement from baseline to week 16 on the PGI-S-SP measure as the target anchor change category that constitutes a clinically meaningful within-patient change as the majority of patients reported "Moderate" (n = 409 [43.8%]) or "Severe" (n = 287 [30.7%]) skin pain at Baseline and a 2-category improvement would imply "None" or "Mild" skin pain as measured by the PGI-S-SP measure at week 16. Table 2 shows the change in HSSDD Worst Skin Pain scores from Baseline to Week 16 by change in the PGI-S-SP measure in Study HS0003. Patients who experienced a 2-point improvement in the PGI-S-SP measure had a mean change in HSSDD Worst Skin Pain score of -3.95 and a median change of -4.1. Table 3 shows the change in HSSDD Worst Skin Pain scores from Baseline to Week 16 by change in the PGI-S-SP measure in Study HS0004. Patients who experienced a 2-point improvement in the PGI-S-SP measure had a mean change in HSSDD Worst Skin Pain score of -3.95 and a median change of -3.7.

Reviewer's comment(s): *In general, the PGI-S-SP and PGI-C-SP measures appear to be reasonable for use as external anchors to interpret the HSSDD Worst Skin Pain item. The measurement concepts and recall period appear to align. While the PGI-S-SP includes a high number of response categories, collapse some of the response categories (e.g., Severe/Very severe) could help minimize poor distribution of responses across the categories for the anchor-based analyses.*

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Table 2. Change form Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0003)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
PGI-S-SP Response at Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
3-point improvement	10 (2.0)	-5.27	2.053	-7.8	-1.7	-7.4	-6.7	-5.8	-3.9	-2.0	9 (1.8)
2-point improvement	38 (7.5)	-3.95	1.846	-7.5	0.2	-6.6	-5.0	-4.1	-2.4	-1.9	28 (5.5)
1-point improvement	108 (21.4)	-2.09	2.161	-7.3	2.2	-5.4	-3.2	-2.0	-0.7	0.5	54 (10.7)
No Change	86 (17.0)	-0.82	1.633	-5.0	4.0	-3.0	-2.0	-0.7	0.1	1.2	50 (9.9)
1-point worsening	22 (4.4)	0.91	1.795	-1.1	5.6	-0.6	-0.1	0.2	1.9	3.1	16 (3.2)
2-point worsening	4 (0.8)	2.18	1.885	0.6	4.8	0.6	0.9	1.7	3.5	4.8	4 (0.8)
4-point worsening	0										1 (0.2)
Missing	11 (2.2)	-1.83	3.161	-6.2	2.0	-5.7	-5.0	-2.0	1.6	1.9	64 (12.7)

Source: Applicant's IR Response Received August 6, 2024 (Table D3)
Abbreviations: PGI-S-SP, Patient Global Impression of Severity in Skin Pain; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

Reference ID: 5461541

Table 3. Change form Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0004)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
PGI-S-SP Response at Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	N missing (%)
4-point improvement	0										1 (0.2)
3-point improvement	9 (1.8)	-4.78	2.425	-9.3	-0.7	-9.3	-5.6	-5.3	-4.0	-0.7	4 (0.8)
2-point improvement	49 (9.6)	-3.95	2.184	-8.4	0.0	-7.0	-5.6	-3.7	-2.3	-1.2	30 (5.9)
1-point improvement	115 (22.6)	-2.28	1.978	-7.6	6.0	-4.4	-3.5	-2.5	-1.0	0.0	48 (9.4)
No Change	118 (23.2)	-0.42	1.804	-4.6	4.7	-2.9	-1.7	-0.2	0.6	1.8	23 (4.5)
1-point worsening	35 (6.9)	0.72	1.486	-3.9	3.9	-1.2	0.0	0.9	1.6	2.5	20 (3.9)
2-point worsening	4 (0.8)	0.25	1.991	-2.2	2.4	-2.2	-1.3	0.4	1.8	2.4	1 (0.2)
Missing	8 (1.6)	-2.54	3.642	-5.8	4.6	-5.8	-5.4	-3.5	-0.6	4.6	44 (8.6)

Source: Applicant's IR Response Received August 6, 2024 (Table D4)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

The Applicant additionally inspected the eCDF curves for change from baseline to week 16 in HSSDD score by change in the PGI-S-SP measure in each study (see Figure 2 and Figure 3; shown on next page) and found sufficient separation between the target anchor change category of a 2-point improvement in the PGI-S-SP measure and other anchor change categories, supporting their proposed anchor change category to define clinically meaningful within-patient change thresholds.

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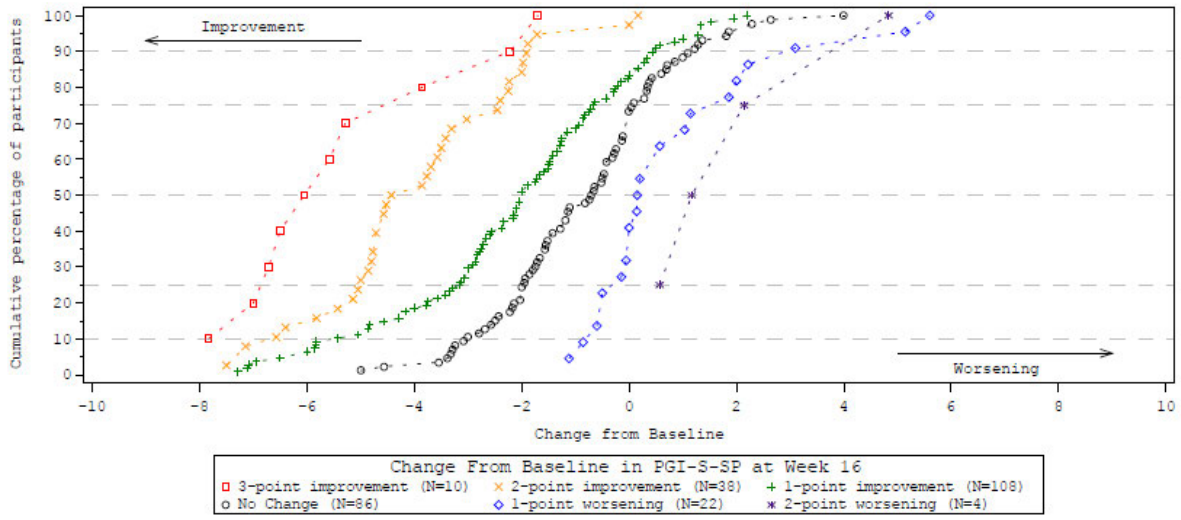
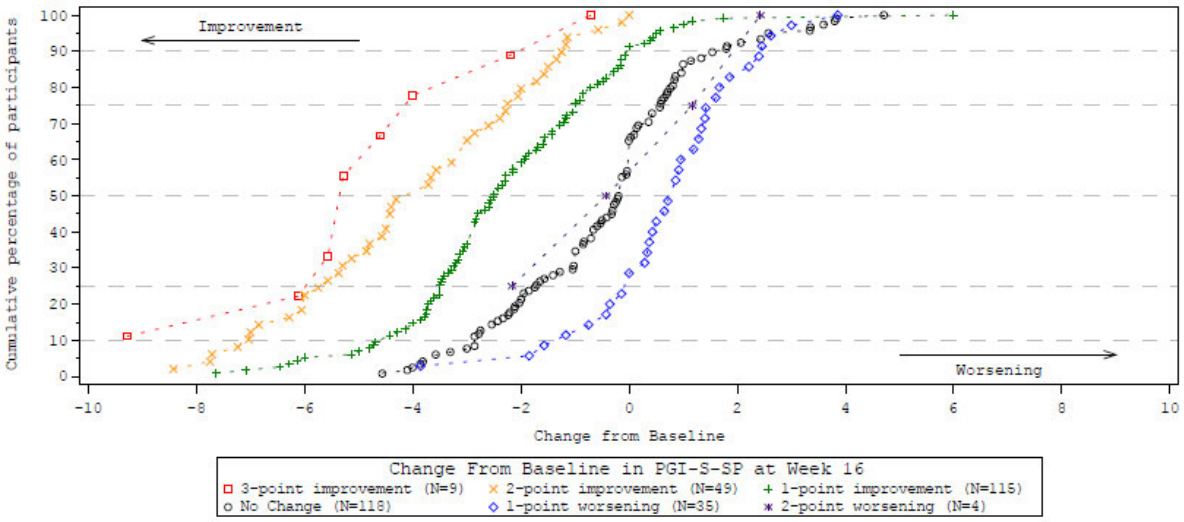
Figure 2. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D1)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Figure 3. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D2)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Additionally, the Applicant proposed "Much better" on the PGI-C-SP measure as the target anchor category on the supportive anchor. Patients who reported "much better" skin pain at Week 16 had a mean change from baseline to week 16 in HSSDD Worst Skin Pain score of -3.17 and a median change of -2.8 in Study HS0003 (see Table 4). Patients who reported "much better" skin pain at week 16 had a mean change from baseline to week 16 in HSSDD Worst Skin Pain score of -3.32 and a median change of -3.3 in Study HS0004 (see Table 5; shown on next page). Based on these mean and median change scores of the HSSDD Worst Skin Pain item from Baseline to Week 16 for the target anchor change categories, the Applicant proposed a clinically meaningful within-patient change threshold range of a 3-point to 4-point improvement.

Table 4. Change from Baseline in HSSDD Worst Skin Pain Score at Week 16 by PGI-C-SP at Week 16 (HS0003)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
Change in PGI-C-SP from Baseline to Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
Much Better	107 (21.2)	-3.17	2.291	-7.8	2.2	-6.5	-5.0	-2.8	-1.7	-0.3	62 (12.3)
A Little Better	100 (19.8)	-1.14	2.228	-7.1	5.6	-4.0	-2.5	-1.0	0.2	1.3	48 (9.5)
No Change	44 (8.7)	-0.65	2.055	-5.0	4.0	-3.4	-2.0	-0.4	0.5	1.9	35 (6.9)
A Little Worse	20 (4.0)	-0.61	1.649	-3.8	2.3	-3.4	-1.5	-0.5	0.6	1.4	13 (2.6)
Much Worse	6 (1.2)	0.86	1.814	-2.1	3.1	-2.1	-0.1	1.2	2.0	3.1	5 (1.0)
Missing	2 (0.4)	-0.35	2.377	-2.0	1.3	-2.0	-2.0	-0.3	1.3	1.3	63 (12.5)

Source: Applicant's IR Response Received August 6, 2024 (Table D5)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

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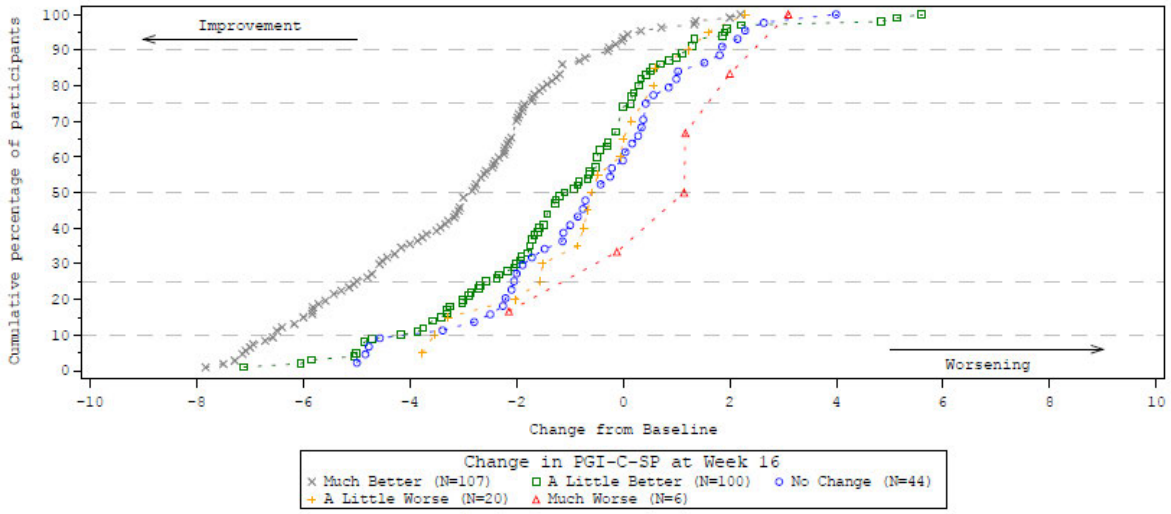
Table 5. Change from Baseline in HSSDD Worst Skin Pain Score at Week 16 by PGI-C-SP at Week 16 (HS0004)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
Change in PGI-C-SP from Baseline to Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
Much Better	114 (22.4)	-3.32	2.172	-9.3	3.0	-6.3	-4.6	-3.3	-1.9	-0.5	43 (8.4)
A Little Better	132 (25.9)	-1.17	2.071	-7.1	4.7	-3.7	-2.7	-1.0	0.1	0.9	51 (10.0)
No Change	64 (12.6)	-0.66	2.049	-6.0	3.6	-3.2	-2.0	-0.2	0.6	1.8	26 (5.1)
A Little Worse	18 (3.5)	1.17	1.782	-1.2	6.0	-0.4	-0.1	0.7	2.6	3.8	10 (2.0)
Much Worse	10 (2.0)	1.25	1.470	-1.2	3.9	-1.0	0.8	1.3	2.2	3.1	2 (0.4)
Missing	0										39 (7.7)

Source: Applicant's IR Response Received August 6, 2024 (Table D6)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

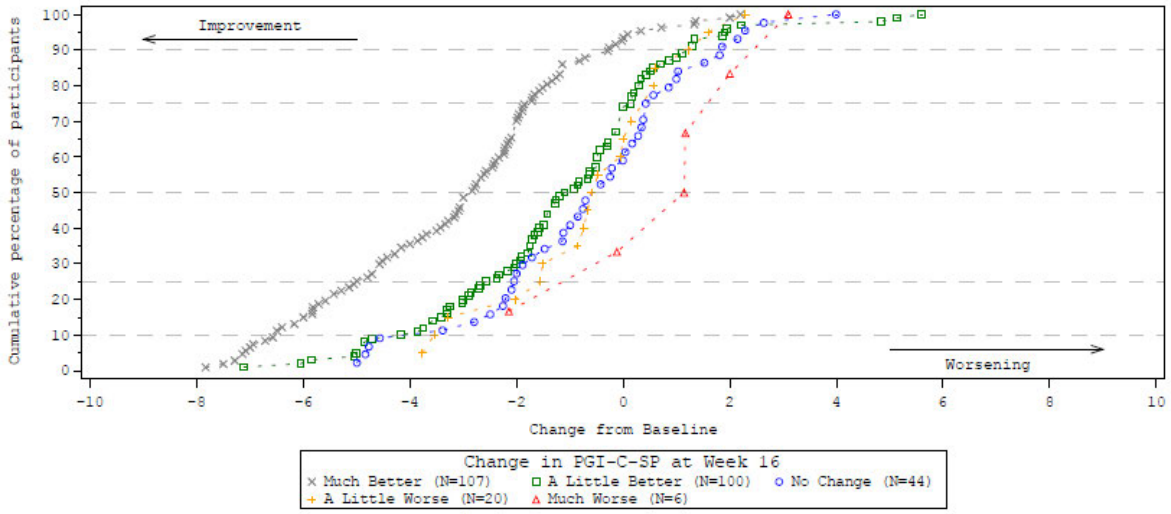
The Applicant inspected the eCDF curves for change from baseline to week 16 in HSSDD Worst Skin Pain score by the PGI-C-SP measure at Week 16 in each study (see Figure 4 and Figure 5; shown on next page) and found sufficient separation between the target anchor category of "Much better" and other anchor change categories, supporting their proposed anchor category to define clinically meaningful within-patient change thresholds.

Figure 4. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-C-SP at Week 16 (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D3)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Figure 5. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-C-SP at Week 16 (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D4)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

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Based on these analyses, the Applicant proposed a meaningful within-patient change threshold range of 3-point to 4-point improvement on HSSDD Worst Skin Pain score from Baseline to Week 16.

Reviewer comments: *The Applicant's anchor-based analyses supplemented by eCDF curves is largely appropriate. Notably, while the Applicant did not explicitly discuss misclassification rates of patients based on their threshold range, the observed misclassification rates of patients who reported no change or worsening on the PGI-S-SP or PGI-C-SP measures at the meaningful within-patient change range of 3-point to 4-point improvement on HSSDD Worst Skin Pain item was below 20%, which is acceptable. However, what patients consider to be clinically meaningful improvement may be impacted by the patient's baseline skin pain severity. Patient's baseline symptom severity should be considered when determining clinically meaningful within-patient change thresholds. Below is the Agency's evaluation of patient's baseline skin pain symptom severity on meaningful within-patient change thresholds.*

Table 6 and Table 7 (shown on next page) show the distribution of change in HSSDD Worst Skin Pain scores from Baseline to Week 16 for patients who achieved a 2-category improvement on the PGI-S-SP measure. The median change in the HSSDD Worst Skin Pain item is between -2.4 and -4.8 in Study HS0003 and between -3.0 and -4.4 in Study HS0004. The amount of change patients consider meaningful tends to smaller the more severe skin pain they reported at baseline. Based on the results of the anchor-based analyses supplemented by eCDF curves and the assessment of baseline symptom severity, the final clinically meaningful within-patient change range should be between -4.8 and -2.4, which includes the Applicant's proposed range (i.e., -3 to -4) so that, for patients who achieved a 2-category improvement on the PGI-S-SP measure, at least 50% of patients who reported moderate, severe, or very severe skin pain at baseline are categorized as having experienced a meaningful improvement.

Table 6. Distribution of Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-S-SP at Baseline for Patients who Achieved a 2-category Improvement in PGI-S-SP at Week 16 (HS0003)

		HSSDD Change Score									
						Percentiles					
PGI-S-SP Response at Baseline	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
Moderate	9 (13.6)	-4.53	1.724	-7.1	-2.0	-7.1	-5.1	-4.8	-3.5	-2.0	7 (10.6)
Severe	22 (33.3)	-4.05	1.835	-7.5	0.2	-6.6	-5.1	-3.8	-3.0	-1.9	16 (24.2)
Very Severe	7 (10.6)	-2.88	1.847	-4.8	0.0	-4.8	-4.7	-2.4	-1.7	0.0	5 (7.6)

Source: Applicant's IR Response Received August 6, 2024 (Table D7)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Reference ID: 5461541

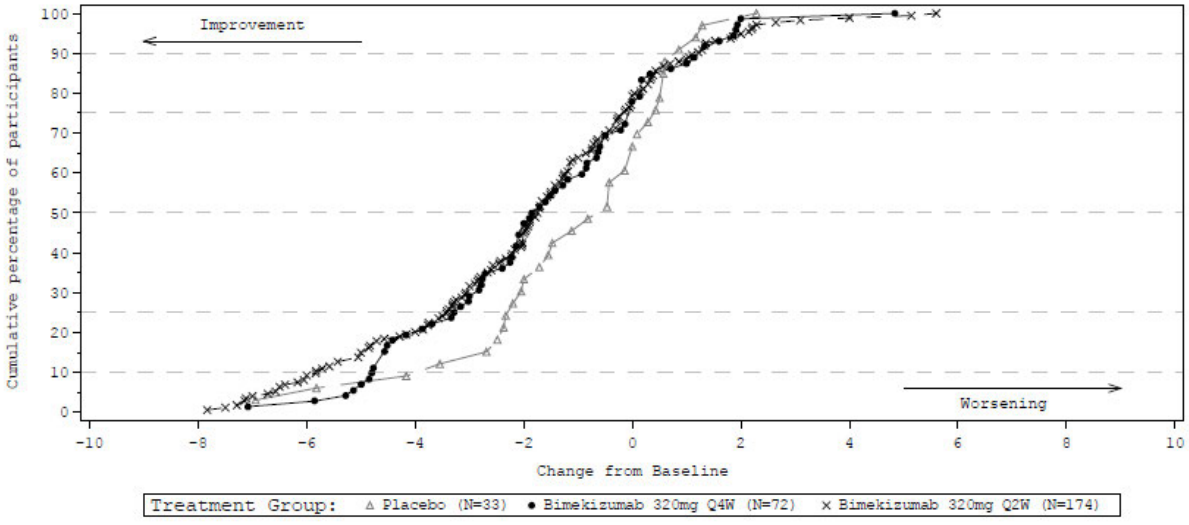
Table 7. Distribution of Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-S-SP at Baseline for Patients who Achieved a 2-category Improvement in PGI-S-SP at Week 16 (HS0004)

		HSSDD Change Score									
						Percentiles					
PGI-S-SP Response at Baseline	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
Moderate	15 (19.0)	-4.60	2.157	-8.4	-1.3	-7.8	-6.0	-4.4	-3.0	-2.1	12 (15.2)
Severe	29 (36.7)	-3.75	2.249	-7.2	0.0	-7.0	-5.6	-3.7	-1.7	-0.6	14 (17.7)
Very Severe	5 (6.3)	-3.16	1.706	-6.0	-1.5	-6.0	-3.0	-3.0	-2.3	-1.5	4 (5.1)

Source: Applicant's IR Response Received August 6, 2024 (Table D8)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

As seen in Figure 6 and Figure 7 (shown on next page), there is adequate separation between the eCDF curves for the placebo arm and the bimekizumab arms. The difference in proportion of patients reported as experiencing a meaningful improvement between the placebo and bimekizumab treatment arms is between approximately 12% and 21% in Study HS0003 and between approximately 11% and 22% in Study HS0004 in the range patients consider meaningful (i.e., -4.8 and -2.4).

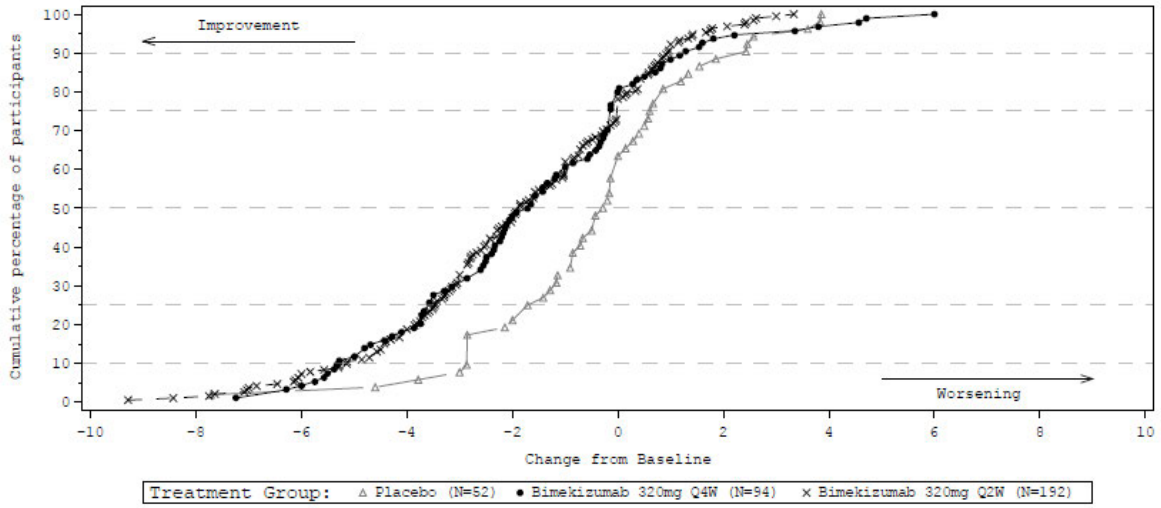
Figure 6. Empirical Cumulative Distribution Function Plot for Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Treatment Group (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D5)
Abbreviations: HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

Reference ID: 5461541

Figure 7. Empirical Cumulative Distribution Function Plot for Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Treatment Group (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D6)
Abbreviations: HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

Conclusion

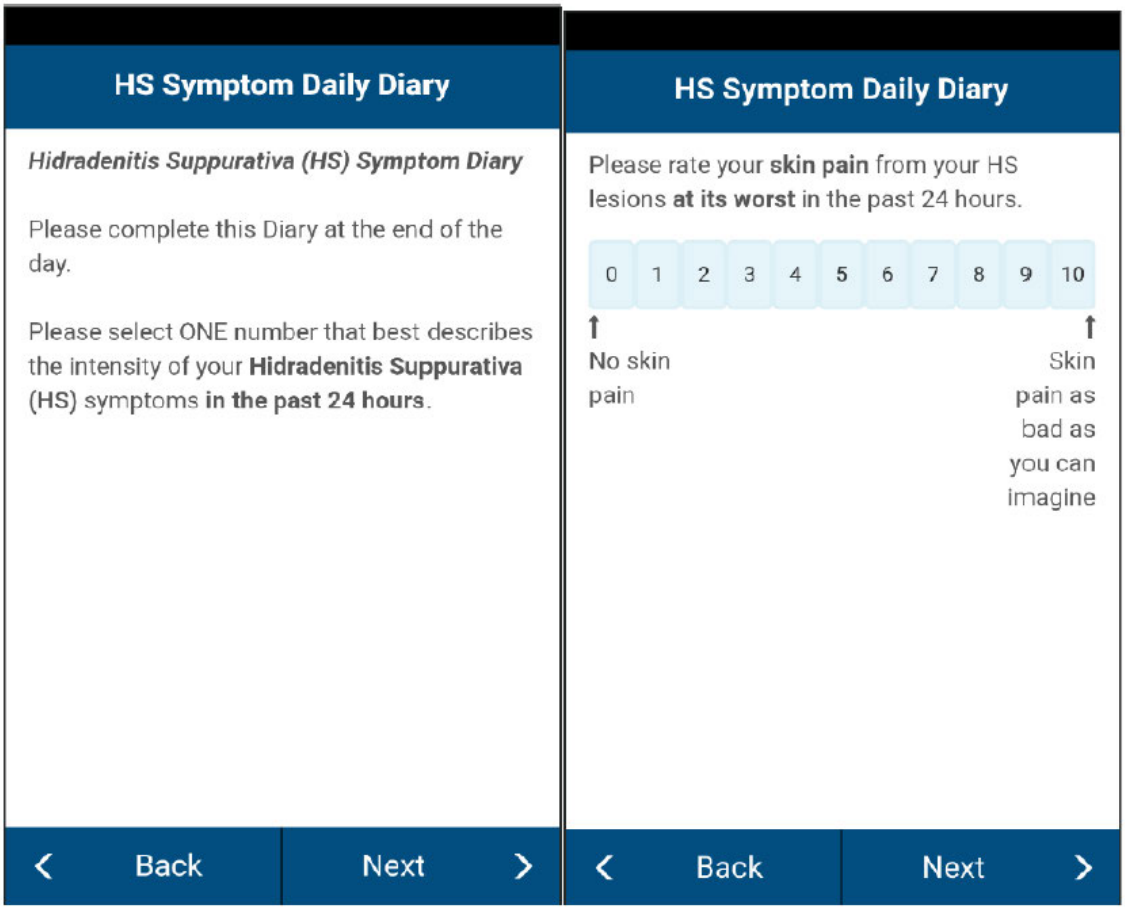
Anchor-based analyses to assess meaningful within-patient change in HSSDD Worst Skin Pain score between Baseline and Week 16 indicates patients consider a reduction of between 2.4 and 4.8 points to be meaningful. The observed treatment effect substantiated a clinically meaningful within-patient improvement in patients receiving bimekizumab compared to placebo.

6. APPENDICES

Appendix A: Hidradenitis Suppurative Symptom Daily Diary (HSSDD) Worst Skin Pain item
Appendix B: Copies of Anchor Measures

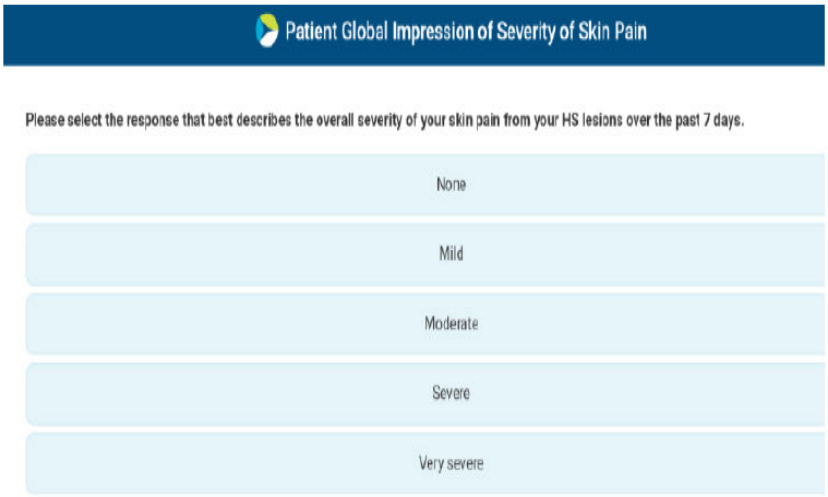
Reference ID: 5461541

Appendix A: HSSDD Worst Skin Pain Item

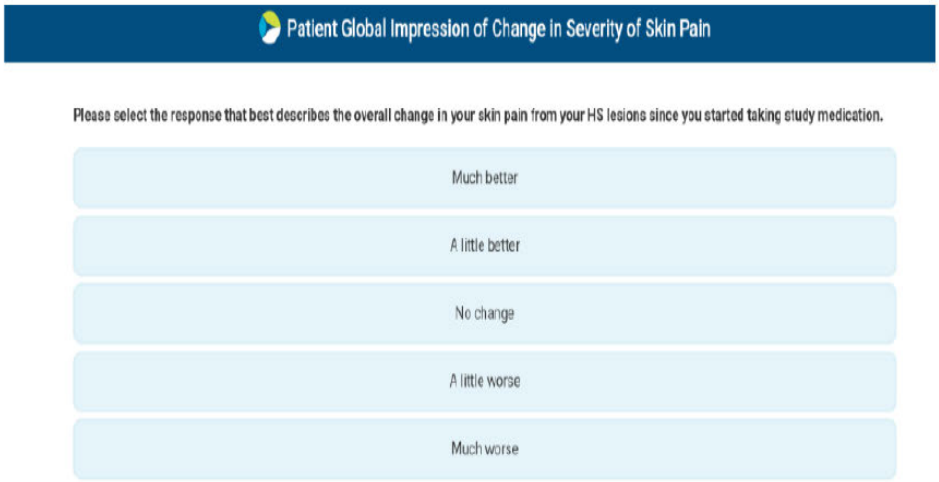


Appendix B: Copies of Anchor Measures

Patient Global Impression of Severity of Skin Pain



Patient Global Impression of Change of Severity of Skin Pain



Please select the response that best describes the overall severity of your HS over the past 7 days.

- None
- Mild
- Moderate
- Severe
- Very Severe

Please select the response that best describes the overall change in your HS since you started taking the study medication.

- Much better
- A little better
- No change
- A little worse
- Much worse

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/

SELENA R DANIELS
10/11/2024 10:25:48 AM

STATISTICAL REVIEW AND EVALUATION
FILING REVIEW OF AN NDA/BLA

NDA/BLA #:	BLA 761151
Supplement #:	S-010
Related IND #:	134700
Product Name:	BIMZELX (bimekizumab) injection
Indication(s):	Moderate to severe hidradenitis suppurativa (HS)
Applicant:	UCB, Inc.
Dates:	Stamp Date: 1/19/2024 PDUFA Date: 11/19/2024
Review Priority:	Standard
Biometrics Division:	Division of Biometrics III
Statistical Reviewer:	Matthew Guerra, PhD
Concurring Reviewers:	Matthew Guerra, PhD
Medical Division:	Division of Dermatology and Dentistry
Clinical Team:	Kevin Clark, MD & Jessica Nguyen, MD / Melinda McCord, MD
Project Manager:	Strother Dixon

1. Summary of Efficacy/Safety Clinical Trials to be Reviewed

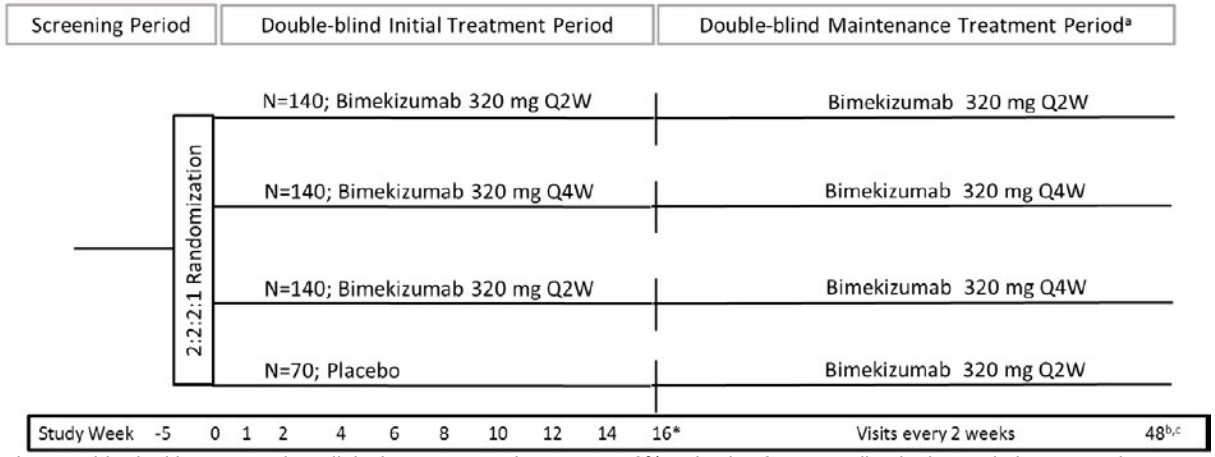
Table 1: Summary of Trials to be Assessed in the Statistical Review

Trial ID	Design	Treatment/Sample Size	Primary Endpoint
HS0003	MC, R, DB, PG, PC	Initial Treatment Period (Weeks 0-16): ° Bimekizumab 320 mg Q2W: 289 ° Bimekizumab 320 mg Q4W: 144 ° Placebo: 72 Maintenance Treatment Period (Weeks 16-48): ° Bimekizumab 320 mg Q2W/Q2W: 129 ° Bimekizumab 320 mg Q2W/Q4W: 129 ° Bimekizumab 320 mg Q4W/Q4W: 125 ° Placebo/bimekizumab 320mg Q2W: 65	Proportion of subjects achieving Hidradenitis Suppurativa Clinical Response 50 ($HiSCR_{50}$) at Week 16. $HiSCR_{50}$ defined as at least a 50% reduction in the total abscess and inflammatory nodule (AN) count with no increase from baseline in abscess or draining tunnel count.
HS0004	MC, R, DB, PG, PC	Initial Treatment Period (Weeks 0-16): ° Bimekizumab 320 mg Q2W: 291 ° Bimekizumab 320 mg Q4W: 144 ° Placebo: 74 Maintenance Treatment Period (Weeks 16-48): ° Bimekizumab 320 mg Q2W/Q2W: 131 ° Bimekizumab 320 mg Q2W/Q4W: 130 ° Bimekizumab 320 mg Q4W/Q4W: 133 ° Placebo/bimekizumab 320mg Q2W: 69	

MC: multicenter, R: randomized, DB: double-blind, PG: parallel group, PC: placebo controlled, Q2W: every 2 weeks; Q4W: every 4 weeks

Reference ID: 5355214

Figure 1: Study Design Schematic for Trials HS0003 and HS0004



HiSCR: Hidradenitis Suppurativa Clinical Response; $HiSCR_{50}$: a ≥50% reduction from Baseline in the total abscess and inflammatory nodule count with no increase from Baseline in abscess or draining tunnel count; IMP: investigational medicinal product; Q2W: every 2 weeks; Q4W: every 4 weeks

[a] Subjects discontinued from the study from Week 32 on if no partial response was achieved (partial response was defined as ≥25% improvement in abscess and inflammatory nodule count relative to Baseline [Week 0] lesion values).

[b] Subjects who achieved an improvement of at least 25% in abscess and inflammatory nodule count were permitted to continue in HS0005 (Extension Study).

[c] Twenty-week Safety Follow-Up (from last IMP injection) for any subject who discontinued from the study prior to Week 48, or who did not continue in HS0005.

Patient Population

For enrollment, the protocols specified the following key inclusion criteria:

- Adult male or female who is at least 18 years of age
- A diagnosis of HS based on clinical history and physical examination for at least 6 months prior to the baseline visit
- HS lesions present in at least 2 distinct anatomic areas (e.g., left and right axilla), 1 of which must be at least Hurley Stage II or Hurley Stage III at both the screening and baseline visits
- Moderate to severe HS, defined as a total of ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules) at both the screening and baseline visits
- Subject must have had an inadequate response to a course of a systemic antibiotic for treatment of HS as assessed by the investigator through study participant interview and review of medical history. The protocols specified that subjects who meet any of the following are NOT automatically excluded from the trial:
    - Demonstrated intolerance to (or became intolerant to) systemic antibiotics
    - Had a contraindication to systemic antibiotics
    - Responded to course(s) of systemic antibiotic(s) and subsequently exhibited recurrence after discontinuation of the antibiotic
- Subjects with a draining tunnel count of >20 at baseline will be excluded from the trials

Primary Efficacy Endpoints

The protocol-specified primary efficacy endpoint was the proportion of subjects achieving Hidradenitis Suppurativa Clinical Response 50 ($HiSCR_{50}$) at Week 16. $HiSCR_{50}$ is defined as at least a 50% reduction in the total AN count with no increase from baseline in abscess or draining tunnel count.

Key Secondary Efficacy Endpoints

The protocols specified the following key secondary efficacy endpoints (controlled for multiplicity):

- Proportion of subjects achieving $HiSCR_{75}$ at Week 16
- Proportion of subjects who experience at least one flare by Week 16, with flare defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to baseline [ONLY Trial HS0004]
- Absolute change from baseline in DLQI Total Score at Week 16
- Absolute change from baseline in the Worst HS Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the HS Symptom Daily Diary (HSSDD)
- Proportion of subjects with a ≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16 among subjects with a baseline score ≥ 3

Preliminary Evaluation of Efficacy

Table 2 presents the results for the primary and key secondary efficacy endpoints for the two Phase 3 trials.

Table 2: Results of the Primary and Key Secondary Efficacy Endpoints (RS[1])

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
Primary Endpoint						
$HiSCR_{50}$ at Week 16						
Proportion	48%	45%	29%	52%	54%	32%
Difference from placebo (95% CI)[2]	18% (6%, 30%)	15% (2%, 29%)		20% (8%, 32%)	21% (8%, 35%)	
P-value[2]	0.006	0.030		0.004	0.003	
Significant per MTP[4]	Yes	No		Yes	Yes	
Secondary Endpoints						
$HiSCR_{75}$ at Week 16						
Proportion	33%	25%	18%	36%	34%	16%
Difference from placebo (95% CI)[2]	15% (4%, 27%)	6% (-6%, 19%)		20% (10%, 31%)	18% (6%, 30%)	
P-value[2]	0.021	0.350		0.002	0.007	
Significant per MTP[4]	Yes	No		Yes	Yes	
At least 1 flare by Week 16						
Proportion	25%	36%	48%	29%	24%	28%
Difference from placebo (95% CI)[2]	-	-	-	1% (-10%, 12%)	-4% (-16%, 8%)	
P-value[2]	-	-	-	0.868	0.497	
Significant per MTP[4]	-	-	-	No	No	
Change from baseline in DLQI at Week 16 LS Mean[3]	-5.2	-5.1	-2.5	-4.7	-4.8	-2.4
Difference from placebo (95% CI)[2]	-2.7 (-4.2, -1.2)	-2.6 (-4.2, -0.9)		-2.3 (-3.5, -1.1)	-2.4 (-3.7, -1.1)	
P-value[3]	<0.001	0.002		<0.001	<0.001	
Significant per MTP[4]	Yes	No		No	No	

	Trial HS0003			Trial HS0004		
	Bimekizumab 320 mg			Bimekizumab 320 mg		
	Q2W (N=289)	Q4W (N=144)	Placebo (N=72)	Q2W (N=291)	Q4W (N=144)	Placebo (N=74)
Change from baseline in Worst HS Skin Pain score at Week 16						
LS Mean[3]	-2.2	-1.5	-1.0	-1.6	-1.2	-0.3
Difference from placebo (95% CI)[3]	-1.2 (-2.1, -0.3)	-0.6 (-1.5, 0.4)		-1.3 (-1.9, -0.6)	-0.9 (-1.6, -0.2)	
P-value[3]	0.002	0.201		<0.001	0.010	
Significant per MTP[4]	Yes	No		No	No	
	N=190	**N=103**	**N=46**	**N=209**	**N=108**	**N=49**
≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16						
Proportion	32%	22%	15%	32%	29%	11%
Difference from placebo (95% CI)[2]	19% (3%, 34%)	8% (-8%, 24%)		20% (7%, 32%)	17% (3%, 30%)	
P-value[2]	0.041	0.367		0.010	0.028	
Significant per MTP[4]	Yes	No		No	No	

[1] Randomized Set (RS): all randomized subjects. For the binary efficacy endpoints, subjects who experienced an intercurrent event (i.e., receipt of systemic antibiotic rescue medication or discontinuation of study treatment due to an AE or lack of efficacy prior to Week 16) were treated as non-responders. For continuous efficacy endpoints, subjects who experienced an intercurrent event were treated as missing following the intercurrent event. Missing data was imputed using multiple imputation (MI).
[2] Difference, 95% CI, and p-value were based on logistic regression with treatment, Hurley Stage at baseline, baseline antibiotic use, and analgesic use (only Worst HS Skin Pain endpoint) were used as fixed effects.
[3] LS mean, difference, 95% CI, and p-value were based on ANCOVA with fixed effects of treatment, Hurley Stage at baseline, baseline antibiotic use, and analgesic use (only Worst HS Skin Pain endpoint) and baseline value as a covariate.
[4] Multiplicity Testing Procedure (MTP): a closed testing procedure under a parallel gatekeeping framework was used.
Source: Applicant's Analysis (clinical study reports for Trials HS0003 and HS0004)

2. Assessment of Protocols and Study Reports

Table 3: Summary of Information Based Upon Review of the Protocol(s) and the Study Report(s)

Content Parameter	Response/Comments
Designs utilized are appropriate for the indications requested.	**Yes**
Endpoints and methods of analysis are specified in the protocols/statistical analysis plans.	**Yes**
Interim analyses (if present) were pre-specified in the protocol with appropriate adjustments in significance level. DSMB meeting minutes and data are available.	**NA**
Appropriate details and/or references for novel statistical methodology (if present) are included (e.g., codes for simulations).	**NA**
Investigation of effect of missing data and discontinued follow-up on statistical analyses appears to be adequate.	**Yes**

3. Electronic Data Assessment

Table 4: Information Regarding the Data

Content Parameter	Response/Comments
Dataset location	\\CDSESUB1\EVSPROD\bla761151\0116\m5\datasets\
Were analysis datasets provided?	Yes
Dataset structure (e.g., SDTM or ADaM)	SDTM and ADaM
Are the define files sufficiently detailed?	Yes
List the dataset(s) that contains the primary endpoint(s)	ADFA.xpt
Are the *analysis datasets* sufficiently structured and defined to permit analysis of the primary endpoint(s) without excess data manipulation? *	Yes
Are there any initial concerns about site(s) that could lead to inspection? If so, list the site(s) that you request to be inspected and the rationale.	No
Safety data are organized to permit analyses across clinical trials in the NDA/BLA.	Yes

* This might lead to the need for an information request or be a refuse to file issue depending on the ability to review the data.

4. Filing Issues

Table 5: Initial Overview of the NDA/BLA for Refuse-to-file (RTF):

Content Parameter	Yes	No	NA	Comments
Index is sufficient to locate necessary reports, tables, data, etc..	X			
ISS, ISE, and complete study reports are available (including original protocols, subsequent amendments, etc.).	X			
Safety and efficacy were investigated for gender, racial, ethnic, and geriatric subgroups.	X			For safety and efficacy, the Applicant did not conduct subgroup analyses based on ethnicity.
Data sets are accessible, sufficiently documented, and of sufficient quality (e.g., no meaningful data errors).	X			
Application appears to be free from any other deficiency that render the application unreviewable, administratively incomplete, or inconsistent with regulatory requirements.	X			

IS THE APPLICATION FILEABLE FROM A STATISTICAL PERSPECTIVE?

Yes

5. Comments to be Conveyed to the Applicant

5.1. Refuse-to-File Issues

None

Reference ID: 5355214

5.2. Information Requests/Review Issues

- The statistical analysis plans (SAPs) and clinical study report for the Phase 3 trials (HS0003 and HS0004) state that "if participants undergo lesion interventions as specified in the study protocol, the affected lesions will be counted by the Investigator as permanently present, thus accounting for potential bias due to the intervention." Submit detailed information on the process (e.g., capturing, documentation, and tracking) for lesion intervention as it is not clear how these lesions were counted as permanently present. In addition, we have found at least one instance where a lesion that received lesion intervention was not counted as permanently present. Subject (b) (6) had an abscess receive lesion intervention (i.e., "INCISION & DRAINAGE" according to ADHSLIT.xpt) at Week 2; however, the abscess count at Week 16 is 0 for this subject. Therefore, it is not clear whether lesions that received intervention were counted as permanently present. Clarification is needed.

- For safety and efficacy, submit analyses and discussion by ethnicity subgroups (Hispanic/Latino, Not Hispanic/Latino).

6. Advisory Committee

	Response/Comments
If the Advisory Committee Decision Aid (ACDA) is required for this application (it is required for a new molecular entity or original BLA), do you have any comments relevant to the completion of this document?	
Has the review division determined that an Advisory Committee (AC) meeting is needed?	☐ Yes ☐ No ☐ To be Determined
If an AC meeting may be held for this application, are there any areas of expertise that may be important for AC statistician(s) to have?	

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/

MATTHEW W GUERRA
03/28/2024 12:48:09 PM

U.S. FOOD & DRUG ADMINISTRATION

Memorandum of Assessment:

Submission Tracking Number (STN):	BLA 761151/S010
Subject:	Efficacy supplement for the treatment of moderate to severe hidradenitis suppurativa (HS) in adults.
Date Received:	01/19/2024
Assessment/Revision Date	06/11/2024
Primary Assessor:	Xuhong Li, Ph. D., Chemist, DPQA XVI, OPQA III
Secondary Assessor:	Samuel Mindaye, Ph. D., Lead Interdisciplinary Scientist, DPQA XVI, OPQA III
RBPM:	Kristine Leahy
Consults:	NA
Applicant:	UCB, Inc.
Product:	BIMZELX (bimekizumab-bkzx)
Indication:	Hidradenitis suppurativa
Action Due Date:	11/19/2024

1. Summary Basis of Recommendation:

a. Recommendation:

Approval of this supplemental BLA is deferred to the OND.

b. Justification:

No new CMC information is provided in this supplement. The categorical exclusion request for environmental assessment is acceptable. The assays used for the immunogenicity assessment are acceptable.

2. Assessment:

1. Environmental Assessment:

☒ The sponsor requests categorical exclusion from the requirements of preparing an environmental assessment under 21 CFR 25.31 (c). This is acceptable from an OBP perspective.

2. Origin of Drug Product:

Information Request (Conveyed on 25 Apr 2024)*: The source of the drug product lots used in the clinical trials to support the each of the efficacy supplements was not clear. Provide clarification in tabulated format and list which manufacturing process was used to manufacture the lots used in each of the clinical trials. For drug product lots that were not made by the approved commercial process, please confirm that the drug product is comparable to the commercial product and that the relevant comparability data were provided in the original BLA 761151 submission.*

The Applicant's Response (Received on 01 May 2024): The applicant provides a list of the drug product lots used for the clinical trials. Commercial drug substance Process 5

and PFS drug product process were used to manufacture lots for the Phase 3 studies, HS0003, HS0004 and the ongoing open-label study HS0005. Phase 2 clinical study HS0001 used the clinical drug substance Process 4 used the vial drug product process for batch manufacture.

***Assessor's Comment**: Comparability between Process 4 and Process 5 drug substance, and between drug product vial and PFS were confirmed during the original BLA 761151 review.*

☒ The drug product lots used in the clinical studies to support the new indication were not manufactured and controlled as described in the license (e.g., clinical lots). However, comparability between these drug product lots and the commercial lots were/are demonstrated for the purpose of supporting the marketing of commercial materials as described in the license for the new indication.

3. Immunogenicity Assay Evaluation:

☒ Additional immunogenicity assessment was provided in Module 5 and used to support the new indication. A justification was provided to support the suitability and validation of immunogenicity assays to be used for the assessment in the new patient population.

***Assessment**: Updated section 2.7.1 summary of biopharmaceutic studies and associated analytical method (dated 16 May 2023) and Integrated summary of immunogenicity (dated 22 Aug 2023) are provided. The same immunogenicity assays reported in the original BLA were used to evaluate the immunogenicity samples from the new studies. Per the information provided in the original submission, the impact of the disease state of patient population of psoriasis, psoriatic arthritis, ankylosing spondylitis and hidradenitis suppurativa were evaluated during method validation. The immunogenicity assays are suitable for the assessment of patient blood samples to support this sBLA.*

3. Assessment conclusions:

Acceptable from product quality and immunogenicity assay perspective.

6. PMC/PMR: NA

Xuhong Li

Digitally signed by Xuhong Li
Date: 6/25/2024 12:59:30PM
GUID: 508da7210002a00c7693bc9ce497840f

Samuel Mindaye

Digitally signed by Samuel Mindaye
Date: 6/25/2024 01:00:08PM
GUID: 5dd2d3f60048d8672219510df16c7dd8

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761151Orig1s010

OTHER REVIEW(s)

Medical Officer Consult Review
Division of Gastroenterology

BLA #: BLA 761151
Sponsor: UCB Inc.
Drug: Bimekizumab
Dosage Form: Injection
Indication: Moderate to severe hidradenitis suppurativa
Date Received: 6/21/2024
To: Kevin Clark, MD (Clinical Reviewer)
Melinda McCord, MD (Clinical Team Leader)
Division of Dermatology and Dentistry (DDD)
Clinical Reviewer/Team Leader: Arushi deFonseka, MD / Tara Altepeter, MD

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 chronic inflammatory conditions including psoriasis and hidradenitis suppurativa (HS).

Regulatory Background:

Bimekizumab was approved October 17, 2023, for treatment of moderately to severely active plaque psoriasis in adults who are candidates for systemic therapy or phototherapy. On January 19, 2024, the applicant submitted an efficacy supplement for the proposed indication of moderately to severely active HS.

Consult Request:

"Bimzelx (bimekizumab-bkzx, hereafter referred to as BKZ) for subcutaneous administration is a humanized monoclonal antibody that binds IL-17A and 17F. BKZ was approved October 18, 2023 for the treatment of moderate to severe plaque psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy.

The Applicant has now submitted BLA 761151 S-010 (SDN 165, January 19, 2023) which seeks approval of BKZ for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). DG previously provided consultative reviews dated March 22, 2021 by Dr. Anil Nayyar (Initial BLA submission) and dated May 2, 2023 (BLA resubmission after CR for PsO) by Dr. Tara Altepeter.

Current labeling for BKZ includes inflammatory bowel disease (IBD) in Sections 5 and 6. Data submitted with this sBLA includes reports of subjects with adjudicated IBD events. Please review the submission, provide your assessment of the IBD events, recommendations regarding updates to product labeling, and attend meetings."

See reviews by Anil Nayyar (dated March 22, 2021) and Tara Altepeter (dated May 2, 2023) for further details of prior reviews for the indication of plaque psoriasis.

DG Response:

Brief overview of HS development program:

The clinical development program for the proposed indication of moderately to severely active HS consists of the following studies:

• Phase 2

− HS0001: double-blind, placebo-controlled, active reference arm study assessing the efficacy, safety, and pharmacokinetics (PK) of bimekizumab in study subjects with moderate to severe HS. This study included 3 periods: a Screening Period (≥2 weeks up to a maximum of 4 weeks prior to randomization), a Treatment Period (12 weeks), and a Safety Follow Up Period (20 weeks after the final dose of study medication). Patients were randomized 2:1:1 to receive bimekizumab (640mg at baseline as loading dose, followed by 320mg at Weeks 2, 4, 6, 8, and 10), adalimumab (at the labeled dosing), or matched placebo.

• Phase 3

− HS0003: double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in study subjects with moderate to severe HS

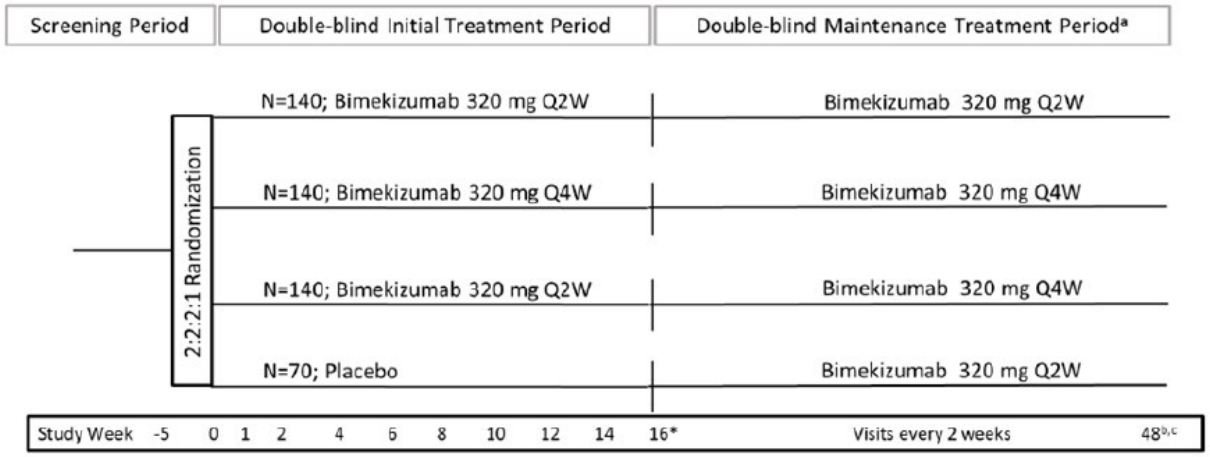
− HS0004: double-blind, placebo-controlled study evaluating the efficacy and safety of bimekizumab in study subjects with moderate to severe HS

− HS0005: an OLE study up to 118 weeks for study subjects who completed HS0003 and HS0004 through Week 48

HS0003 and HS0004 were studies with identical designs conducted at non-overlapping study sites. These studies included a Screening Period (≥2 weeks up to a maximum of 5 weeks prior to randomization) and a double-blind 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period. Patients were randomized into one of four arms, in a 2:2:1:1 ratio as outlined in Figure 1 below (Study diagram for HS0003 and HS0004). Dosing in the initial 16 week treatment period was bimekizumab 320mg Q2W, bimekizumab 320mg Q4 weeks, or placebo, and patients were continued in the maintenance period on either 320mg Q2W or 320mg Q4 weeks as indicated in the figure below for up an additional 32 weeks. .A Safety Follow Up Period (20 weeks after the final dose of study medication) was also included for study subjects not enrolling into HS0005. At the end of HS0003 or HS0004, subjects were assessed for responder status on the basis of lesion counts at

Weeks 36, 40, 44; responders received 320mg Q4W in HS0005, and non-responders received 320mg Q2W. See Figure 2 below for study diagram for HS0005.

Figure 1: HS0003 and HS0004 Study Schematic



AN=abscess and inflammatory nodule; CSR=Clinical Study Report; HiSCR=Hidradenitis Suppurativa Clinical Response; $HiSCR_{50}$=a ≥50% reduction from Baseline in the total AN count with no increase from Baseline in abscess or draining tunnel count; Q2W=every 2 weeks; Q4W=every 4 weeks

Note: Week 16=primary endpoint ($HiSCR_{50}$ bimekizumab vs placebo).

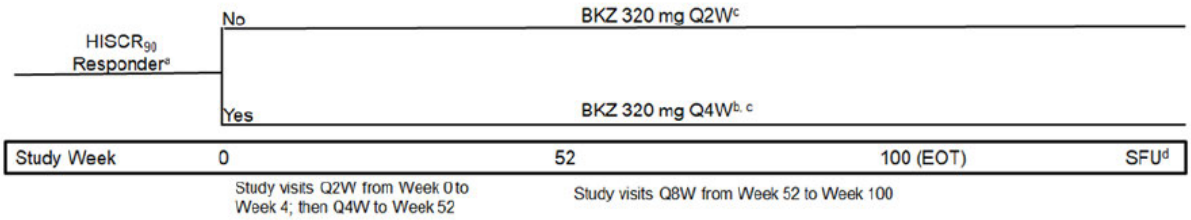
[a] Study participants discontinued from the study from Week 32 on if no partial response was achieved (partial response was defined as ≥25% improvement in AN count relative to Baseline [Week 0] lesion values).

[b] Study participants who achieved an improvement of ≥25% in AN count were permitted to continue in HS0005 (Extension Study).

[c] Twenty-week Safety Follow-Up (from last study medication injection) for any study participant who discontinued from study prior to Week 48, or who did not continue in HS0005.

Source: Applicant submission, ISS, page 23. The asterisk in the figure above refers to the Note: Week 16 = primary endpoint.

Figure 2: HS0005 Study Schematic



AN=abscess and inflammatory nodule; BKZ=bimekizumab; EOT=End of Treatment; HiSCR=Hidradenitis Suppurativa Clinical Response; HiSCR90=a ≥90% reduction in the total AN count with no increase from Baseline in abscess or draining tunnel count; OLE=Open-Label Extension; Q2W=every 2 weeks; Q4W=every 4 weeks; SFU=Safety Follow-Up

[a] Treatment allocation is based on HiSCR90 responder status using the average lesion counts from Week 36, Week 40, and Week 44 of the study participant's feeder study (HS0003 or HS0004) compared against Baseline of their feeder study.

[b] For study participants NOT sustaining an average improvement in AN count of ≥90% versus Baseline (feeder study Baseline) over any 8-week consecutive period (based on lesion assessments performed at scheduled visits), or if the participant has ≤75% improvement from Baseline (feeder study Baseline) in AN count at any single visit, the Investigator in consultation with the study participant may increase the dose to 320mg Q2W. No further dosing adjustments can occur for the study participant during the OLE Period. While it is the sole decision of the Investigator to adjust the dose, dose adjustments should be discussed with the Medical Monitor or Sponsor Study Physician.

[c] Study participants should discontinue from the study if no partial response is achieved (partial response is defined as ≥25% improvement in AN count relative to Baseline of the feeder study) over any 8-week consecutive period (based on lesion assessments performed at scheduled visits).

[d] Twenty weeks after final dose of bimekizumab.

Source: Applicant submission, ISS, page 24

IBD Adjudication Committee:

Given the known association between HS and inflammatory bowel disease (IBD) as well as the class (IL 17 inhibitor) related risk of IBD, the applicant established an independent Inflammatory Bowel Disease Adjudication Committee (IBD-CAC) to review treatment emergent adverse events (TEAEs) that may be related to IBD; the IBD-CAC was blinded to treatment assignments. Based on the available information, IBD events were classified by diagnostic type and then further classified as definite, probable, or possible. Events may also have been adjudicated as 'not consistent with IBD' or 'not enough information to adjudicate'. See Table 1 below for full listing of IBD types. The charter for the IBD-CAC (Version 3.0, submitted March 24, 2023) was reviewed and appears acceptable. The list of terms preferred terms (PT) used to identify potential cases for adjudication is comprehensive. See Table 2 below for full listing of preferred terms. The list of preferred terms is comprehensive and includes the occurrence of diarrhea and abdominal pain if they occurred within 7 days of each other, as well as diarrhea reported for a duration of ≥42 days. 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 3.0.

Table 1: Inflammatory Bowel Disease Event Types

Event Type Code	Event Type	Classification
1	Possible Inflammatory Bowel Disease – Crohn's Disease	Possible
2	Probable Inflammatory Bowel Disease – Crohn's Disease	Probable
3	Definite Inflammatory Bowel Disease – Crohn's Disease	Definite
4	Possible Inflammatory Bowel Disease – Ulcerative Colitis	Possible
5	Probable Inflammatory Bowel Disease – Ulcerative Colitis	Probable
6	Definite Inflammatory Bowel Disease – Ulcerative Colitis	Definite
7	Possible Inflammatory Bowel Disease – Unclassified	Possible
8	Probable Inflammatory Bowel Disease – Unclassified	Probable
9	Definite Inflammatory Bowel Disease – Unclassified	Definite
10	Symptoms not consistent with Inflammatory Bowel Disease	Not applicable
11	Possible Inflammatory Bowel Disease – Microscopic Colitis	Possible
12	Probable Inflammatory Bowel Disease – Microscopic Colitis	Probable
13	Definite Inflammatory Bowel Disease – Microscopic Colitis	Definite
14	Possible Inflammatory Bowel Disease – no further differentiation possible	Possible
15	Probable Inflammatory Bowel Disease – no further differentiation possible	Probable
16	Definite Inflammatory Bowel Disease – no further differentiation possible	Definite
99	Not enough information to adjudicate	Not applicable

IBD=inflammatory bowel disease.
Note: The event types are copied verbatim from the inflammatory bowel disease adjudication committee charter.
Note: IBD diagnoses of "microscopic colitis" and "no further differentiation possible" were added in an adjudication charter amendment, accounting for the event type numbering.

Source: Applicant submission, ISAP, page 87

Table 2: Preferred Terms For IBD Events

MeDRA 19.0 (adult studies) and 23.1 (pediatric studies) Preferred Terms for IBD events

- Acute Haemorrhagic ulcerative colitis
- Allergic colitis
- Anal abscess
- Anal Fistula
- Autoimmune colitis
- Cholangitis sclerosingColectomy
- Colitis
- Colitis erosive
- Colitis ischaemic
- Colitis microscopic
- Colitis ulcerative
- Colonic fistula
- Crohn's disease
- Diarrhoea ≥42 days
- Diarrhoea and Abdominal Pain within 7 days of each other (Abdominal pain or Abdominal pain lower or Abdominal pain upper)
- Diarrhoea Haemorrhagic
- Diverticular fistula
- Enteritis
- Enterocolitis haemorrhagic
- Eosinophilic colitis
- Enterocolonic fistula
- Fistula of small intestine
- Gastrointestinal fistula
- Haematochezia
- Inflammatory bowel disease
- Intestinal fistula
- Intestinal resection
- Necrotising colitis
- Neutropenic colitis
- Oesophageal fistula
- Perirectal abscess
- Primary sclerosing cholangitis
- Proctitis
- Proctitis haemorrhagic
- Proctitis ulcerative
- Pseudopolyposis
- Rectal abscess

Source: IBD-CAC Version 3.0, submitted March 24, 2023

DG's Review of Adjudicated Cases:

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. Of note, subjects with a prior diagnosis of Crohn's disease (CD) or ulcerative colitis (UC) were permitted to enroll provided that they did not have signs or symptoms of active disease at baseline or screening. As of the 120-day safety update, there were 8 cases identified across the phase 3 studies HS0003 and HS0004 as well as the open label extension study HS0005 of "definite" or "probable" IBD. The following table contains a summary of these 8 cases, 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. Of these 8 cases, 7 were identified at the time of the original database lock for the original submission. The additional case identified at the 120 day safety update is noted in the table below, and the cases that the applicant proposed to include in labeling are highlighted.

Study #/ Patient ID	Clinical History	Event/Diagnosis	Reviewer Comment
HS0003/ (b) (6)	48-year-old white female with a history of drug hypersensitivity (flucloxacillin and doxycycline allergy) and iron deficiency. Her lifestyle history included current tobacco use of 30 years (average of 1.14 cigarettes per day). She was diagnosed with HS in 2017. Concomitant medications: triclosan, dexchlorpheniramine, clindamycin, probiotics, and inulin. Received covid vaccine same day as diarrhea onset. She was randomized to bimekizumab 320mg sc Q2W in HS0003, and she received the first dose of the study drug on 08 Nov 2021. At Week 16 (b) (6) she started treatment with bimekizumab 320mg sc Q4W.	On (b) (6) the subject experienced moderate rectal hemorrhage and mild diarrhea. The event occurred days 268 days after the first and 2 days after the most recent bimekizumab injections. The action taken with study drug was reported as drug interrupted due to the diarrhea. The study drug was restarted on (b) (6) which was also the final dose of study drug. The event resolved on (b) (6), 48 days after onset. On (b) (6), the she underwent a colonoscopy which revealed a normal terminal ileum and mild macroscopic colitis extending from the rectum to 20cm (pathology: UC). Findings were positive for ulcerative colitis. Per the Investigator, no treatment was provided at this time, and the event was considered as related to the study drug as the she did not have any history of colitis prior to the study drug commencement.	This SAE of ulcerative colitis was assessed as “probably related” to study drug, and “not resolved.” These assessments appear reasonable.
HS0003/ (b) (4)	19-year-old white female with a history of diabetes mellitus. She was diagnosed with	The subject experienced a nonserious AE of moderate diarrhea (second event) on (b) (6) (b) (6) The event occurred 194 days after the first and 4 days after the most recent	The nonserious event of Crohn’s disease was assessed as “probably related” to study drug, and “not resolved”. These

	HS in 2020. Concomitant medications: metformin and birth control. She was randomized to bimekizumab 320mg sc Q4W in HS0003, and she received the first dose of the study drug on [redacted] At Week 16 [redacted] she continued to receive bimekizumab 320mg sc Q4W.	bimekizumab injections. The action taken with study drug was reported as drug withdrawn due to the diarrhea. She experienced a nonserious AE of moderate Crohn's disease on [redacted] The event occurred 331 days after the first and 141 days after the most recent bimekizumab injections.	assessments appear reasonable given the temporal association; however, details regarding how the diagnosis of Crohn's disease was made were not provided.
HS0004/ 40286-18096	24-year-old white female with a history of Cushing syndrome and IBS (with chronic nausea, vomiting, and diarrhea). She had no history of IBD. Her lifestyle history included tobacco use. She was diagnosed with HS in 2014. Concomitant medications included birth control, clobetasol, loperamide, metopimazine, and betamethasone. She was randomized to bimekizumab 320mg sc Q4W in HS0004, and she received the first dose of the study drug on [redacted] At Week 16 [redacted] she continued to receive bimekizumab 320mg sc Q4W.	On [redacted] she had pain at the right hypochondrium, nausea, and diarrhea. A fecal calprotectin test was negative. The symptoms worsened. Nausea was still persisting even after vomiting. She had documented weight loss of 5kg. There was moderate suspicion of Crohn's disease. The event occurred 185 days after the first and 17 days after the most recent bimekizumab injections. On 15 Jun 2021, treatment with the study drug was temporarily discontinued. On [redacted] symptoms improved/resolved. On 28 Jun 2021, treatment with the study drug was restarted. She experienced a nonserious AE of moderate hepatocellular injury on [redacted] and therapy with the study drug was anently discontinued. This event occurred 240 days after the first and 13 days after the most recent bimekizumab injections. O [redacted] laboratory test results	This serious event of Crohn's disease was assessed as "possibly related" to study drug, and "not resolved". These assessments appear reasonable.

		revealed ALT 182IU/L. On (b) (6) she was suggested to start treatment with adalimumab. On (b) (6), aspartate aminotransferase (AST) was 75IU/L and ALT was 198IU/L with normal total bilirubin; however, there were associated symptoms of diarrhea, vomiting, and nausea. On (b) (6) (b) (6) her liver function tests had become almost normal with slightly abnormal transaminase value possibly due to hepatic steatosis. On (b) (6), she underwent an EGD which showed a small sessile polyp of 2mm in the body of the stomach which was possibly glandular-cystic but without certainty. On the same day (b) (6)), a colonoscopy showed inflammation (erythema) and ulceration of the first 12cm of the ileum, slightly erythematous sigmoid region with disappearance of the vascular markings and presence of a few aphthous ulcerations of 1mm; and the clinical picture was suggestive of Crohn's disease (severe intensity) with bulbar, ileal, and sigmoid involvement without stenosis. The event occurred 284 days after the first and 57 days after the most recent bimekizumab injections.	
HS0004/ (b) (6)	36-year-old white female with a history of laser epilation. She had no history of IBD.	The subject experienced an SAE of ulcerative colitis and severe diarrhea on (b) (6).	These serious events of proctitis and ulcerative colitis were

	Her lifestyle history included past tobacco use, stopped in (b) (6). She was diagnosed with HS in 2013. Concomitant medications included birth control. She was randomized to bimekizumab 320mg sc Q2W in HS0004, and she received the first dose of the study drug on (b) (6)	The SAE of ulcerative colitis occurred 89 days after the first and 4 days after the most recent bimekizumab injections. Since 04 Jun 2021, the subject experienced continuous bleeding, weight loss, and severe reduced general condition. She was found to have anemia. On (b) (6) she underwent a colonoscopy which revealed proctitis (nonserious AE) with mild activity. On (b) (6) (b) (6) she underwent a colonoscopy. Multiple histology samples taken during the colonoscopy were not able to differentiate between other infections or chronic inflamed proctitis because of the low activity of the inflammation. She received treatment with mesalazine for proctitis and iron infusion for her iron deficiency. The action taken with study drug was reported as drug withdrawn due to the SAE of ulcerative colitis. The reaction abated after stopping the study drug. On (b) (6), she underwent a colonoscopy, and the diagnosis of the ulcerative colitis was confirmed by histology. She received mesalazine and temporary budesonide for distal ulcerative colitis, and there was a gradual improvement. On (b) (6) (b) (6) an ileocolonoscopy revealed distal ulcerative colitis in gradual remission. Rectal examination revealed non irritated perianal	assessed as “probably related” to study drug, and “not resolved”. These assessments appear reasonable.

		region with no hemorrhoids and normal sphincter tone.	
HS0005/ [redacted]	29-year-old Asian male who was first diagnosed with HS in 2012. Concomitant medications were loperamide, sertraline, and rabeprazole. On [redacted] he was randomized to bimekizumab 320mg sc every 2 weeks in HS0003. He received the first dose of study drug on [redacted] At Week 16 (26 Oct 2021), the study participant started treatment with bimekizumab 320mg sc Q4W. The study participant completed the study and received the final dose on [redacted]. He then entered HS0005 on [redacted]. He received the first dose of bimekizumab 320mg sc Q4W on [redacted].	The subject experienced a nonserious AE of gastroenteritis on [redacted]. He experienced a nonserious AE of moderate colitis on [redacted], 344 days after the first bimekizumab injection in HS0003, and 10 days after the first and the most recent bimekizumab injection in HS0005. He received mesalazine and prednisone as treatment for the event. On [redacted], a colonoscopy was performed which showed pancolitis. The action taken with study drug was reported as drug withdrawn due to the colitis. The event was reported as not resolved at the time of this report.	This nonserious event of colitis was assessed as “probably related” to study drug, and “not resolved”. These assessments appear reasonable.
HS0005/ 50202-18562	44-year-old female with a history of migraine, pilonidal cyst, knee deformity, IBD, Crohn's disease, UC, papilloma virus infection and appendicitis. Her lifestyle history included current tobacco use. She was first diagnosed with HS in 1999. Concomitant medications included	The subject experienced a nonserious AE of mild erythema nodosum on [redacted]. She experienced a nonserious AE of moderate Crohn's disease on [redacted] 357 days after the first bimekizumab injection in HS0004, and 21 days after the first and 7 days after the most recent bimekizumab injections in HS0005. The nonserious AE of moderate gingival pain a few days later. The action	This nonserious event of Crohn’s disease flare in a subject with a history of IBD were assessed as “possibly related” to study drug, and “not resolved”. Details of the diagnostic workup were not

	cannabidiol, clobetasol, birth control, ketoconazole, urea, and NSAIDs. She entered HS0004 on (b) (6) and was randomized to bimekizumab 320mg sc Q2W. She received the first dose of study drug on (b) (6) At Week 16 (b) (6) (b) (6)), she continued to receive bimekizumab 320mg sc Q2W. The study participant completed the study and received the final dose on (b) (6). She then entered HS0005 on (b) (6). She received the first dose of bimekizumab 320mg sc Q2W on (b) (6)	taken with study drug was reported as drug withdrawn due to the Crohn's disease and gingival pain. The events were reported as not resolved at the time of this report.	provided; however, these assessments appear reasonable.
HS0005/ (b) (6)	21-year-old white female with a history of keratosis pilaris, psoriasis, IBD and ulcerative colitis. Her lifestyle history included no tobacco use. She was first diagnosed with HS in 2019. Concomitant medications included mesalamine, cyproterone with ethinylestradiol, mometasone, amoxicillin, probiotics, and tylenol with codeine. She was randomized to bimekizumab 320mg sc every 2 weeks in HS0003. She received the first dose of study drug on (b) (6) (b) (6) At Week 16 (b) (6) she started treatment with bimekizumab 320mg	The subject experienced a nonserious AE of mild ulcerative colitis (first event) on (b) (6) (b) (6), 417 days after the first bimekizumab injection in HS0003, and 81 days after the first and 19 days after the most recent bimekizumab injections in HS0005. She received mesalazine and prednisolone as treatment medications for the event. The action taken with study drug was reported as drug interrupted due to the ulcerative colitis (first event). Previously, she received the study drug from (b) (6). The study drug was restarted on (b) (6). The event resolved on (b) (6), 81 days after onset. She experienced a nonserious AE	These nonserious events of ulcerative colitis flare in a subject with a history of UC were assessed as “possibly related” to study drug, and “not resolved”. Details of the diagnostic work up were not provided; however, these assessments appear reasonable.

	sc Q4W. She completed the study and received the final dose on (b) (6). She then entered HS0005 on (b) (6). She received the first dose of bimekizumab 320mg sc Q4W on 06 Oct 2021.	of mild ulcerative colitis (second event) on 16 Jan 2023, 804 days after the first bimekizumab injection in HS0003, and 468 days after the first and 20 days after the most recent bimekizumab injections in HS0005. She received mesalazine and prednisolone as treatment medications for the event. The action taken with study drug was reported as drug withdrawn due to the ulcerative colitis (second event). The event was reported as not resolved at the time of this report.	
HS0005/ (b) (6)* *Note: This case was identified in the 120 day safety update.	63-year-old white female with a history of IBD, ulcerative colitis, and vitamin D deficiency. Her lifestyle history included no tobacco use. She was first diagnosed with HS in 2018. Concomitant medications included vitamin D, iron, mesalazine, and birth control. She was randomized to bimekizumab 320mg sc Q2W in HS0003. She received the first dose of study drug on (b) (6). At Week 16 (b) (6)), she continued to receive bimekizumab 320mg sc Q2W. She completed the study and received the final dose on (b) (6). She then entered HS0005 on (b) (6). She received the	The subject experienced a nonserious AE of mild ulcerative colitis flare on (b) (6) 529 days after the first bimekizumab injection in HS0003, and 192 days after the first and 10 days the most recent bimekizumab injections in HS0005. The action taken with study drug was reported as dose not changed due to the ulcerative colitis (ulcerative colitis flare). The event resolved on (b) (6) 4 days after onset. She continued in the study.	This nonserious event of ulcerative colitis flare in a subject with a history of UC was assessed as “possibly related” to study drug, and “resolved”. Details of the diagnostic work up and treatment of the UC flare were not provided; however, these assessments are probably reasonable

	first dose of bimekizumab 320mg sc Q2W on (b) (6).		

In general, based on the clinical summaries/narratives provided by the applicant, the 8 cases that were adjudicated as “definite” or “probable” appear reasonably likely to represent IBD. Three of the cases occurred in subjects with a history of IBD, two of whom were on concomitant medications for the treatment and maintenance of IBD. Of the three cases that occurred in subjects with a history of IBD, two resulted in discontinuation of therapy, and in one case flare symptoms were successfully treated and study therapy was continued. A clear relationship between every 2 week dosing vs every 4 week dosing and development of IBD symptoms wasn’t observed; however, the numbers of subjects in the study who developed new onset IBD or who had preexisting IBD were too small to draw definitive conclusions.

Recommendations for labeling:

Section 5: WARNINGS AND PRECAUTIONS

The applicant did not proposed any changes to the previously negotiated Warning related to IBD, this appears appropriate, and no additional revisions are recommended to section 5.5.

5.5 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: ADVERSE REACTIONS, Clinical Trials Experience

The applicant proposed the following addition in section 6.1 under “Hidradenitis Suppurative Clinical Trials, Specific Adverse Reactions”

(b) (4)

We do not agree that microscopic colitis should be included in the discussion of inflammatory bowel disease cases. Microscopic colitis is a chronic inflammatory condition of the colon that is distinct from Crohn’s disease, ulcerative colitis, and inflammatory bowel disease, with clinical

characteristics, epidemiology, associated risks, endoscopic findings, and histologic findings that are also distinct. Therefore, we did not include subjects with microscopic colitis (HS0004/ (b) (6) (b) (6) or HS0004 (b) (6) in our analysis. However, upon review of the subject narratives, we did include HS0005/ (b) (6) and HS0005/ (b) (6) in our analysis of the number of cases of IBD that were seen. Additionally, we used exposure data (number of patients and patient years) from the phase 3 studies at the time of the original submission/database lock rather than including the phase 2 study (given that the dosage and duration of bimekizumab treatment differed between the phase 2 and 3 studies as well as that all other safety analyses intended for inclusion in labeling focus on the phase 3 studies) or the 120 day safety update. Therefore, we recommend the following revisions (~~strikeout~~ = deletion; double underline = addition) of section 6.1 to reflect the adjudicated cases of IBD in the HS studies:

> *Inflammatory Bowel Disease*: In clinical trials in subjects with hidradenitis suppurativa, subjects with active inflammatory bowel disease were excluded. In these trials, which included (b) (4) 995 subjects exposed to BIMZELX accounting for (b) (4) 1272 patient-years, adjudicated cases of new onset of inflammatory bowel disease (including ulcerative colitis (UC), Crohn's disease (CD) and (b) (4) undetermined) occurred in (b) (4) 5 subjects (0. (b) (4) 39 per 100 patient-years); the majority of these cases were serious, and all resulted in discontinuation of therapy. Additionally, flares of pre-existing IBD occurred in 2 subjects, which resulted in discontinuation of BIMZELX in both.

On 10/23/2024 the applicant accepted our recommendations with only minor changes.

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/s/

ARUSHI M DEFONSEKA
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TARA A ALTEPETER
10/31/2024 10:51:11 AM

Division of Dermatology and Dentistry

REGULATORY PROJECT MANAGER LABELING REVIEW

Application: BLA 761151 S-010

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

Applicant: UCB, Inc.

Labeling Reviewed

Submission Date: January 19, 2024

Receipt Date: January 19, 2024

Background and Summary Description:
BLA 761151 Bimzelx (bimekizumab-bkzx) injection, for subcutaneous use was approved on October 17, 2023. This Prior Approval Supplement (PAS) (BLA 761151 S-0109) submitted on January 19, 2024, provides for the addition of adults with moderate to severehidradenitis suppurativa indication.

The Applicant also submitted efficacy supplements to add indications (S-005: Adults with active psoriatic arthritis, S-006: Adults with active ankylosing spondylitis, and S-007: Adults with active non-radiographic axial spondyloarthritis, which were reviewed in the Division of Rheumatology & Transplant Medicine. These supplements were approved on September 20, 2024. In addition, the efficacy supplement S-009 to add a new primary container (the 2mL prefilled syringe, which is assembled into two new 2mL device presentations, a single-dose prefilled syringe and a single-dose prefilled autoinjector) was submitted to the Division of Dermatology and Dentistry on December 13, 2023, and approved on October 11, 2024.

Review

The Prescribing Information submitted was in Physician Labeling Rule (PLR) and Pregnancy and Lactation Labeling Rule (PLLR) format.

The review team (consisting of the Associate Director for Therapeutic Review, Clinical, Clinical Pharmacology, Office of Product Quality Assessment, Associate Director for Labeling, Division of Medical Policy Programs, Clinical Outcomes Assessment, Division of Psychiatry, Division of Gastroenterology, Division of Hepatology and Nutrition/Drug-induced Liver Injury Team, Office of Prescription Drug Promotion, and Division of Medication Error Prevention and Analysis) reviewed the Applicant's proposed labeling and provided the initial recommendations in the labeling which was conveyed in the Agency proposed labeling to the Applicant on

Reference ID: 5481272

October 15, 2024.

The Applicant was asked to incorporate the proposed changes in the current, approved labeling. The Applicant provided the requested labeling on October 23, 2024. The Agency responded to the Applicant's edits on November 4, 2024. The Applicant responded on November 6, 2024, and requested that Dr. Jill Lindstrom and Dr. Nikolay Nikolov review the labeling. On November 12, the review team met with Dr. Jill Lindstrom and Dr. Nikolay Nikolov to review the labeling. The labeling was returned to the Applicant on November 14, 2024. The Applicant responded on November 15, 2024. On November 18, 2024, the Agency met (via teleconference) with the Applicant to discuss the Agency's proposed changes to section 5 of the labeling. The Applicant submitted agreed upon labeling on November 18, 2024.

A comparison of the labels dated October 17, 2023, and January 19, 2024, was conducted. No discrepancies or changes other than the ones relevant to this supplement were noted.

Recommendations

Approval is recommended with the labeling received from the Applicant on November 18, 2024.

Strother D. Dixon	November 18, 2024
Regulatory Project Manager	Date
CAPT Renmeet Grewal, PharmD, MS, RAC	November 18, 2024
Director, Project Management Staff, Division of Regulatory Operations for Immunology and Inflammation (DRO – II)	Date

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

/s/

STROTHER D DIXON
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RENMEET GREWAL
11/19/2024 01:59:49 PM

CLINICAL OUTCOME ASSESSMENT (COA) CONSULT REVIEW

COA Tracking ID:	C2024047
BLA# (Reference IND#)	sBLA 761151 S-010 / IND 134700
Applicant:	UCB, Inc.
Established Name/Trade Name:	BIMZELX® (bimekizumab)
Indication:	Treatment of adult patients with moderate to severe hidradenitis suppurativa.
PDUFA Goal Date:	November 19, 2024
Review Division:	Division of Dermatology and Dentistry
Clinical Reviewer:	Kevin Clark, M.D.
Clinical Team Leader (TL)	Melinda McCord, M.D.
Regulatory Project Manager:	Strother Dixon
COA Reviewer:	Yasmin Choudhry, M.D.
COA Deputy Director:	Selena Daniels, PharmD., Ph.D.
COA Division Director:	David Reasner, Ph.D.
Patient-Focused Statistical Scientists (PFSS) Reviewer:	Monica Morell, Ph.D.
Instruments reviewed:	1. Hidradenitis Suppurativa Symptom Daily Diary ☒ Patient-reported outcome (PRO)
	2. Hidradenitis Suppurativa Quality of Life ☒ Patient-reported outcome (PRO)

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6. APPENDICES 33

Reference ID: 5461541

APPENDIX A: HSSDD WORST SKIN PAIN ITEM 34
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1. EXECUTIVE SUMMARY

In this submission, the Applicant is seeking to update the United States Prescribing Information (USPI) for BIMZELX® (bimekizumab) to include a new indication for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS). The specific COA-related labeling claims are for improvement in worst skin pain and health-related quality of life (HRQoL) based on data from two identical, multi-center randomized, double-blind, placebo-controlled phase 3 studies (Studies HS0003 and HS0004).

The primary objective of this review is to evaluate from a COA perspective if the submitted information supports the COA-related labeling claims related to the concept of interest.

The secondary efficacy COA endpoints (adjusted for multiplicity) proposed for labeling are:

- Absolute change from Baseline in the Worst HS Skin Pain score at Week 16, as assessed by the "worst pain" item (11-point numeric rating scale) in the Hidradenitis Suppurativa Symptom Daily Diary (HSSDD)
- Pain response (defined as a decrease from Baseline in HSSDD weekly worst skin pain score at or beyond the threshold for clinically meaningful change) at Week 16

The exploratory efficacy COA endpoint proposed for labeling is:

- Absolute change from Baseline in Hidradenitis Suppurativa Quality of Life (HiSQOL) domain scores (symptoms, psychosocial, activities, adaptations)

Data from Study HS0003 demonstrated that bimekizumab Q2W was not statistically superior to placebo for pain response (i.e., ≥ 3-point decrease from baseline in Worst HS Skin Pain score at Week 16). Therefore, statistical superiority of bimekizumab Q4W over placebo cannot be claimed for any of the secondary efficacy endpoints per the multiplicity testing strategy. In Trial HS0004, both bimekizumab Q2W and bimekizumab Q4W were statistically superior to placebo on the 1st secondary endpoint (i.e., HiSCR75 at Week 16); however, both dose regimens of bimekizumab were not statistically significant to placebo (p-values ≥ 0.497) for the 2nd secondary endpoint (i.e., at least 1 flare by Week 16). Consequently, per the multiplicity testing procedure, statistical significance of the remaining secondary endpoints cannot be claimed in Trial HS0004 (which includes the Worst HS Skin Pain-based endpoints).

For both studies, the HisQOL-based endpoints were exploratory endpoints and, as such, there was no formal hypothesis testing.

From a COA perspective, the HSSDD Worst HS Skin Pain score could potentially support labeling claims, if supported by the clinical trial study design and statistical analysis. Given that

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the results for the HSSDD Worst HS Skin Pain-based endpoints were not statistically significant, DCOA ultimately defers to the Division whether a descriptive claim is acceptable. However, we recommend that the term "skin pain" should be further defined. The HiSQOL-based endpoints were collected for exploratory purposes, and therefore was not reviewed at the request of the Division.

2 REVIEW CONCLUSIONS

The Applicant submitted an evidence dossier for HSSDD. The HSSDD Worst HS Skin Pain item was reviewed for content validity and other measurement properties, as well as score interpretability (i.e., interpretation of meaningful within-patient score change).

Review Summary

- The HSSDD Worst HS Skin Pain item assesses an important aspect of HS (i.e., pain intensity).
- The HSSDD Worst HS Skin Pain item appears to be well-understood; however, patients did not use the term skin pain when characterizing their HS experience.
- The Applicant has generally established the other measurement properties for the HSSDD Worst HS Skin Pain item.
- Anchor-based analyses to assess meaningful within-patient change in the HSSDD Worst Skin Pain score between Baseline and Week 16 indicates patients consider a reduction of between 2.4 and 4.8 points to be meaningful. The observed treatment effect on the HSSDD Worst Skin Pain endpoint substantiated a clinically meaningful within-patient improvement in patients receiving bimekizumab compared to placebo.

Key Issues Identified

- Issue 1: Content Validity
    - While pain is a relevant and an important concept for the target population, based on the patient interview transcripts, the term "skin pain" was not used by patients when describing their HS experience. Participants described their HS-related pain generally using the following terms: sore, extreme pain, very painful, feeling like pinching/hurts, thumping sensation, and stabbing. All participants reported that the pain was related to the lesions, boils, and cysts.

3 RECOMMENDATIONS FOR FUTURE STUDIES

For future clinical trials in this indication, sponsors should consider the following:

- Qualitative studies should be designed to provide a complete understanding of the disease and/or treatment including presentation of symptoms and associated impacts (e.g., bother) in the target population, as well as establish the appropriateness (content relevance) and comprehensiveness of the assessment (e.g., conceptual coverage). Qualitative studies should generating in-depth information about the patient experience in

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their own words; this should help inform the wording of the measurement concept in the COA.

4 BACKGROUND AND CORRESPONDENCE ON CLINICAL OUTCOME ASSESSMENT(S)

Regulatory Background:

- There have been previous communications related to the sponsor's COA measurement strategy, which included the following (not an exhaustive list):

    - Advice/Information Request letter dated 16 Aug 2022 (IND 134700)
        - Communicated that the results of the interim analyses for the responder definition and clinically important difference in Skin Pain were inconclusive.
        - Requested a rationale and justification for the primary target anchor change category that represents a clinically meaningful change to patients on the Patient Global Impression of Severity (PGIS) measure.
        - Requested a rationale and justification for the target Patient Global Impression of Change (PGIC) response category that represents a clinically meaningful change to patients.

      Reviewer's comment(s): *The Applicant's results of the interim analyses dated 17 Feb 2022 were reviewed to evaluate the score interpretability of the HSSDD Worst Skin Pain score. Refer to the PFSS Review dated June 26, 2022 (DARRTS Reference ID: 5005358).*

    - Advice/Information Request letter dated 21 Jan 2020 (IND 134700)
        - Requested exact copies of the COAs and anchor measures that would be administered in Studies HS0003 and HS0004.
        - Commented on the power calculation assumptions for the COAs (i.e., based on a mean change from baseline value).
        - Agreed that a single item 11-point numeric rating scale, in principle, is fit-for-purpose to assess pain intensity at its worst.
        - Requested details on the scoring of the HSSDD Skin Pain item score.
        - Requested evidence of content relevancy of the Dermatology Life Quality Index (DLQI).
        - Identified limitations of the proposed anchor scales (e.g., indistinguishable response categories, recall period does not match target instrument).
        - Suggested exit interviews or surveys to cognitively interview patients.

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- Type B End-of-Phase 2 Meeting Minutes dated 01 Aug 2019
  - Agreed that the Patient Global Assessment (PGA) of skin pain may be an acceptable option to assess pain intensity.
  - Recommended assessing pain intensity at its worst for the secondary endpoint instead of 30% reduction in pain.
  - Recommended using anchor-based methods to determine meaningful change thresholds in the target COAs (using phase 2 data).

- Advice/Information Request letter dated 26 Sept 2017 (IND 134700)
  - Identified limitations of the DLQI (issues of content validity, multibarreled items etc.)

Disease Background:
Hidradenitis suppurativa is a chronic, inflammatory, and recurrent skin condition characterized by painful, deep-seated, and inflamed lesions typically located in the intertriginous areas of the body (e.g., axillae, inguinal, and anogenital regions). The inflamed nodules can progress to abscess formation and may rupture to form fistulas and subsequent scarring which can lead to contractures and limitations in limb mobility.

Investigational Product:
Bimekizumab is a humanized, full-length monoclonal antibody of immunoglobulin G1 subclass. Bimekizumab has a high affinity for human interleukin (IL)-17A and IL-17F which are key pro-inflammatory cytokines that play important roles in autoimmune and inflammatory diseases.

Materials reviewed:
The materials reviewed for this submission are summarized in Table 1.

Table 1. Materials reviewed

Document	SDN	eCTD #	Date Received
sBLA Submission including • Study protocols • Clinical study reports	165	0116	19 Jan 2024
• HS PRO Evidence Dossier HSSDD			
Response to 31 Jul 2024 Information Request			06 Aug 2024
• EVM-26511 HS CDUT Interviews transcripts			

• Studies HS0003 HS0004 anchor scales screenshots		
Communications and Reviews	**DARRTS Ref ID**	**Date**
Information Request (BLA 761151)	5422968	31 July 2024
Information Request/Advice letter	5030901	16 Aug 2022
Information Request/Advice letter	4549196	21 Jan 2020
Type B End-of-Phase 2 Meeting Minutes	4470936	01 Aug 2019
Advice/Information Request letter	4157109	26 Sept 2017
Statistical Review and Evaluation	5005358	27 Jun 2022
Advice Information Request letter	4549196	21 Jan 2020
Previous COA Review: C2022190_IND 134700_Choudhry	5020025	29 Jul 2022
Previous COA Review: C2019461_ IND 134700_Choudhry	4542990	07 Jan 2020
Previous COA review: C2019172_IND 134700_Choudhry	4534196	19 Dec 2019
Previous COA review: C2017191_IND 134700_Choudhry	4143194	15 Sept 2017

5 CLINICAL OUTCOME ASSESSMENT REVIEW

5.1 Clinical Trial Population

The target population for Studies HS0003 and HS0004 were adults (≥18 years) with a diagnosis of HS[1]. Eligible participants must have had:

- HS lesions present in at least two distinct anatomic areas (e.g., left and right axilla), one of which must be at least Hurley Stage II or Hurley Stage III at both the Screening and Baseline visits.

[1] Based on clinical history and physical examination for at least 6 months prior to the Baseline visit; diagnosis must be verifiable through medical notes and documentation.

- Moderate to severe HS defined as a total of ≥5 inflammatory lesions (ie, number of abscesses plus number of inflammatory nodules) at both the Screening and Baseline visits.

A complete list of the inclusion and exclusion criteria is summarized in Section 5.1 of the clinical study protocol for Studies HS0003 and HS0004.

Reviewer's comment(s):
For Study HS0003, the randomized set consisted of 144 study participants in the bimekizumab 320mg Q4W group, 289 study participants in the bimekizumab 320mg Q2W group, and 72 study participants in the placebo group. The mean age of all study participants was 36.7 years, with a range of 18 to 78 years of age. More than half of the participants were female (63.0%), and the majority of study participants were White (77.8%), not of Hispanic or Latino ethnicity (92.3%), and in the nonJapanese ethnic subgroup (99.2%). The mean body weight and mean BMI overall were 98.42kg and 33.79kg/m^2, respectively. Study participants were most commonly enrolled in the following countries: United States (40.8%), Germany (10.3%), Greece (8.9%), and France (7.5%).

For Study HS0004, the randomized set consisted of 144 study participants in the bimekizumab 320mg Q4W group, 291 study participants in the bimekizumab 320mg Q2W group, and 74 study participants in the placebo group. The mean age of all study participants was 36.6 years of age, with a range of 18 to 75 years of age. Half of the participants were female (50.7%), and the majority of study participants were White (81.5%), not of Hispanic or Latino ethnicity (93.7%), and in the non-Japanese ethnic subgroup (94.1%). The mean body weight and mean BMI overall were 96.09kg and 32.34kg/m^2, respectively. Study participants were most commonly enrolled in the following countries: Poland (24.4%), the United States (22.2%), Bulgaria (12.0%), and France (10.2%).

Baseline demographics and disease characteristics (pooled; n=1014) were reflective of the study population with moderate to severe HS. The mean and median HSSDD worst skin pain scores were 5.47 and 5.7, respectively.

Clinical Trial Design

The Applicant conducted two identical randomized, double-blind, placebo-controlled, multicenter, phase 3 studies (Studies HS0003 and HS0004)[2] to evaluate the efficacy and safety of bimekizumab in study participants with moderate to severe HS.

The studies consisted of a:

- Screening Period of 14 days to up to 5 weeks;

[2] Note that some of the secondary endpoints differed across the two studies.

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- Double-blind, 48-week Treatment Period comprising a 16-week Initial Treatment Period and 32-week Maintenance Treatment Period; and
- 20-week Safety Follow-up Period following the final injection of investigational medicinal product if study participants did not enter a subsequent extension study (HS0005) or withdraw prematurely from treatment.

Study participants were randomized in a 2:2:2:1 ratio (stratified by Hurley Stage and current antibiotic use) to 1 of 4 treatment sequences:

- Bimekizumab 320mg Q2W from Weeks 0 to 48
- Bimekizumab 320mg Q4W from Weeks 0 to 48
- Bimekizumab 320mg Q2W to Week 16, continuing on 320mg Q4W from Weeks 16 to 48
- Placebo to Week 16, continuing on bimekizumab 320mg Q2W from Weeks 16 to 48

5.2 Endpoint Position and Definition

The placement of the COAs in the endpoint hierarchy, including the endpoint definition Studies HS0003 and HS0004 is summarized below:

Primary efficacy endpoint

- Hidradenitis Suppurativa Clinical Response (HiSCR50), defined as at least a 50% reduction from Baseline in the total abscess and inflammatory nodule count, with no increase from Baseline in abscess or draining tunnel count at Week 16.

Secondary efficacy endpoints (multiplicity adjusted)

- HiSCR50 at Week 16
- Flare (defined as a ≥25% increase in AN count with an absolute increase in AN count of ≥2 relative to Baseline) by Week 16 (Study HS0003 only)
- Absolute change from Baseline in Dermatology Life Quality Index (DLQI) Total Score at Week 16
- Absolute change from Baseline in Skin Pain score at Week 16, as assessed by the Worst Skin Pain item (11-point numeric rating scale) in the HSSDD
- Pain response (defined as a decrease from Baseline in HSSDD weekly Worst Skin Pain score at or beyond the threshold for clinically meaningful change) at Week 16

Reviewer's comment(s): *For the key secondary endpoint, change from Baseline in worst skin pain score was defined as the average Week 16 HSSDD Worst Skin Pain score minus the Baseline worst skin pain score.*

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5.3 Targeted Clinical Outcome Assessment-Related Labeling Claim(s)

The Applicant has proposed the following specific targeted COA-related labeling claims (in *blue italicized text*):

(b) (6)

Reviewer's comment(s):
From a COA perspective, (b) (6) *, this reviewer defers to the Division whether a descriptive claim is acceptable. If a descriptive claim is given, this reviewer recommends that the term "skin pain" be qualified as lesion pain. Based on the review of the anchor-based analyses supplemented with empirical cumulative distribution function (eCDF) curves, a 3-4 point change in the HSSDD Worst Skin Pain score falls within the meaningful change threshold range of 2.4 to 4.8 and appears clinically meaningful.*

Based on discussion with the Division, the HiSQOL-based endpoints will not be labeled as they were exploratory endpoints.

5.4 Clinical Outcome Assessment(s) Clinical Outcome Assessment Description(s)

5.4.1.1 Hidradenitis Suppurativa Symptom Daily Diary (HSSDD) Worst Skin Pain item

The HSSDD Worst Skin Pain item (Appendix A) is a single item within the HSSDD, a 5-item PRO instrument designed to assess HS signs/symptoms of HS. The Worst Skin Pain item is designed to assess skin pain intensity at its worst using an 11-point numeric rating scale (NRS) ranging from 0 ("No skin pain") to 10 ("Skin pain as bad as you can imagine"). The recall period is the previous 24 hours. The HSSDD Worst Skin Pain was administered electronically daily (at

the end of the day) from Screening through Week 16.

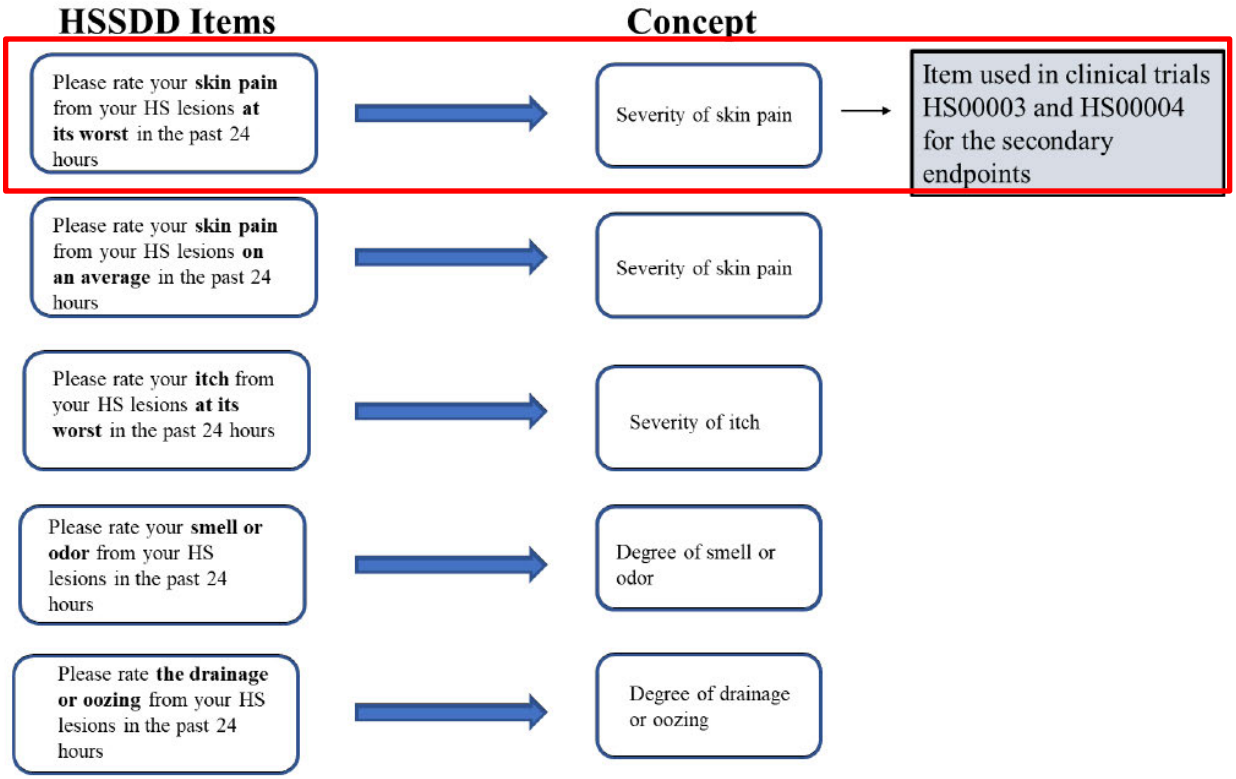
Reviewer's comment(s): *The copy of the HSSDD included in the BLA submission does not include the instructions to the participants. However, the Applicant developed instructions for the investigators/clinical site staff for use of the electronic patient-reported outcome (ePRO) device, including preparation of the device for participant use and the handling of device hardware components. Training materials were not specifically developed for participants. The ePRO device was handed out to the participants who were asked to complete the HSSDD daily in a quiet place.*

5.4.2 Conceptual Framework(s)

5.4.2.1 HSSDD Worst Skin Pain item

The conceptual framework of the HSSDD is shown in Figure 1. The HSSDD Worst Skin Pain item is outlined in a red box.

Figure 1. Conceptual framework of HSSDD



Abbreviations: HS = Hidradenitis Suppurativa; HSSDD = Hidradenitis Suppurativa Symptom Daily Diary

Source:Applicant's PRO evidence dossier (Figure 4-1)

5.4.3 Scoring Algorithm

5.4.3.1 HSSDD Worst Skin Pain item

The HSSDD Worst Skin Pain item generates a single item score that ranges from 0 to 10, with a higher score indicating greater skin pain intensity.

Weekly averages were derived for the HSSDD Worst Skin Pain item for weeks matching the post-Baseline dosing weeks up to Week 16. A weekly average was calculated as the sum of the scored item over the course of the study week divided by the number of days on which the item was completed. The weekly averages were relative to the respective visit date except for Baseline, which was anchored to the first dose of study drug.

A weekly average was only calculated if at least four non-missing values (not necessarily consecutive) were available. Otherwise, the HSSDD weekly average score for the given question was set to missing. Baseline was computed as the average from the first seven consecutive day period in which there were at least four non-missing entries. That is, the first seven consecutive days prior to the Baseline visit were considered, but not including the Baseline visit day itself. If there were at least 4 non-missing values (not necessarily consecutive), then the Baseline average was calculated. If there were less than four values, the seven consecutive day period was moved one day earlier. If there were at least four non-missing values (not necessarily consecutive) in that period, then the Baseline average was calculated. This continued until there were at least four non-missing values in a seven consecutive day period in the 14 days prior to Baseline. If there was no period in which there were at least four non-missing entries, then the Baseline value was set to missing.

Reviewer's comment(s): *Missing data imputation was applied to the weekly averages and not to the individual daily PRO data. Refer to the Statistical Review for mode details regarding imputation methods.*

The Applicant conducted a simulation analysis to assess the appropriateness of the current weekly scoring rule (i.e., 4 out of 7 daily scores required for a given week) used to derive the weekly symptom item scores of the HSSDD.

The simulation analysis results showed that there were no significant differences in SDs of weekly symptom item scores observed when comparing the current scoring rule with the zero-day missing scenario across different timepoints (Baseline, Weeks 2, 4, 6, 8, 10, 12, 14, and 16).

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5.4.4 Content Validity

5.4.4.1 HSSDD Worst Skin Pain Item

The Applicant completed the following instrument development activities to evaluate the content validity of the HSSDD Worst Skin Pain Item:

- Literature review and PRO Gap Analysis
- Expert input (interviews with key opinion leaders)
- Item generation
- Patient input (cognitive interviews and usability testing)

A summary of the results for each activity is described below. Refer to Section 5 and Appendix D of the Applicant's PRO evidence dossier ("Patient-Reported Outcome Dossier: Hidrdenitis Suppurativa Symptom Daily Diary (HSSDD) dated 05 May 2023 Version 1.0") for full details regarding the methodology and results of each activity.

5.4.4.1.1 Literature review and PRO Gap Analysis

Literature Review

A review of published literature was conducted to identify concepts of interest in HS to inform the development of the HSSDD. Three qualitative studies were identified along with 41 published studies from Medline/Embase and 12 ongoing trials from clinicaltrials.gov. The main concepts measured in all retrieved references were disease severity, HRQoL, and pain. Specifically, results from this review showed that HS is a chronic and painful skin condition presenting with inflammatory nodules and abscesses associated with pain, depression, anxiety, and disability.

The Applicant also conducted a post-hoc literature review to further understand, from the patient perspective, the experience of skin pain related to HS and other core HS symptoms (smell/odor, oozing/drainage from HS lesions, and itch), and to support the content validity of the preliminary HSSDD, an additional targeted literature review of both published and grey literature was performed. Searches were conducted using Ovid (Medline, Embase, and PsycINFO) databases, grey literature sources (Google Scholar), and clinical trial databases (clinicaltrial.gov, clinicaltrialsregister.eu). Searches combined condition-related terms with assessment-related terms using Boolean operators and were tailored to focus on literature which discussed skin pain, odor, oozing, and itch in relation to HS.

In total, 318 articles were reviewed for title/abstract, and 112 trials were reviewed for COAs, resulting in 430 total articles. From this 430, 69 publications and 64 trials were identified as eligible for full text review, and from these, a total of 10 articles were selected for the literature review. Pain was mentioned in all articles included in the literature review. Skin pain and odor were discussed in 4 (40%) articles, while itching and drainage were mentioned in 6 (60%). All articles reported the negative impact of HS symptoms on HRQoL for patients. A summary of

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each article's contents and relevant discussion points is presented in Table 5–2 of the Applicant's PRO evidence dossier.

PRO Gap Analysis

From a review of existing PRO measures in the published literature, the Dermatology Life Quality Indext (DLQI) was the most common instrument used in HS (23 of the 41 published studies and 3 of the 12 ongoing trials identified). In addition, the Skindex, Hidradenitis Suppurativa Impact Assessment, 36-item Short Form Health Survey (SF-36), Treatment Satisfaction Questionnaire for Medication, Hidradenitis Suppurativa Symptom Assessment, and EQ-5D were used to assess HRQoL in HS patients. Based on these findings, the Applicant identified strengths and weaknesses for each PRO measure. Although the DLQI was the most common PRO measure, the Applicant concluded that there was a lack of information on internal consistency reliability in HS, and further evidence was needed regarding its responsiveness in HS.

5.4.4.1.2 Expert Input

The Applicant conducted one-on-one telephone interviews with two key opinion leaders (KOLs). participated in a semi-structured, 1-on-1 telephone interview. The KOLs mentioned that the most important symptom that causes discomfort and complaints in their HS patients is pain. These experts indicated that the inflammatory lesions are very painful, and that they cause further discomfort when they drain.

Although both KOLs perceived that the DLQI was the most common tool for assessing HRQoL in HS, 1 KOL stated that the measure fails to capture problems specific to HS patients. The KOL added that a disease-specific questionnaire addressing pain and all factors that affect patients is needed. Other PRO tools mentioned by the KOLs included the EQ-5D, Health Assessment Questionnaire, Functional Assessment of Chronic Illness Therapy – Fatigue, and SF-36.

Reviewer's comment(s): *Per the Applicant, a formal report was not developed. However, the interview transcripts were provided as an appendix to the PRO evidence dossier (Appendix E).*

5.4.4.1.3 Item Generation

The HSSDD was developed based on the literature review and expert input. It included five items that measure HS sign/symptom severity in the previous 24 hours. The HSSDD items assess itch, smell/odor, and drainage/oozing due to HS.

Reviewer's comment(s): *The Applicant did not conduct concept elicitation interviews prior to generating the content of the HSSDD.*

5.4.4.1.4 Patient Input

The Applicant conducted 90-minute cognitive interviews using the web-based teleconference platform Zoom to:

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- Confirm the relevance of the sign/symptoms covered by the HSSDD for participants with HS
- Evaluate the comprehension of the content in the electronic versions of the HSSDD
- Evaluate the acceptability and usability of the electronic version of the HSSDD,

One-on-one video interviews were conducted with 20 US HS participants recruited from one academic medical center between September and November 2021. Participants had to have:

- a clinically confirmed diagnosis of HS* for at least six months prior to Screening.
- moderate-to-severe HS defined as a total of ≥ five inflammatory lesions (abscess and/or inflammatory nodules) at Screening
- HS lesions present in at least two distinct anatomic areas (e.g., left and right axilla), one of which must be at least Hurley Stage II or Hurley Stage III at Screening.

Reviewer's comment(s): *The inclusion criteria for the qualitative study appears to be comparable to those for the registration studies.*

The results from these interviews are summarized below.

- A total of 20 adult participants were interviewed. The majority of the participants were White (n=12/20, 60.0%), Non-Hispanic (n=17/20, 85.0%), females (n=16/20 , 80%) with a mean age of 40 years (standard deviation [SD]: 4.26; median: 41.5 years; range: 20.0 to 64.0) and at least some college education (n= 16/20, 80.0%).
- The majority of participants (n=15/20, 75.0%) reported living with an HS diagnosis for five years or longer. Slightly more than half (n=11/20, 55.0%) considered the severity of their HS as moderate, and rated their health as fair or poor (n=12/20, 60.0%).
- On average, participants were diagnosed with moderate HS based on the Hurley Stage grading system (n=15/20, 75%) for at least eight years (SD=8.95). Antibiotics (e.g., doxycycline), antiandrogenic medication (e.g., spironolactone), immunosuppressive drugs, and minor surgeries or procedures were common past and current therapies/procedures that participants used to manage their HS.
- Most participants used electronic devices such as tablets and iPads, smartphones, laptops with touch screens (n=11 to 18, 55.0% to 90.0%) in their daily lives. Many participants (n=15/20, 75.0%) reported being very or extremely familiar with touch screen devices, and being very or extremely comfortable using such devices (n=14/20, 70.0%). Difficulty reading or using electronic devices in general was not an issue for the majority of the interview sample (n=19/20, 95.0%).
- Thirteen participants (65.0%) reported the symptom that led them to the doctor was pain. Several participants (n=11/20, 55.0%) described draining or oozing as a symptom that led them to the doctor, while four (20%) reported odor or smell as one of the reasons. No participants reported itching as a symptom that led them to the doctor.

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- All participants (n=20/20, 100.0%) reported at least one other HS symptom that led them to visit the doctor. These included lesions or its variations (e.g., boils, lumps, abscesses, cysts, tumors, pockets, nodules, pustules, abnormal pimples, sores, and blackheads; n=19/20, 95.0%; infections, puss, or swelling (n=5/20, 25.0%); bleeding or wounds (n=4/20, 20.0%); and tunneling, tracts, or sinus canals (n=4/20, 20.0%).
- Several participants (n=5/20, 25.0%) reported triggers that exacerbated their HS symptoms. These included diet (e.g., increased sugar intake; n=5/5, 100.0%), stress (n=4/5, 80.0%), smoking and alcohol intake (n=1/5, 20.0%), sweating (n=1/5, 20.0%), touching the site of flare-up (n=1/5, 20.0%), shaving (n=1/5, 20.0%), constriction (e.g., wearing tight clothing or wrapping with bandages; n=1/5, 20.0%), menstruation (n=1/5, 20.0%), soaps (n=1/5, 20.0%), and delaying time to address flare-ups (n=1/5, 20.0%).
- All core HS symptoms (drainage/oozing, skin pain, itching, smell/odor) were highly reported by more than 90% of participants. Symptoms most commonly appeared in the underarm and groin. Most participants (n=15/20, 75%) reported other symptoms, such as boils, bleeding, cysts, swelling, and tunneling.
- Common body locations where HS symptoms were experienced included the back, breast, buttocks/anus, chest, face/neck, genitals, groin/bikini line, legs/thighs, stomach, and underarms armpits.
- Most participants (n=9/20, 45.0%) rated their HS as moderate because they were symptomatic with active HS widespread across the body, or experienced flare-ups. Three participants (33.0%) considered their condition moderate because they felt their HS was less severe compared to the past (e.g., in teenage years, prior to procedure).
- Of the nineteen participants asked, most (n=18/19, 94.7%) reported change in their symptoms since diagnosis. Half of participants (n=9/18, 50.0%) reported only improvement, while others (n=7/18, 38.9%) reported only worsening. Two participants (11.1%) reported aspects of their HS that both improved and worsened.
- Some participants (n=3/9, 33.0%) reported impacts on daily activities (e.g., unable to remain in hot places for extended periods of time) and emotional health (e.g., mental exhaustion). Other impacts mentioned were limp (n=1/20, 5.00%) and embarrassment (n=1/20, 5.00%).

- Regarding the HSSDD,
    - Participants (n=10/20, 50.0%) described it as “simple,” “easy,” and “self-explanatory.” Several participants (n=10/20, 50.0%) spontaneously mentioned that the questionnaire asked the “right” or “spot on” questions relevant to HS.
        - Other feedback from participants included that the questionnaire was limiting with a 24-hour recall period, since HS can vary based on flare-up frequency (n=4/20, 20.0%), and potentially be useful for disease tracking purposes (n=2/20, 10.0%).
        - Participants also liked that the questionnaire utilized a good recall period (n=2/20, 10.0%), was short (n=1/20, 5.0%), allowed them to select rather

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than input an answer (n=1/20, 5.0%), and was not personal or offensive (n=1/20, 5.0%).

- All participants (n=20/20, 100.0%) reflected on the 24-hour recall period when answering the HSSDD items, and felt they were accurately able to recall their HS experience during this timeframe. However, two participants (10.0%) also reflected on broader recall periods, such as "in general" or "bad days."
  - Of the 15 participants asked, all but one participant (n=14/15, 93.0%) considered both daytime and evening/nighttime hours. The other participant considered daytime hours only.
- All participants (n=20/20, 100.0%) shared that the HSSDD instructions were clear by restating so in their own words, including but not limited to reflecting on HS-related symptoms, thinking about the past 24 hours, selecting only one answer, or completing at the end of the day.
- Most participants (n=19/20, 95.0%) were able to differentiate between the 0 to 10 numerical response options to select their answer. Only one participant (5.0%) reported some difficulty differentiating response options for the average skin pain item.
- All but one participant (n=19/20, 95.0%) correctly interpreted the worst skin pain item. The participant who did not understand suggested the item was asking about change in pain severity, rather than an assessment of pain severity within a specific time period. Of those participants who understood, two did not explicitly mention or highlight that the item asked about worst skin pain.

- Regarding the electronic handheld device,
  - Most participants (n=13/20, 65.0%) mentioned that it was "fine," "clear," "easy," or "self-explanatory" with a "nice set-up." Some participants (n=4/20, 20.0%) also stated that they thought it would be a helpful tool for logging and tracking HS-related information for everyday use, measuring trends, and sharing with medical professionals. Other feedback mentioned by three participants each (15.0%) included the following: the handheld questionnaire was preferred and more convenient to paper, easy to navigate and select answers, and compact (e.g., similar to a cell phone).
  - All participants (n=20/20; 100.0%) reported no difficulty completing the questionnaire on the electronic symptom daily diary, navigating from screen to screen, or manually selecting an answer with their finger. Additionally, all participants (n=20/20; 100.0%) reported no problems with viewing the questions or response options, noting that the text could be clearly read and words appeared large enough. No participants suggested changing the way the questions appeared on the screen.
  - Of the sample, only five participants (25.0%) needed to change their answer, and did not report any problems doing so. An error message appeared for only one participant (5.0%). All participants (n=20/20, 100.0%) saw and understood the final verification screen that displayed "Select OK" and "Next."

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Reviewer's comment(s): *While the Applicant referred to these as cognitive interviews, there was some time carved out in the interviews to query the participants about their HS experience. Because there was not a defined concept elicitation portion, the qualitative study lacked certain key information related to the patient experience of HS symptoms. For example, it is unclear how the pain presents (sharp, burning, etc.) and origin (e.g., lesion), what attributes of pain are most important (e.g., severity, frequency), or how participants refer to their HS-related pain in their own words, etc. Therefore, an information request (IR) was sent to the Applicant on July 31, 2024 requesting patient interview transcripts for the cognitive interviews, as well as clarification on whether concept elicitation interviews were conducted in patients with HS.*

The Applicant confirmed that concept elicitation was included in the 1.5-hour long interviews described in the Cognitive Interviewing and Usability Testing of the Electronic HSSDD, HSSQ, and HiSQOL qualitative interview report (EVM-26511-00, Sections 3.4.1 and 4.5; Appendix D of the evidence dossier. The Applicant also submitted the patient interview transcripts.

Based on review of the patient interview transcripts, this reviewer notes the following:

- *Participants (n=20) described their pain using one or more of the following terms: Sore, extreme pain, very painful, feeling like pinching/hurts, thumping sensation, or stabbing etc.)*
    - *All participants reported that the pain was related to the lesions, boils, and cysts.*
    - *All participants reported that the big boils, cysts, bleeding and pain were the reasons to seek medical advice.*

- *None of the 20 participants interviewed spontaneously mentioned "skin pain."*

- *Every participant was asked directly about skin pain (e.g., "Do you experience skin pain currently?," "Where do you have your skin pain?," " Do you ever experience skin pain?" etc.)*

- *Of the 20 participants,*
    - *Three (15 %) participants (ID# (b) (6) stated that they were not experiencing any pain at the time of the interview.*
    - *One participant (ID# 001-009) did not understand the question as intended and therefore did not provide an answer.*
    - *The remaining 16 participants responded to the interviewer's question on skin pain by describing their pain in terms extreme pain, very painful etc.*
        - *Two of the 16 (12 %) participants reported that their pain was on the skin and also below the surface.*

- *One participant (ID# (b) (6) stated "…Please rate your skin from your HS lesions as worst—" My skin pain. Just basically the pain overall from my lesions over—at its worst over the last 24 hours.*

This reviewer believes that pain is a relevant symptom in the target patient population and suggests that the term "skin pain" either be labeled as "pain"or qualified in parentheses as (b) (6) ." Based on the qualitative data, the HSSDD Worst Skin Pain item appears to be well-understood.

Overall, findings from the qualitative study generally appear to support the content validity of the HSSDD Worst Skin Pain item.

5.4.5 Other Measurement Properties

The Applicant used pooled blinded data from Studies HS0003 and HS0004 to evaluate the other measurement properties of the HSSDD Worst Skin Pain item.

The analysis population consisted of 934 participants (n=458 [49.0%] from Study HS0003 andn= 476 [51.0%] from Study HS0004).[3] The majority of participants were White (n=722/934, 77.3%), Non-Hispanic (n=832/934, 89.1%), females (n=525/934, 56.2%) with a mean (SD) age of 37 (12.2) years at Baseline. Overall, 56% of participants were Hurley Stage II at Baseline and 43% were Hurley Stage III, indicative of a moderate-to-severe HS.

At Baseline, the Patient Global Impression of Change in Severity of Skin Pain (PGI-S-SP) indicated that the majority of study participants initiated the study with moderate (43.8%) to severe (30.7%) skin pain. Study participants also reported moderate (45.7%) to severe (27.7%) HS on the Patient Global Impression of Hidradenitis Suppurativa Severity (PGI-S-HS) at Baseline.

Reviewer's comment(s): *Per the Applicant, demographics were generally similar between the HS0003 and HS0004 HSSDD Analysis Sets, except for gender, where there were more female participants in Study HS0003.*

Psychometric analyses were conducted on the blinded HSSDD analysis set, defined as all randomized study participants from both studies who had at least 1 non-missing weekly symptom item score of the HSSDD at any scheduled assessment visit. The analyses focused on Week 16 (prioritized) and Baseline.

A summary of the psychometric findings from Studies HS0003 and HS0004 is provided in the following subsections. For more details on the methodology and results of these analyses, refer to Section 6 and Appendix B of the PRO evidence dossier.

3 The analysis set was defined as all randomized study participants from both studies who had at least 1 non-missing weekly symptom item score of the HSSDD at any scheduled assessment visit.

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5.4.5.1 HSSDD Worst Skin Pain Item

5.4.5.1.1 Item descriptives and response distributions

- A total of 847 out of 934 study participants had non-missing Baseline HSSDD scores (9.3% missing).
- The mean (SD) and median HSSDD Worst Skin Pain item scores at Baseline was 5.5 (2.5) and 5.7, respectively. The mean (SD) and median HSSDD Worst Skin Pain item score at Week 16 was 3.8 (2.6) and 3.4, respectively.
- 1.5% of study participants endorsed a score of 0 at Baseline on the HSSDD Worst Skin Pain item. Less than 5% of the study participants endorsed a score of 10 at Baseline on the HSSDD Worst Skin Pain item.

Reviewer's comment(s):
There were no observed floor or ceiling effects.

5.4.5.1.2 Reliability

5.4.5.1.2.1 Test-Retest Reliability

Test-retest reliability assesses whether instrument scores are reasonably consistent over time within clinically stable patients. Test-retest reliability was assessed by estimating the intra-class correlation coefficient (ICC) for the HSSDD Worst Skin Pain score among stable study participants[4]. Based on this analysis, the ICC was 0.83.

Reviewer's comment(s): *In general, the ICC was within an acceptable and reasonable range for the analysis.*

5.4.5.1.3 Construct validity

5.4.5.1.3.1 Convergent validity

Convergent validity assesses how closely related two or more measures are that are intended to assess the same construct (concept). Convergent validity was assessed for the HSSDD Worst Skin Pain item using Spearman correlations with scores from reference measures at Baseline and Week 16. Specifically, at Baseline, the reference measures used were the International Hidradenitis Suppurativa Severity Score System (IHS4), DLQI, and HiSQOL. The strength of the correlation between two variables was interpreted as weak, moderate, strong, or very strong when the correlation coefficient was <0.3, ≥ 0.3 to <0.7, ≥ 0.7 to <0.9, or ≥ 0.9, respectively. All correlations were positive as hypothesized by the Applicant.

[4] A stable population was defined as participants with no change in the PGI-S-SP score between Baseline and Week 4.

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Based on the correlation analyses,

- The correlation (r) between the HSSDD Worst Skin Pain item and IHS4 at Baseline was 0.25. At Week 16, the correlation (r) was 0.38.

  Reviewer's comment(s): *The correlation between the HSSDD Worst Skin Pain item and IHS4 observed at Baseline was weak, whereas the correlation observed at Week 16 was moderate. Per the Applicant, the lower correlation coefficients at Baseline were likely due to inclusion criteria, which required that study participants had moderate-to-severe HS, defined as a total of ≥5 inflammatory lesions (i.e., number of abscesses plus number of inflammatory nodules, which are both included in the IHS4 score calculation at both the Screening and Baseline visits. The Applicant further states that these lower correlations between the HSSDD and IHS4 are aligned with findings from the literature where divergence between clinician-reported outcomes and PROs in general have been widely reported across disease areas.*

  This reviewer notes that the IHS4 assesses HS severity which is based on the number of nodules, abscesses, and draining tunnels [fistulae/sinuses]. It is unknown whether there is a relationship between disease severity and symptom severity.

- Correlations (r) between the HSSDD Worst Skin Pain item and DLQI item and total scores at Baseline ranged from 0.27 to 0.60. At Week 16, correlations (r) ranged from 0.25 to 0.52.

  Reviewer's comment(s): *Most of the correlations observed between the HSSDD Worst Skin Pain item and DLQI item and total scores were moderate. However, there weak correlations observed between the HSSDD Worst Skin Pain item and DLQI items 7 ("Prevented Working/Studying"; Baseline and Week 16), 8 ("Partner, Close Friends, or Relatives"; Baseline), and 9 ("Sexual Difficulties"; Baseline).*

- Correlations (r) between the HSSDD Worst Skin Pain item and HiSQOL domain and total scores at Baseline ranged from 0.35 to 0.62. At Week 16, correlations (r) ranged from 0.40 to 0.66.

  Reviewer's comment(s): *All correlations observed between the HSSDD Worst Skin Pain item and HiSQOL domain and total scores were moderate. This reviewer notes that the HiSQOL is an HS-specific measure. As expected, the correlations are higher with the Symptom domain. The lower correlations were observed with the domains that measured more distal concepts (e.g., Psychosocial).*

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5.4.5.1.3.2 Known-groups validity

Known-groups validity assesses whether instrument scores can discriminate among groups of participants known to be clinically different. Descriptive statistics and boxplots were used to assess known-groups validity. Known-groups were defined by the Hurley Stage and PGI-S-HS.

- When defining known groups by Hurley Stage at Week 16,
  - TheHSSDD worst skin pain scores differed between each of the stages (I, II, and III).
  - The HSSDD Worst Skin Pain score in the Hurley Stage II group differed from the Hurley Stage I group by a mean (95% CI) of 0.49 (-0.31, 1.30).
  - The HSSDD Worst Skin ain score in the Hurley Stage III group differed from the Hurley Stage II group by a mean (95% CI) of (0.68, 1.51).

- When defining known groups by the PGI-S-HS at Week 16, due to the small sample size in the very severe group (n=7), the "Severe" and "Very severe" groups were combined.
  - The HSSDD Worst Skin Pain scores differed between each response level (None, Mild, Moderate, and Severe or Very severe).
  - The HSSDD Worst Skin Pain score in the group responding "Mild" on the PGI-S-HS differed from the group responding "None" on the PGI-S-HS by a mean (95% CI) of 1.22 (0.71, 1.74).
  - The HSSDD Worst Skin Pain score in the group responding "Moderate" on the PGI-S-HS group differed from the group responding "Mild" on the PGI-S-HS by a mean (95% CI) of 2.14 (1.79, 2.49).
  - The HSSDD Worst Skin Pain score in the group responding "Severe" or "Very severe" on the PGI-S-HS differed from the group responding "Moderate" on the PGI-S-HS by a mean (95% CI) of 2.50 (1.99, 3.00).

- When defining known groups by IHS4 score at Week 16,
  - The HSSDD Worst Skin Pain scores differed between each of the levels (Mild, Moderate, and Severe).
  - The HSSDD Worst Skin Pain score in the IHS4 "Moderate" group differed from the IHS4 "Mild" group by a mean (95% CI) of 1.17 (0.65, 1.70)
  - The HSSDD Worst Skin Pain score in the IHS4 "Severe" group differed from the IHS4 "Moderate" group by a mean (95% CI) of 1.12 (0.68, 1.57).

- When defining known groups by the HS Physician's Global Assessment (PGA) at Week 16,
  - The HSSDD Worst Skin Pain score in the "Minimal" HS PGA group differed from the "Clear" HS PGA group by a mean (95% CI) of 0.81 (-0.65, 2.27).
  - The HSSDD Worst Skin Pain score in the "Mild" HS PGA group differed from the "Minimal" HS PGA group by a mean (95% CI) of -0.33 (-1.30, 0.64), with the

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difference in the medians also being negative (2.14 vs. 2.86, respectively; a difference of -0.72).
- The HSSDD Worst Skin Pain score in the "Moderate" HS PGA group differed from the "Mild" HS PGA group by a mean (95% CI) of 1.18 (0.67, 1.68).
- The HSSDD Worst Skin Pain score in the "Severe" HS PGA group differed from the "Moderate" HS PGA group by a mean (95% CI) of 1.02 (0.05, 1.99).
- The HSSDD Worst Skin Pain score in the "Very severe" group differed from the "Severe" HS PGA group by a mean (95% CI) of 0.41 (-0.61, 1.42), with the difference in medians being negative (5.00 vs. 5.18, respectively; a difference of -0.18).

Reviewer's comment(s):
Overall, for most of the known-group analyses, the HSSDD Worst Skin Pain item appears to be able to distinguish among clinically distinct groups as evidenced by higher HSSDD Worst Skin Pain scores for groups with more severe Hurley Stage, PGIS-HS, and IHS4. The exception was the HS PGA. Per the Applicant, the differences going in the unexpected direction for the HS PGA (i.e., decreasing worst skin pain score with more severe HS PGA group) is likely due to the small sample sizes in the clear (n=32) and minimal (n=24) groups, leading to larger uncertainty around the sample mean and distribution in the minimal group, in particular, as seen by the distribution and the wide CI in the observed score for the "Minimal" group vs. the "Mild" group (mean [95% CI]: 2.88 [1.72, 4.04] vs. 2.55 [2.17, 2.93]). Additionally, the Applicant states that it may also be that the difference between the definitions of "Clear" and "Minimal" on the HS PGA, which is the presence of at least one non-inflammatory nodule, may not have a clear or direct impact on worst skin pain. Regarding, the smaller difference in the HSSDD Worst Skin Pain score between the "Very severe"and "Severe" HS PGA groups than in the other comparisons, the Applicant suggests that it is likely due to the small sample size in the "Severe" group (n=28). This reviewer questions the adequacy of the HS PGA as a reference measure due to potential overlap of the responses.

5.4.5.1.4 Responsiveness

Responsiveness assesses the ability of an instrument to measure any degree of change when a known change in the concept of interest has occurred. Responsiveness was evaluated by (1) examining correlation coefficients (Spearman, including p-values) between the change in HSSDD Worst Skin Pain item score at Week 16 from Baseline and the change in a given external anchor and (2) comparing the change score at Week 16 from Baseline in HSSDD Worst Skin Pain item score between groups defined by the level of change (e.g., Improvement, No change, Worsening) in a given external anchor. The PGI-S-SP and PGI-C-SP measures were considered as potential anchors for the HSSDD Worst Skin Pain item.

Based on these correlation analyses,

- Spearman correlation coefficients between the changes in the HSSDD Worst Skin Pain item and changes in the potential anchors from Baseline at Week 16 were:
  - PGI-S-SP: 0.63 ($p < 0.001$)

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- PGI-C-SP: 0.51 ($p < 0.001$)

- When using PGI-S-SP as an anchor,
  - The HSSDD Worst Skin Pain item LS mean change score (95% CI) in the 'No change 'category was below 0 (-0.78 [-1.11, -0.45); however, the effect size was small (-0.31 [-0.41, -0.22]), as hypothesized by the Applicant.
  - The response groups with 1, 2, and 3 levels of improvement on the PGI-S-SP had LS mean change scores (95% CI) of -2.09 (-2.39, -1,79), -3.61 (-4.05, -3.17), and -4.51 (-5.39, -3.63), respectively.

- When using PGI-C-SP as an anchor,
  - The HSSDD Worst Skin Pain item LS mean change score (95% CI) in the 'No change' category was below 0 (-0.70 [-1.10, -0.30); however, the effect size was small (-0.28 [-0.44, -0.13]) as hypothesized by the Applicant.
  - The response groups with 1 and 2 levels of improvement on the PGI-C-SP had LS mean change scores (95% CI) of -1.24 (-1.55, -0.93) and -3.22 (-3.53, -2.91).

Reviewer's comment(s):
The HSSDD Worst Skin Pain item score appears to be moving in the anticipated direction (i.e., an increase in score corresponds to worsening on the PGI-S-SP and PGI-C-SP); however, CIs for both levels of worsening included 0. The Applicant suggests that it is likely due to the small sample sizes (57 and 10, respectively) and/or relatively small effect sizes of change.

Overall, the HSSDD Worst Skin Pain item appears to be responsive to improvement in other measures assessing a similar construct in the target population. Per the Applicant, its responsiveness to worsening remains to be further verified. This reviewer agrees with this conclusion.

5.4.6 Interpretation of Meaningful Within-Patient Score Changes

The following section was authored by the Patient-Focused Statistical Scientists (PFSS) team.

Background

The Agency recommends the use of anchor-based methods to establish meaningful within-patient change in COA-based endpoint scores, although other methods (e.g., qualitative evidence) can be used (April 20235). The Applicant conducted anchor-based analyses supplemented with eCDF curves to evaluate clinically meaningful within-patient change in HSSDD worst skin pain item from baseline to week 16 using the PGI-S-SP and PGI-C-SP as anchor measures (Appendix B) and data collected from their Phase 3 studies (HS0003 and HS0004). The Applicant identified a range of clinically meaningful within-patient change

5 https://www.fda.gov/regulatory-information/search-fda-guidance-documents/patient-focused-drug-development-incorporating-clinical-outcome-assessments-endpoints-regulatory

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thresholds from baseline to week 16 of a 3- to 4- point decrease, which corresponds to the mean and median decrease in the HSSDD Worst Skin Pain item for patients who reported a 2-category improvement on the PGI-S-SP measure and the mean decrease in the HSSDD Worst Skin Pain for patients who reported "much better" on the PGI-C-SP measure.

In order to review the Applicant's anchor-based analyses, the review team issued an information request on July 31, 2024, for exactr copies of the anchor scales and additional figures and tables for studies HS0003 and HS0004.

Assessment

The Applicant proposed a 2-category improvement from baseline to week 16 on the PGI-S-SP measure as the target anchor change category that constitutes a clinically meaningful within-patient change as the majority of patients reported "Moderate" (n = 409 [43.8%]) or "Severe" (n = 287 [30.7%]) skin pain at Baseline and a 2-category improvement would imply "None" or "Mild" skin pain as measured by the PGI-S-SP measure at week 16. Table 2 shows the change in HSSDD Worst Skin Pain scores from Baseline to Week 16 by change in the PGI-S-SP measure in Study HS0003. Patients who experienced a 2-point improvement in the PGI-S-SP measure had a mean change in HSSDD Worst Skin Pain score of -3.95 and a median change of -4.1. Table 3 shows the change in HSSDD Worst Skin Pain scores from Baseline to Week 16 by change in the PGI-S-SP measure in Study HS0004. Patients who experienced a 2-point improvement in the PGI-S-SP measure had a mean change in HSSDD Worst Skin Pain score of -3.95 and a median change of -3.7.

Reviewer's comment(s): *In general, the PGI-S-SP and PGI-C-SP measures appear to be reasonable for use as external anchors to interpret the HSSDD Worst Skin Pain item. The measurement concepts and recall period appear to align. While the PGI-S-SP includes a high number of response categories, collapse some of the response categories (e.g., Severe/Very severe) could help minimize poor distribution of responses across the categories for the anchor-based analyses.*

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Table 2. Change form Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0003)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
PGI-S-SP Response at Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
3-point improvement	10 (2.0)	-5.27	2.053	-7.8	-1.7	-7.4	-6.7	-5.8	-3.9	-2.0	9 (1.8)
2-point improvement	38 (7.5)	-3.95	1.846	-7.5	0.2	-6.6	-5.0	-4.1	-2.4	-1.9	28 (5.5)
1-point improvement	108 (21.4)	-2.09	2.161	-7.3	2.2	-5.4	-3.2	-2.0	-0.7	0.5	54 (10.7)
No Change	86 (17.0)	-0.82	1.633	-5.0	4.0	-3.0	-2.0	-0.7	0.1	1.2	50 (9.9)
1-point worsening	22 (4.4)	0.91	1.795	-1.1	5.6	-0.6	-0.1	0.2	1.9	3.1	16 (3.2)
2-point worsening	4 (0.8)	2.18	1.885	0.6	4.8	0.6	0.9	1.7	3.5	4.8	4 (0.8)
4-point worsening	0										1 (0.2)
Missing	11 (2.2)	-1.83	3.161	-6.2	2.0	-5.7	-5.0	-2.0	1.6	1.9	64 (12.7)

Source: Applicant's IR Response Received August 6, 2024 (Table D3)
Abbreviations: PGI-S-SP, Patient Global Impression of Severity in Skin Pain; HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

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Table 3. Change form Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0004)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
PGI-S-SP Response at Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	N missing (%)
4-point improvement	0										1 (0.2)
3-point improvement	9 (1.8)	-4.78	2.425	-9.3	-0.7	-9.3	-5.6	-5.3	-4.0	-0.7	4 (0.8)
2-point improvement	49 (9.6)	-3.95	2.184	-8.4	0.0	-7.0	-5.6	-3.7	-2.3	-1.2	30 (5.9)
1-point improvement	115 (22.6)	-2.28	1.978	-7.6	6.0	-4.4	-3.5	-2.5	-1.0	0.0	48 (9.4)
No Change	118 (23.2)	-0.42	1.804	-4.6	4.7	-2.9	-1.7	-0.2	0.6	1.8	23 (4.5)
1-point worsening	35 (6.9)	0.72	1.486	-3.9	3.9	-1.2	0.0	0.9	1.6	2.5	20 (3.9)
2-point worsening	4 (0.8)	0.25	1.991	-2.2	2.4	-2.2	-1.3	0.4	1.8	2.4	1 (0.2)
Missing	8 (1.6)	-2.54	3.642	-5.8	4.6	-5.8	-5.4	-3.5	-0.6	4.6	44 (8.6)

Source: Applicant's IR Response Received August 6, 2024 (Table D4)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

The Applicant additionally inspected the eCDF curves for change from baseline to week 16 in HSSDD score by change in the PGI-S-SP measure in each study (see Figure 2 and Figure 3; shown on next page) and found sufficient separation between the target anchor change category of a 2-point improvement in the PGI-S-SP measure and other anchor change categories, supporting their proposed anchor change category to define clinically meaningful within-patient change thresholds.

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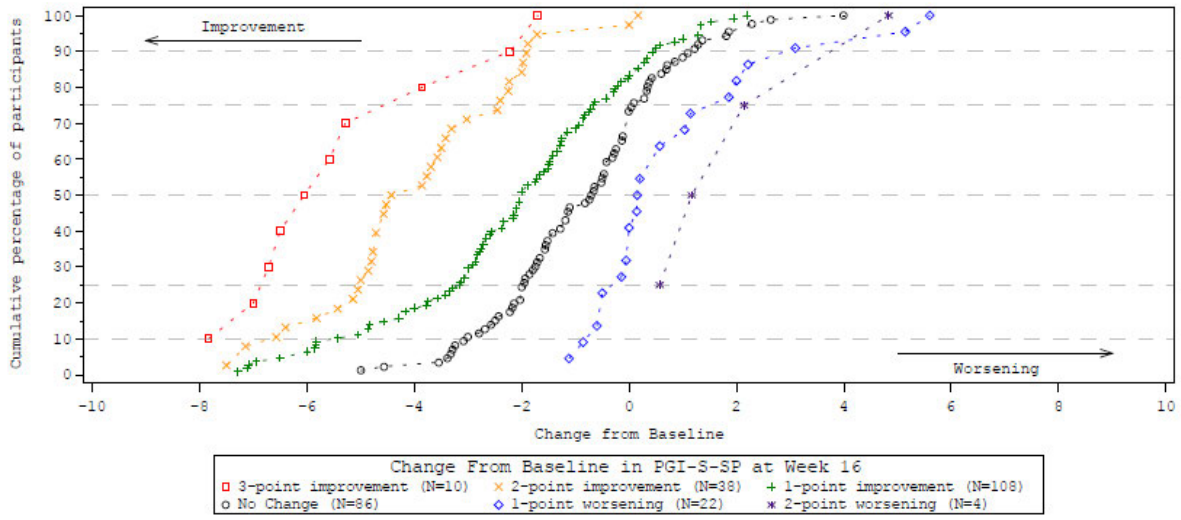
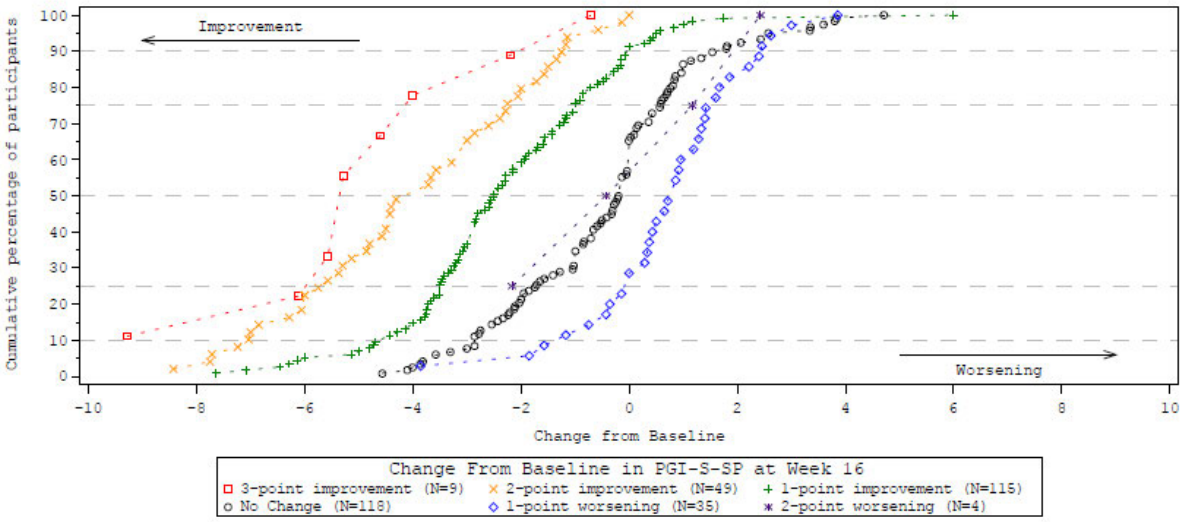
Figure 2. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D1)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Figure 3. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by Change from Baseline to Week 16 in PGI-S-SP (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D2)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Additionally, the Applicant proposed "Much better" on the PGI-C-SP measure as the target anchor category on the supportive anchor. Patients who reported "much better" skin pain at Week 16 had a mean change from baseline to week 16 in HSSDD Worst Skin Pain score of -3.17 and a median change of -2.8 in Study HS0003 (see Table 4). Patients who reported "much better" skin pain at week 16 had a mean change from baseline to week 16 in HSSDD Worst Skin Pain score of -3.32 and a median change of -3.3 in Study HS0004 (see Table 5; shown on next page). Based on these mean and median change scores of the HSSDD Worst Skin Pain item from Baseline to Week 16 for the target anchor change categories, the Applicant proposed a clinically meaningful within-patient change threshold range of a 3-point to 4-point improvement.

Table 4. Change from Baseline in HSSDD Worst Skin Pain Score at Week 16 by PGI-C-SP at Week 16 (HS0003)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
Change in PGI-C-SP from Baseline to Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
Much Better	107 (21.2)	-3.17	2.291	-7.8	2.2	-6.5	-5.0	-2.8	-1.7	-0.3	62 (12.3)
A Little Better	100 (19.8)	-1.14	2.228	-7.1	5.6	-4.0	-2.5	-1.0	0.2	1.3	48 (9.5)
No Change	44 (8.7)	-0.65	2.055	-5.0	4.0	-3.4	-2.0	-0.4	0.5	1.9	35 (6.9)
A Little Worse	20 (4.0)	-0.61	1.649	-3.8	2.3	-3.4	-1.5	-0.5	0.6	1.4	13 (2.6)
Much Worse	6 (1.2)	0.86	1.814	-2.1	3.1	-2.1	-0.1	1.2	2.0	3.1	5 (1.0)
Missing	2 (0.4)	-0.35	2.377	-2.0	1.3	-2.0	-2.0	-0.3	1.3	1.3	63 (12.5)

Source: Applicant's IR Response Received August 6, 2024 (Table D5)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

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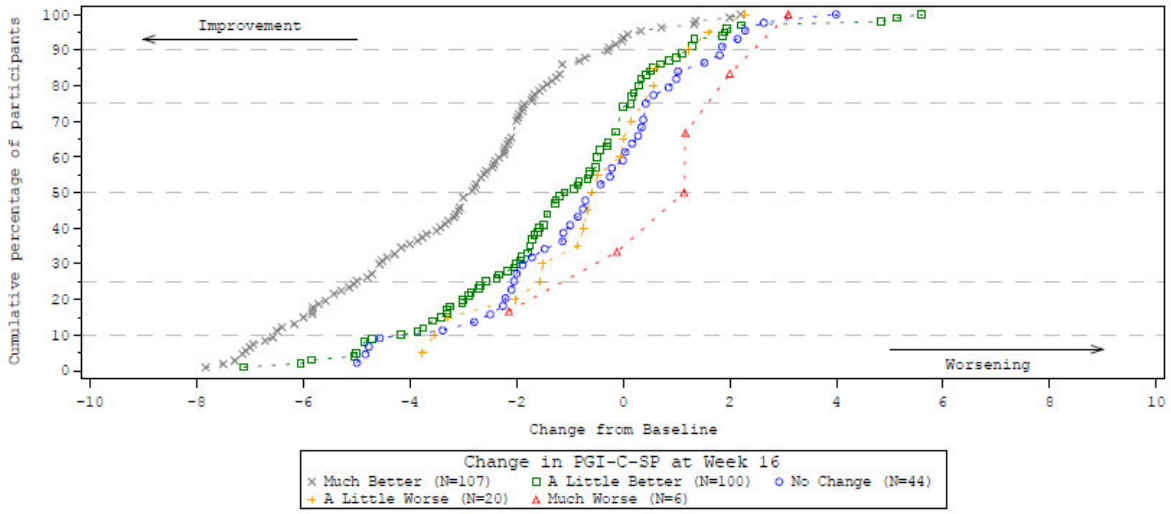
Table 5. Change from Baseline in HSSDD Worst Skin Pain Score at Week 16 by PGI-C-SP at Week 16 (HS0004)

		Change in HSSDD scores from Baseline to Week 16									
						Percentiles					
Change in PGI-C-SP from Baseline to Week 16	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{missing}$ (%)
Much Better	114 (22.4)	-3.32	2.172	-9.3	3.0	-6.3	-4.6	-3.3	-1.9	-0.5	43 (8.4)
A Little Better	132 (25.9)	-1.17	2.071	-7.1	4.7	-3.7	-2.7	-1.0	0.1	0.9	51 (10.0)
No Change	64 (12.6)	-0.66	2.049	-6.0	3.6	-3.2	-2.0	-0.2	0.6	1.8	26 (5.1)
A Little Worse	18 (3.5)	1.17	1.782	-1.2	6.0	-0.4	-0.1	0.7	2.6	3.8	10 (2.0)
Much Worse	10 (2.0)	1.25	1.470	-1.2	3.9	-1.0	0.8	1.3	2.2	3.1	2 (0.4)
Missing	0										39 (7.7)

Source: Applicant's IR Response Received August 6, 2024 (Table D6)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

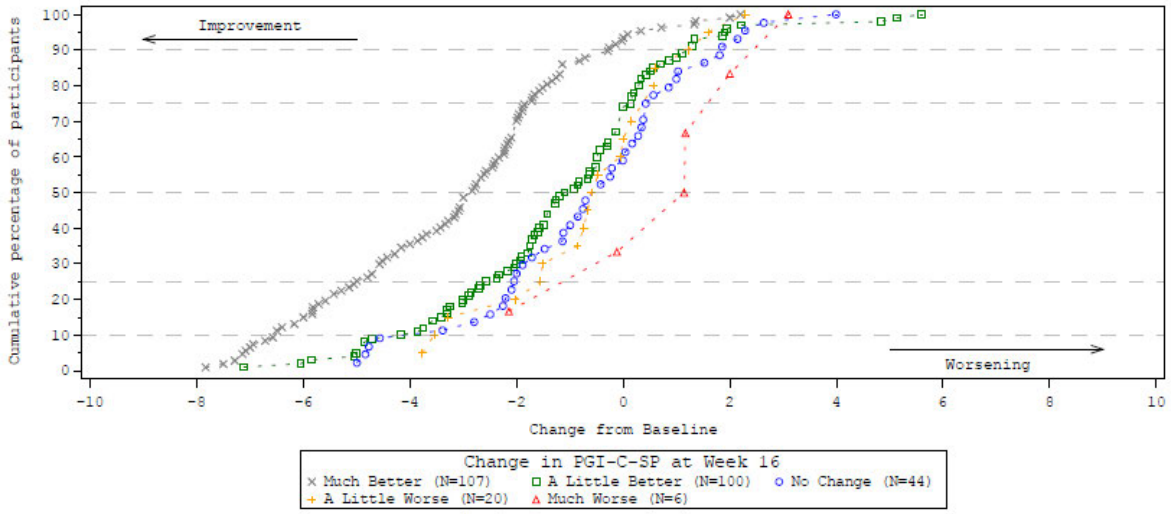
The Applicant inspected the eCDF curves for change from baseline to week 16 in HSSDD Worst Skin Pain score by the PGI-C-SP measure at Week 16 in each study (see Figure 4 and Figure 5; shown on next page) and found sufficient separation between the target anchor category of "Much better" and other anchor change categories, supporting their proposed anchor category to define clinically meaningful within-patient change thresholds.

Figure 4. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-C-SP at Week 16 (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D3)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

Figure 5. Empirical Cumulative Distribution Function Plot for Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-C-SP at Week 16 (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D4)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

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Based on these analyses, the Applicant proposed a meaningful within-patient change threshold range of 3-point to 4-point improvement on HSSDD Worst Skin Pain score from Baseline to Week 16.

Reviewer comments: *The Applicant's anchor-based analyses supplemented by eCDF curves is largely appropriate. Notably, while the Applicant did not explicitly discuss misclassification rates of patients based on their threshold range, the observed misclassification rates of patients who reported no change or worsening on the PGI-S-SP or PGI-C-SP measures at the meaningful within-patient change range of 3-point to 4-point improvement on HSSDD Worst Skin Pain item was below 20%, which is acceptable. However, what patients consider to be clinically meaningful improvement may be impacted by the patient's baseline skin pain severity. Patient's baseline symptom severity should be considered when determining clinically meaningful within-patient change thresholds. Below is the Agency's evaluation of patient's baseline skin pain symptom severity on meaningful within-patient change thresholds.*

Table 6 and Table 7 (shown on next page) show the distribution of change in HSSDD Worst Skin Pain scores from Baseline to Week 16 for patients who achieved a 2-category improvement on the PGI-S-SP measure. The median change in the HSSDD Worst Skin Pain item is between -2.4 and -4.8 in Study HS0003 and between -3.0 and -4.4 in Study HS0004. The amount of change patients consider meaningful tends to smaller the more severe skin pain they reported at baseline. Based on the results of the anchor-based analyses supplemented by eCDF curves and the assessment of baseline symptom severity, the final clinically meaningful within-patient change range should be between -4.8 and -2.4, which includes the Applicant's proposed range (i.e., -3 to -4) so that, for patients who achieved a 2-category improvement on the PGI-S-SP measure, at least 50% of patients who reported moderate, severe, or very severe skin pain at baseline are categorized as having experienced a meaningful improvement.

Table 6. Distribution of Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-S-SP at Baseline for Patients who Achieved a 2-category Improvement in PGI-S-SP at Week 16 (HS0003)

		HSSDD Change Score									
						Percentiles					
PGI-S-SP Response at Baseline	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
Moderate	9 (13.6)	-4.53	1.724	-7.1	-2.0	-7.1	-5.1	-4.8	-3.5	-2.0	7 (10.6)
Severe	22 (33.3)	-4.05	1.835	-7.5	0.2	-6.6	-5.1	-3.8	-3.0	-1.9	16 (24.2)
Very Severe	7 (10.6)	-2.88	1.847	-4.8	0.0	-4.8	-4.7	-2.4	-1.7	0.0	5 (7.6)

Source: Applicant's IR Response Received August 6, 2024 (Table D7)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

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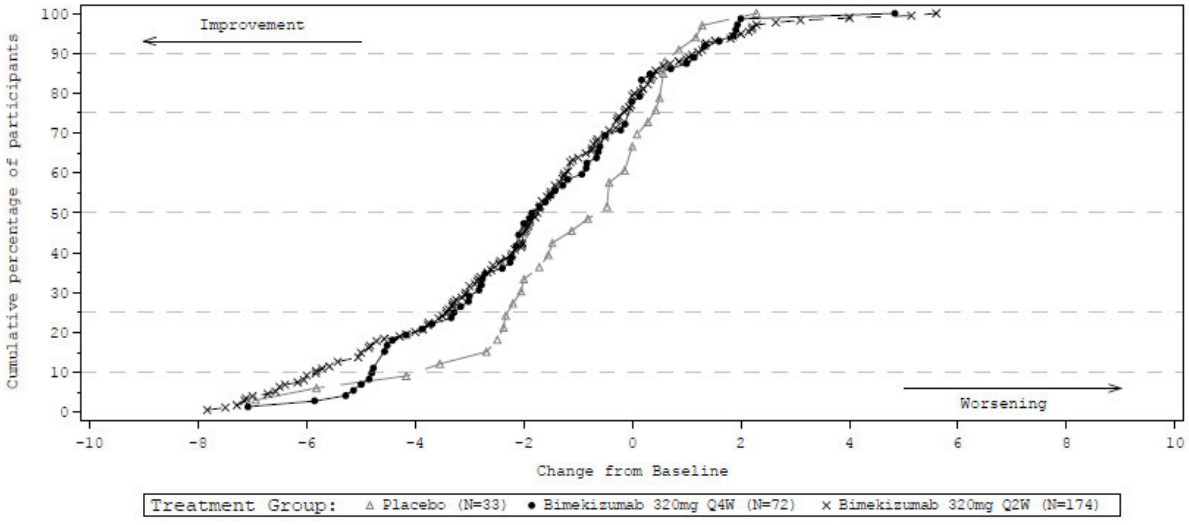
Table 7. Distribution of Change From Baseline to Week 16 in HSSDD Worst Skin Pain Score by PGI-S-SP at Baseline for Patients who Achieved a 2-category Improvement in PGI-S-SP at Week 16 (HS0004)

		HSSDD Change Score									
						Percentiles					
PGI-S-SP Response at Baseline	N (%)	Mean	SD	Min	Max	10th	25th	50th	75th	90th	$N_{Missing}$ (%)
Moderate	15 (19.0)	-4.60	2.157	-8.4	-1.3	-7.8	-6.0	-4.4	-3.0	-2.1	12 (15.2)
Severe	29 (36.7)	-3.75	2.249	-7.2	0.0	-7.0	-5.6	-3.7	-1.7	-0.6	14 (17.7)
Very Severe	5 (6.3)	-3.16	1.706	-6.0	-1.5	-6.0	-3.0	-3.0	-2.3	-1.5	4 (5.1)

Source: Applicant's IR Response Received August 6, 2024 (Table D8)
Abbreviations: PGI-S-SP: Patient Global Impression of Severity in Skin Pain; HSSDD: Hidradenitis Suppurativa Symptom Daily Diary

As seen in Figure 6 and Figure 7 (shown on next page), there is adequate separation between the eCDF curves for the placebo arm and the bimekizumab arms. The difference in proportion of patients reported as experiencing a meaningful improvement between the placebo and bimekizumab treatment arms is between approximately 12% and 21% in Study HS0003 and between approximately 11% and 22% in Study HS0004 in the range patients consider meaningful (i.e., -4.8 and -2.4).

Figure 6. Empirical Cumulative Distribution Function Plot for Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Treatment Group (HS0003)



Source: Applicant's IR Response Received August 6, 2024 (Figure D5)
Abbreviations: HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

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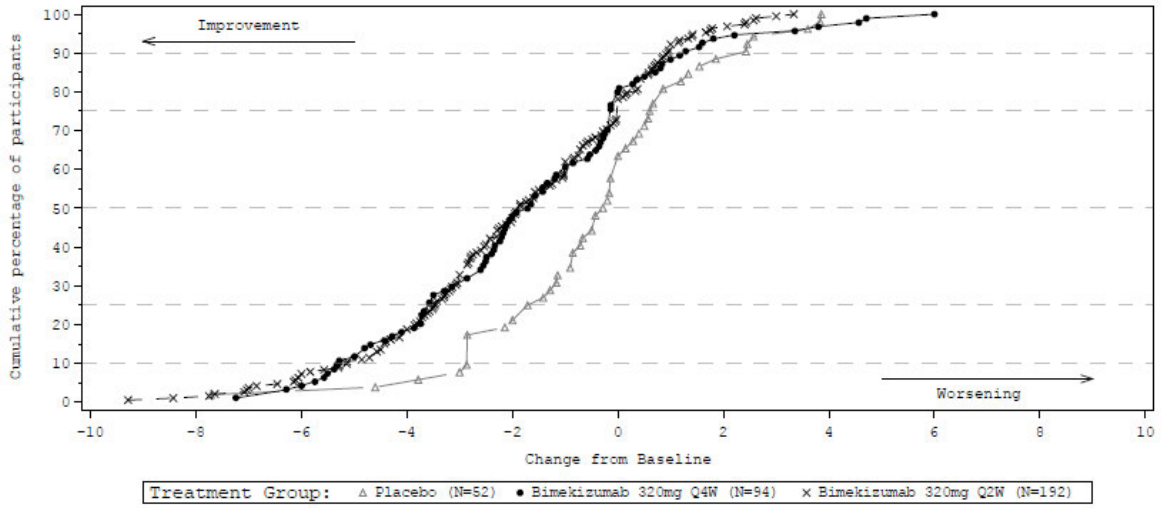
Figure 7. Empirical Cumulative Distribution Function Plot for Change from Baseline to Week 16 in HSSDD Worst Skin Pain Score by Treatment Group (HS0004)



Source: Applicant's IR Response Received August 6, 2024 (Figure D6)
Abbreviations: HSSDD, Hidradenitis Suppurativa Symptom Daily Diary

Conclusion

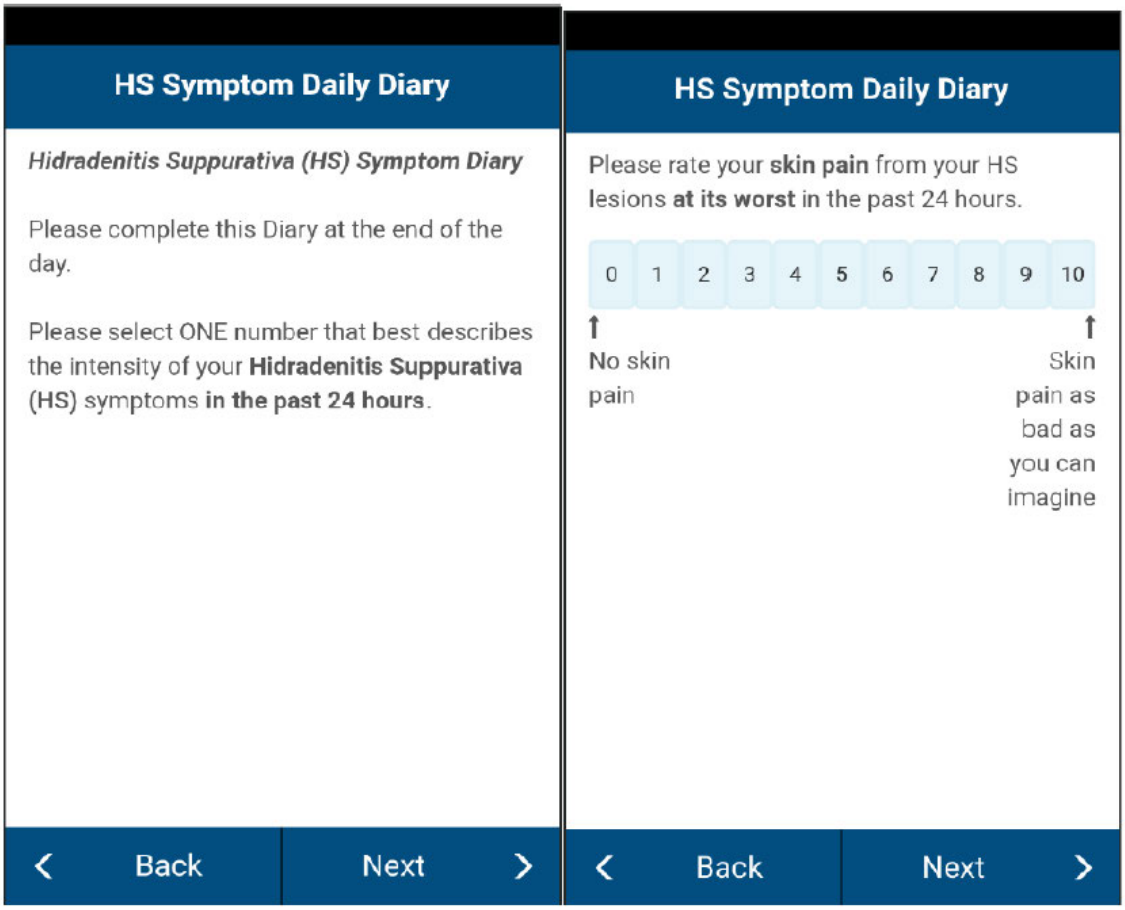
Anchor-based analyses to assess meaningful within-patient change in HSSDD Worst Skin Pain score between Baseline and Week 16 indicates patients consider a reduction of between 2.4 and 4.8 points to be meaningful. The observed treatment effect substantiated a clinically meaningful within-patient improvement in patients receiving bimekizumab compared to placebo.

6. APPENDICES

Appendix A: Hidradenitis Suppurative Symptom Daily Diary (HSSDD) Worst Skin Pain item
Appendix B: Copies of Anchor Measures

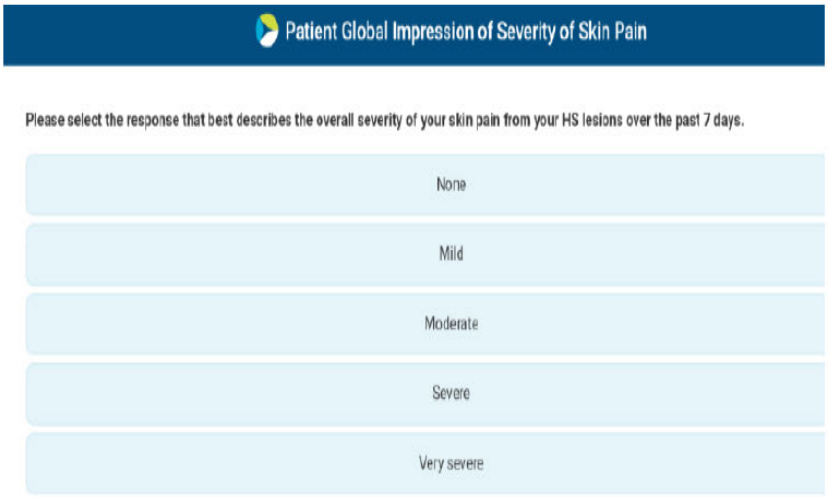
Reference ID: 5461541

Appendix A: HSSDD Worst Skin Pain Item

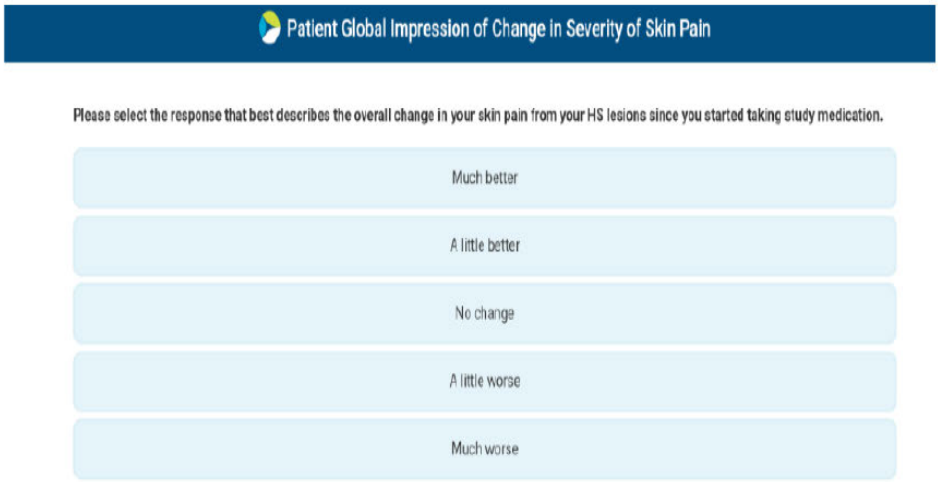


Appendix B: Copies of Anchor Measures

Patient Global Impression of Severity of Skin Pain



Patient Global Impression of Change of Severity of Skin Pain



Please select the response that best describes the overall severity of your HS over the past 7 days.

- None
- Mild
- Moderate
- Severe
- Very Severe

Please select the response that best describes the overall change in your HS since you started taking the study medication.

- Much better
- A little better
- No change
- A little worse
- Much worse

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/s/

SELENA R DANIELS
10/11/2024 10:25:48 AM

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

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

Memorandum

Date: 9/26/2024

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

Kevin Clark, Clinical Reviewer, DDD

Matthew White, Associate Director for Labeling, DDD

From: Montherson L. Saint Juste, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: James Dvorsky, Team Leader, OPDP

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

BLA: 761151, S-010

Background:
In response to DDD's consult request dated February 6, 2024, OPDP has reviewed the proposed Prescribing Information (PI), and Medication Guide for supplement 010 for BIMZELX® (bimekizumab-bkzx). This supplement seeks to add moderate to severe hidradenitis suppurativa (HS) in adults as an indication.

PI/Medication Guide:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on September 13, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed Medication Guide, and comments were sent under separate cover on September 20, 2024.

Thank you for your consult. If you have any questions, please contact Montherson L. Saint Juste at 301-796-1200 or Montherson.SaintJuste@fda.hhs.gov.

Following this page, 30 Pages of Draft Labeling have been Withheld in Full as (b)(4)

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/s/

SUSAN W REDWOOD
09/20/2024 01:59:08 PM

MONTHERSON L SAINT JUSTE
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BARBARA A FULLER
09/20/2024 02:20:08 PM

LASHAWN M GRIFFITHS
09/20/2024 02:38:22 PM

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:	July 12, 2024
Requesting Office or Division:	Division of Dermatology and Dentistry (DDD)
Application Type and Number:	BLA 761151/S-010
Product Name, Dosage Form, and Strength:	Bimzelx (bimekizumab-bkzx) injection, 160 mg/mL
Product Type:	Combination Product (Biologic-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	UCB, Inc.
FDA Received Date:	January 19, 2024
TTT ID #:	2024-8184
DMEPA 1 Safety Evaluator:	Madhuri R. Patel, PharmD
DMEPA 1 Team Leader:	Yevgeniya Kogan, PharmD, BCSCP
DMEPA 1 Human Factors Team Leader	Murewa Oguntimein, PhD, MHS, CPH, MCHES

Reference ID: 5413006

1 INTRODUCTION

UCB, Inc. submitted an Efficacy Supplement for Bimzelx (bimekizumab-bkzx) injection proposing a new indication for the treatment of moderate to severe hidradenitis suppurativa (HS) in adults. Subsequently, the Division of Dermatology and Dentistry (DDD) requested that we review the proposed Bimzelx Prescribing Information (PI) and Medication Guide (MG) for areas of vulnerability that may lead to medication errors.

2 MATERIALS REVIEWED

This section lists the materials considered for our review of BLA 761151/S-010.

Table 1. Materials Considered for this Label and Labeling Review	
Material(s) Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C

3 CONCLUSION

Our evaluation of the proposed Bimzelx Prescribing Information (PI) and Medication Guide (MG) did not identify areas of vulnerability that may lead to medication errors. Per our Division of Dermatology and Dentistry (DDD) clinical colleagues, they do not expect hand strength or manual dexterity to be affected by moderate to severe hidradenitis suppurativa (HS). We also note that the currently approved dosage form and strength supports the proposed new indication and proposed dose. We have no recommendations at this time.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 2 presents relevant product information for Bimzelx received on January 19, 2024 from UCB, Inc..

Table 2. Relevant Product Information for Bimzelx	
Initial Approval Date	October 17, 2023
Proper Name	bimekizumab-bkzx
Indication	Current treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy Proposed treatment of adult patients with moderate to severe hidradenitis suppurativa
Dosage Form	injection
Strength	160 mg/mL
Route of Administration	subcutaneous
Dose and Frequency	Plaque Psoriasis 320 mg (given as 2 subcutaneous injections of 160 mg each) at Weeks 0, 4, 8, 12, and 16, then every 8 weeks thereafter. For patients weighing ≥ 120 kg, consider a dosage of 320 mg every 4 weeks after Week 16. If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time Hidradenitis Suppurativa (proposed) 320 mg (given as 2 subcutaneous injections of 160 mg each) at Weeks 0, 2, 4, 6, 8, 10, 12, 14, and 16, then every 4 weeks thereafter. If a dose is missed, administer the dose as soon as possible. Thereafter, resume dosing at the regular scheduled time.

Table 2. Relevant Product Information for Bimzelx	
How Supplied	sterile, preservative-free, clear to slightly opalescent, and colorless to pale brownish-yellow solution. Each prefilled autoinjector or prefilled syringe contains 1 mL of a 160mg/mL solution. BIMZELX is supplied as: BIMZELX 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. BIMZELX 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 with BIMZELX 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. BIMZELX does not contain a preservative; discard any unused portion. Not made with natural rubber latex. When necessary, BIMZELX 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 BIMZELX 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.

Table 2. Relevant Product Information for Bimzelx	
Container Closure	The primary packaging for the bimekizumab drug product consists of a 1mL long Type I glass pre-filled syringe (PFS) fitted with a staked 27G, ½" special thin wall needle. The syringe is closed using a [redacted] (b) (4) rubber stopper and a rigid needle shield (RNS) consisting of a [redacted] (b) (4) needle cover and a polypropylene rigid shield. The bimekizumab-SS-1mL consists of the drug product in the pre-filled syringe and plunger rod, small round flange (SRF) sub-assembly, extended finger flange, and overcap sub-assembly. The bimekizumab-AI-1mL consists of the drug product in the pre-filled syringe and the cap remover sleeve, housing cover, syringe unit, and drive unit.

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

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

- Prescribing Information received on January 19, 2024, available from \\CDSESUB1\EVSPROD\bla761151\0116\m1\us\114-labeling\draft\labeling\cir-highlighted-202401-sub.pdf
- Medication Guide received on January 19, 2024, available from \\CDSESUB1\EVSPROD\bla761151\0116\m1\us\114-labeling\draft\labeling\medguide-highlighted-202401-sub.pdf

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

APPENDIX C. PREVIOUS DMEPA REVIEWS

On June 26, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, '761151'. Our search identified one previous review[b] since the date of our last search on May 20, 2024, and we considered our previous recommendations to see if they are applicable for this current review.

[b] Patel, M. Label and Labeling Review for Bimzelx (BLA 761151/S-009). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 24. TTT ID No.: 2023-7488.

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/s/

MADHURI R PATEL
07/12/2024 02:37:30 PM

YEVGENIYA M KOGAN
07/12/2024 03:15:40 PM

OLUWAMUREWA OGUNTIMEIN
07/14/2024 08:45:40 AM

Memorandum

From: Selena DeConti, PharmD, MPH
Safety Analyst, Division of Cardiology and Nephrology
OCHEN/OND/CDER/FDA

Through: Mary Ross Southworth, PharmD
Deputy Director for Safety, Division of Cardiology and Nephrology
OCHEN/OND/CDER/FDA

Norman Stockbridge, MD
Director, Division of Cardiology and Nephrology
OCHEN/OND/CDER/FDA

Date: July 16, 2024

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

This memo responds to the consult requesting a review of cardiovascular (CV) adverse events (AEs) that were reported in the bimekizumab hidradenitis suppurativa (HS) program, and recommendations for labeling. Bimekizumab is approved and marketed for the treatment of moderate to severe plaque psoriasis. We received and reviewed the safety data in the BLA 761151 Supplement-10 submission package: \\CDSESUB1\evsprod\BLA761151\0116.

DCN Summary and Assessment

The primary safety analysis included a review of the CV adverse events[1] reported in the initial treatment period (ITP; 16-week placebo-controlled) for the safety pool, Pool S1, which includes bimekizumab 320 mg Q2W (n=576), bimekizumab 320 mg Q4W (n=285), or placebo (n=146), from the Phase 3 trials HS0003 and HS0004. CV events from the maintenance treatment periods, Phase 2 trial (HS0001), and Phase 3 open-label extension (OLE) trial (HS0005), 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 arms.
- The CV events were reported similarly in the treatment arms; placebo (6%) versus bimekizumab Q2W or Q4W (6% and 5%, respectively). No trend was observed with respect to the type of CV event or time to onset.

[1] any adverse event reported in the MedDRA System Organ Class (SOC) Cardiac Disorders or Vascular Disorders

Reference ID: 5414132

- Serious CV adverse events were reported similarly between treatment arms; placebo (0.7%) versus bimekizumab Q2W or Q4W (0.7% and 0.4%, respectively). No trend was observed with respect to the type of CV event or time to onset.
- There were no adjudicated major adverse cardiac events (MACE) reported in the bimekizumab arms or placebo arm.
- One subject in the bimekizumab Q2W group (0.1%) experienced two adjudicated extended MACE (heart failure exacerbation; acute on chronic heart failure) versus none in the bimekizumab Q4W or placebo arms. This subject had a previous history of heart failure and eventually died due to heart failure at Week 36 of the study. Details provided in the Appendix.
- The incidence of adjudicated CV adverse events was low, 1% in the bimekizumab Q2W arm versus none in the bimekizumab Q4W or placebo arms.

Results of the analysis for the individual trials, maintenance treatment periods, Phase 2 trial, and OLE trial were consistent with these observations.

A review of the CV adverse events described in the periodic safety reports since approval did not identify CV findings of concern.

Overall, the findings did not raise CV safety concerns and no labeling language is necessary.

Consider eliminating the need for CV AEs to be collected as AEs of special interest (AESI) and event adjudication in future development programs for bimekizumab.

Background

Bimekizumab (BLA 761151) is a humanized interleukin-17A and F antagonist approved October 18, 2023 for the treatment of moderate to severe plaque psoriasis (PSO) in adults who are candidates for systemic therapy or phototherapy. The 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.

Previously, DCN provided two consultative reviews[2] of CV events reported in the BLA submission for PSO. MACE was a safety topic of interest for bimekizumab due to epidemiological associations between PSO and CV events, and the potential association between other anti-cytokine (immunomodulating biologic) therapies and CV events. The reviews for the bimekizumab PSO program did not reveal a clinical CV concern and no labeling language was recommended.

Bimekizumab is being developed for HS as published data and studies have shown that IL-17A and IL-17F are upregulated in HS tissue.[3] Similar to PSO, hidradenitis suppurative is associated with an increased prevalence of CV risk factors including obesity, smoking, diabetes, and hyperlipidemia (Garg et al, 2022). In addition, HS patients have an increased risk of vascular inflammation and MACE beyond that attributable to known CV risk factors (Egeberg et al, 2016;

[2] March 3, 2021 (Initial BLA submission for PSO) and April 11, 2023 (BLA resubmission after Complete Response)

[3] BLA Supplement-10 Summary of Clinical Safety

Reference ID: 5414132

González-López et al, 2016). Circulating TNF and IL-6 are elevated in HS and known to drive endothelial dysfunction, atherosclerosis, and thrombosis (Xu et al, 2017). Patients with HS have significantly higher prevalence of hypertension, linked to obesity and tobacco use (Garg et al, 2022, Kwa et al, 2017).

One other monoclonal antibody product targeting IL-17A has been approved for the treatment of HS, secukinumab. No CV adverse reactions are included in the labeling for this product.

The bimekizumab nonclinical development program information was submitted as a part of the PSO initial application. There were no preclinical findings to suggest CV safety concerns.

MACE, defined as CV death, non-fatal myocardial infarction (MI), or stroke, was a pre-specified safety topic of interest. 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 a CV Clinical Event Adjudication Committee (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, Pool S1, includes subjects exposed to bimekizumab 320 mg Q2W (n=576), bimekizumab 320 mg Q4W (n=285), or placebo (n=146), in the initial treatment period (ITP; 16-week placebo-controlled) of the Phase 3 trials HS0003 and HS0004; it is the same pooling as the efficacy pool E1. Both trials had the same design and there was no placebo or active comparator arm in the maintenance treatment period of either trial. Table 3 in the Appendix provides an overview of the relevant trials constituting the safety pools for the bimekizumab HS program.

Treatment Duration

Treatment duration for bimekizumab and placebo is provided in Table 1. Subjects in the bimekizumab total group had approximately 6 times the person-time at risk, with 262.3 patient-years versus 44.6 patient years for placebo. Mean duration of bimekizumab treatment was approximately 107 days.

Table 1. Study Medication Duration during the Initial Treatment Period, Safety Pool S1

	Placebo N=146	BKZ 320mg Q4W N=285	BKZ 320mg Q2W N=576	BKZ Total N=861
Study medication duration (days), n	146	285	576	861
Mean (SD)	107.7 (17.86)	107.3 (15.93)	106.9 (17.96)	107.0 (17.31)
Median	112.0	112.0	112.0	112.0
Min, max	14, 132	28, 126	14, 144	14, 144
Total study medication duration (participant-years)	43.0	83.7	168.6	252.3
Total time at risk (participant-years)	44.6	86.9	175.4	262.3

BKZ=bimekizumab; ISS=Integrated Summary of Safety; ITP=Initial Treatment Period; max=maximum; Min=minimum; Q2W=every 2 weeks; Q4W=every 4 weeks; SD=standard deviation
Note: Total study medication duration was a subset of total time at risk excluding nontreated periods.
Data source: ISS Table 4.1.1

Subject Demographics and Baseline Characteristics

Baseline CV risk factors and history of CV events were relatively evenly distributed between the randomized treatment arms. The demographics were representative of the HS population. Overall, 36% of trial participants had Class III Obesity (morbidly obese), 45% of trial participants were current smokers, and 40% had previous or ongoing hypertension. Six subjects in the bimekizumab arms (0.7%) versus none in the placebo arm had previous or ongoing heart failure.

MACE

Table 2 below summarizes incidences of adjudicated MACE and extended MACE reported for Pool S1 for the safety population. No adjudicated MACE was reported for the bimekizumab arms or placebo in the initial treatment period. For the bimekizumab Q2W arm, one subject experienced two adjudicated extended MACE (cardiac failure and cardiac failure acute); this subject later experienced a fatal outcome at Week 36. The heart failure event did not raise CV safety concerns (description provided in Table 7 in the Appendix).

Table 2. Overview of Adjudicated MACE, Extended MACE, and CV Events, Safety Pool S1

Variable [n (%)]	BMK 320 mg Q4W (N=285)	BMK 320 mg Q2W (N=576)	Placebo (N=146)
Adjudicated MACE	**0**	**0**	**0**
Adjudicated Extended MACE	**0**	**1 (0.2)**	**0**
Cardiac failure		1 (0.2)	
Cardiac failure acute		1 (0.2)	

Variable [n (%)]	BMK 320 mg Q4W (N=285)	BMK 320 mg Q2W (N=576)	Placebo (N=146)

Abbreviations: BKZ=bimekizumab, CV=cardiovascular, MACE=major adverse cardiac event
Source: ISS CSR Table 5.1.9.3.2; verified by reviewer

During the combined maintenance treatment periods and OLE, there were four adjudicated MACE, including one subject experiencing fatal congestive heart failure (discussed in the Appendix). The remaining adjudicated MACE included one subject with acute coronary syndrome, one subject with cerebral infarction, and one subject with ruptured cerebral aneurysm; none of these events led to study discontinuation or withdrawal of bimekizumab.

Cardiovascular Events

Cardiovascular events included any AE reported in the Cardiac Disorders or Vascular Disorders MedDRA System Organ Class (SOC) and are presented in Table 4 in the Appendix. Cardiovascular events were reported similarly in the treatment arms; placebo (6%) versus bimekizumab Q2W or Q4W (6% and 5%, respectively). Serious CV events were reported similarly between treatment arms; placebo (0.7%) versus bimekizumab Q2W or Q4W (0.7% and 0.4%, respectively). The incidence of adjudicated CV events was low, reported in 1% of subjects treated with bimekizumab compared with no subjects treated with placebo. No trend was observed with respect to the type or time to onset of any CV event. Results of the analysis for the individual trials, maintenance treatment periods, Phase 2 trial, and OLE trial were consistent with these observations.

Hypertension

Hypertension was the most reported CV event and had a slightly higher incidence in subjects treated with placebo (3%) than bimekizumab (2%, each arm). There were no SAEs or discontinuations reported with hypertension (Table 5, Appendix). For patients experiencing 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; Table 6; Appendix). Further, this finding was consistent across other bimekizumab HS trials, the bimekizumab PSO program, as well as, the supportive trials in psoriatic arthritis (PA0010, PA0011).

QT Prolongation

Two subjects in the bimekizumab arms (1 subject each in the bimekizumab 320mg Q4W and bimekizumab 320mg Q2W) experienced prolonged QT (at one visit) compared with none in the placebo arm. Both events were reported as non-serious and reviewed by the CV-CAC; neither of these events led to study discontinuation or withdrawal of bimekizumab. Review of the ECG data did not raise concern for proarrhythmic potential.

Postmarketing Reports

A review of the CV events described in the periodic safety reports since approval did not identify CV findings of concern.

Conclusion

There is no clinical concern from the cardiovascular perspective and no safety labeling language is necessary. Consider eliminating the need for CV AEs to be collected as AESI and event adjudication in future development programs for bimekizumab.

References

Egeberg A, Gislason GH, Hansen PR. Risk of major adverse cardiovascular events and all-cause mortality in patients with hidradenitis suppurativa. *JAMA Dermatol*. 2016;152(4):429–434.

Garg A, Malviya N, Strunk A, et al. Comorbidity screening in hidradenitis suppurativa: Evidence-based recommendations from the US and Canadian Hidradenitis Suppurativa Foundations. *J Am Acad Dermatol.* 2022;86(5):1092-1101.

González-López MA, Hernández JL, Lacalle M, et al. Increased prevalence of subclinical atherosclerosis in patients with hidradenitis suppurativa (HS). *J Am Acad Dermatol*. 2016; 75(2):329–335.

Kwa MC, Silverberg JI. Association between inflammatory skin disease and cardiovascular and cerebrovascular co-morbidities in US adults: analysis of nationwide inpatient sample data. *Am J Clin Dermatol.* 2017;18(6):813–823.

Xu H, Xiao X, He Y, et al. Increased serum interleukin-6 levels in patients with hidradenitis suppurativa. *Postepy Dermatol Alergol.* 2017;34(1):82–84.

Appendix

Table 3. Overview of Safety Pools for Bimekizumab HS Trials

Pool name	Studies included in pool	Treatment group/sequences included in pool[a]	Treatment periods included in pool	Primary purpose of pool
S1	HS0003, HS0004	Study participants exposed to: BKZ 320mg Q2W BKZ 320mg Q4W BKZ Total PBO	ITP (Baseline to Week 16)	Summarize safety of BKZ compared to PBO through Week 16
S2	HS0003, HS0004	Study participants receiving at least 1 dose of BKZ and randomized to: BKZ 320mg Q2W/Q2W BKZ 320mg Q4W/Q4W BKZ 320mg Q2W/Q4W PBO/BKZ 320mg Q2W[b] BKZ Total[b]	ITP and MTP (Baseline to Week 48[c])	Evaluate safety of BKZ over continuous dosing for study participants originally randomized to BKZ Q2W who switch to BKZ Q4W, and for BKZ Q2W and BKZ Q4W perpetual groups
S3	HS0001, HS0003, HS0004, HS0005	Study participants exposed to: Phase 3 BKZ 320mg Q2W Phase 3 BKZ 320mg Q4W Phase 3 BKZ Total Phase 2/3 BKZ 320mg Q2W[d] Phase 2/3 BKZ Total	ITP, MTP and OLE	Provide the most comprehensive overview of safety data on BKZ in HS population
S4	HS0003, HS0004, PS0009, PS0013, PA0010, PA0011, AS0010, AS0011	Study participants exposed to: BKZ 160mg Q4W BKZ 320mg Q2W BKZ 320mg Q4W BKZ Total PBO	ITP	Summarize safety of BKZ compared to PBO through Week 16 across BKZ development program for Phase 3 PBO-controlled studies in HS, PSO, PsA and axSpA; this pooling is used to refine the company position regarding BKZ adverse reactions

Source: ISS Table 4-1

axSpA=axial spondyloarthritis; BKZ=bimekizumab; HS=hidradenitis suppurativa; ITP=initial treatment period, MTP=Maintenance Treatment Period, OLE=Open-Label Extension, PBO=placebo; PsA=psoriatic arthritis; PSO=psoriasis; Q2W =every 2 weeks; Q4W=every 4 weeks; SFU-safety follow up

[a] Note the order of the treatment groups presented in this table represents the order in the HS0003 and HS0004 study schematics.

[b] For Pool S2, PBO/BKZ Q2W and BKZ Total are presented for selected analyses.

[c] Available data from SFU are included in Pool S2 for study participants who did not continue into HS0005.

[d] Includes data from all study participants in HS0001 who received bimekizumab 640mg loading dose at Baseline, followed by bimekizumab 320mg Q2W from Week 2 to Week 10, in addition to the data included in the Phase 3 bimekizumab 320mg Q2W treatment group.

Reference ID: 5414132

Table 4. Overview of CV Adverse Events, Safety Pool S1

Variable n (%)	BMK 320 mg Q4W (N=285)	BMK 320 mg Q2W (N=576)	Placebo (N=146)
Any CV Adverse Event[1]	14 (4.9)	33 (5.7)	9 (6.2)
SAE	1 (0.4)	4 (0.7)	1 (0.7)
SAE with fatal outcome[2]	0	1 (0.2)	0
Cardiac failure congestive	0	1 (0.2)	0
AE from CV FMQs[3]	14 (4.9)	31 (5.4)	9 (6.2)
Acute coronary syndrome	0	1 (0.2)	0
Atrial fibrillation	0	1 (0.2)	1 (0.7)
Bradycardia[4]	0	1 (0.2)	2 (0.7)
Cardiac failure[5]	0	1 (0.2)	0
Cerebral infarction	0	1 (0.2)	0
Deep Vein thrombosis	0	1 (0.2)	0
Hypertension[6]	6 (2.1)	13 (2.3)	4 (2.7)
Hypotension	0	2 (0.3)	0
Palpitations	0	1 (0.2)	0
Syncope	1 (0.4)	2 (0.3)	1 (0.7)
Tachycardia	4 (0.7)	4 (0.7)	1 (0.7)
Thrombosis	1 (0.4)	1 (0.2)	0
Thrombophlebitis superficial	1 (0.4)	2 (0.3)	0
Adjudicated CV Event	**0**	**7 (1.2)**	**0**
Heart failure hospitalization	0	1	0
Venous Thromboembolic	0	1	0
Other CV[7]	0	2	0
Non-CV[8]	0	4 (0.5)	0

Source: Reviewer's Table; Analysis Studio; MAED; adae.xpt; adsl.xpt
[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 reported in the Cardiac Disorders or Vascular Disorders MedDRA System Organ Class (SOC)
[2] AE reported in the ITP, but subject death occurred later at Week 36
[3] MedDRA preferred term from narrow FMQs Acute Coronary Syndrome, Arrhythmia, Heart Failure, Hypotension, Myocardial Ischemia, Palpitations, Syncope, Systemic Hypertension
[4] Includes PT sinus bradycardia
[5] Includes PTs cardiac failure, cardiac failure acute, cardiac failure congestive
[6] Includes PT blood pressure increased
[7] Includes PT syncope
[8]Includes PT diastolic dysfunction, dyspnea exertional, peripheral swelling, superficial thrombophlebitis
Abbreviations: AE=adverse event, BKZ=bimekizumab, CV=cardiovascular, FMQ=FDA MedDRA Query, SAE=serious adverse event,

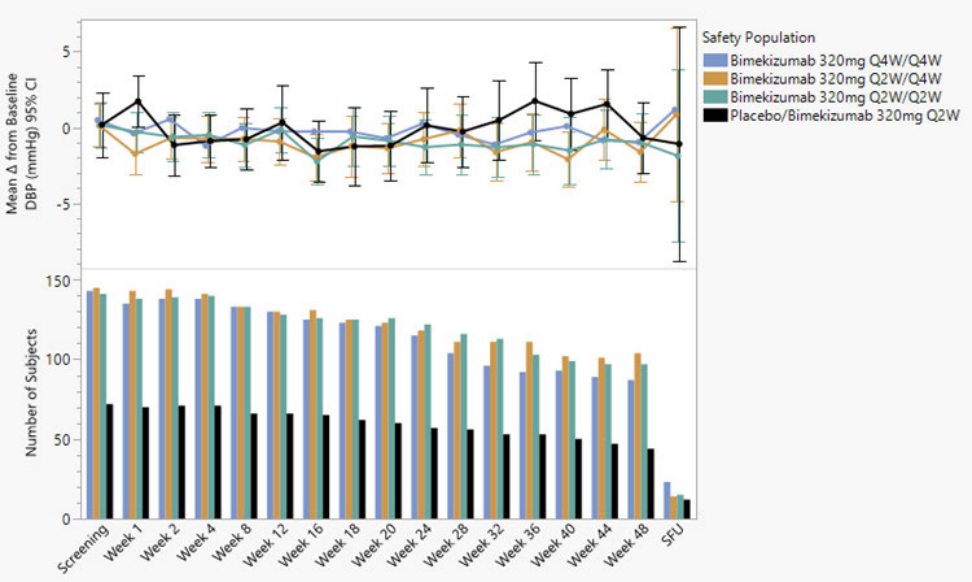
Reference ID: 5414132

Table 5. Overview of Hypertension, Safety Pool S1

Variable n (%)	BMK 320 mg Q4W (N=285)	BMK 320 mg Q2W (N=576)	Placebo (N=146)
Hypertension[2]	6 (2.1)	13 (2.3)	4 (2.7)
SAE	0	0	0
Resulted in Study Discontinuation	0	0	0
AE Severity[3]			
Mild	3 (1.1)	7 (1.2)	3 (2.1)
Moderate	3 (1.1)	6 (1.0)	1 (0.7)
Severe	0	0	0
Action Taken with Study Drug			
Dose not changed	5 (1.8)	12 (2.1)	4 (2.7)
Drug interrupted	1 (0.4)	0	0
Unreported	0	1 (0.2)	0

Source: Reviewer's Table; Analysis Studio, adsl.xpt, adae.xpt; JMP, advs.xpt
[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 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
Abbreviations: AE=adverse event, BL= baseline, BP=blood pressure, BKZ=bimekizumab, DBP=diastolic blood pressure, SBP=systolic blood pressure

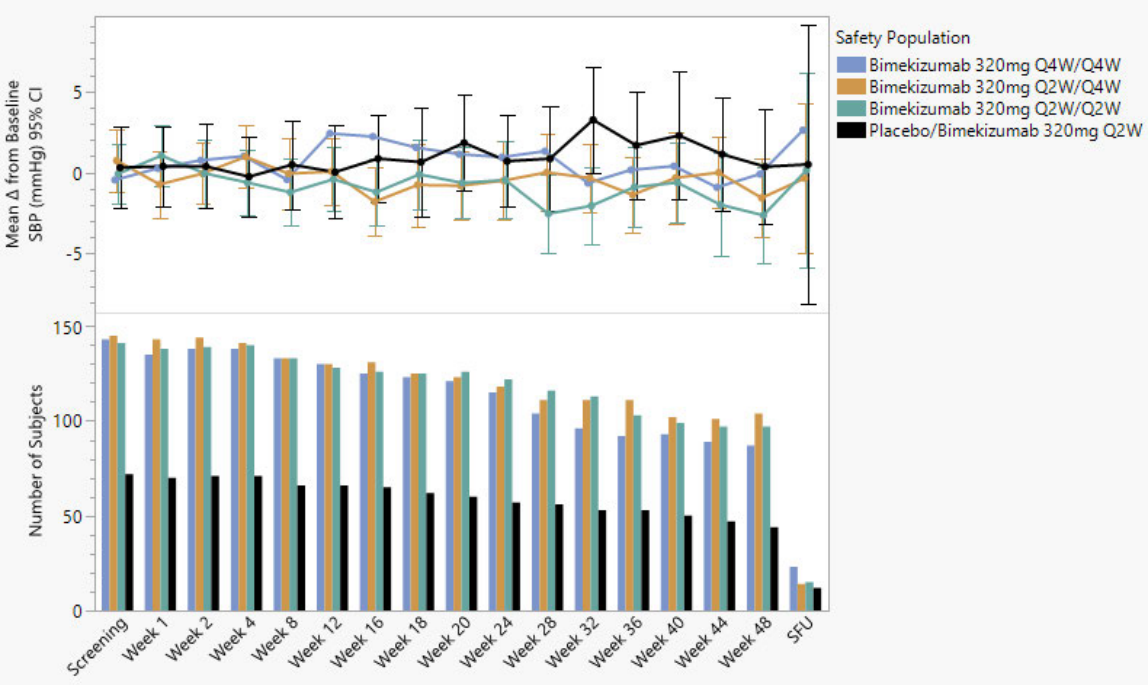
Figure 1. Mean Change from Baseline Diastolic Blood Pressure Measurement by Visit, HS0003, Safety Population



Source: Reviewer's Analysis, JMP Clinical, advs.xpt
Unscheduled visits removed; Baseline as last recorded pre-dose measurement; Placebo switched to Bimekizumab at Week 16
Abbreviations: DBP, diastolic blood pressure; CI, confidence interval; Q, every; SFU, safety follow-up; W, weeks

Reference ID: 5414132

Figure 2. Mean Change from Baseline Systolic Blood Pressure Measurement by Visit, HS0003, Safety Population



Source: Reviewer's Analysis, JMP Clinical, advs.xpt
Unscheduled visits removed; Baseline as last recorded pre-dose measurement; Placebo switched to Bimekizumab at Week 16
Abbreviations: DBP, diastolic blood pressure; CI, confidence interval; Q, every; SFU, safety follow-up; W, weeks

Table 6. Shift from Baseline to maximum post-Baseline SBP and DBP categories, Safety Pool S1

Baseline category Treatment group (Total)	Maximum post-Baseline category					
	Hypotension[a] n (%)	Normal[b] n (%)	Elevated[c] n (%)	Stage 1[d] n (%)	Stage 2[e] n (%)	Hypertensive[f] crisis
Total						
PBO (N=145 [100%])	0	7 (4.8)	12 (8.3)	70 (48.3)	53 (36.6)	3 (2.1)
BKZ 320mg Q4W (N=282 [100%])	0	12 (4.3)	18 (6.4)	140 (49.6)	111 (39.4)	1 (0.4)
BKZ 320mg Q2W (N=575 [100%])	0	30 (5.2)	48 (8.3)	277 (48.2)	214 (37.2)	6 (1.0)
BKZ Total (N=857 [100%])	0	42 (4.9)	66 (7.7)	417 (48.7)	325 (37.9)	7 (0.8)

BKZ=bimekizumab; DBP=diastolic blood pressure; ISS=Integrated Summary of Safety; PBO=placebo; Q2W=every 2 weeks; Q4W=every 4 weeks; SBP=systolic blood pressure
Note: n=number of study participants whose maximum post-Baseline blood pressure category corresponds to the given classification.
Note: Percentages based on the total number of study participants with observed data for the given treatment group.
Note: Includes all post-Baseline assessments including those at unscheduled visits but excluding any that occur more than 140 days after the last administration of study medication, counting a study participant only once.
[a]Hypotension: SBP <90mmHg or DBP <60mmHg.
[b]Normal: SBP ≥90 and <120mmHg *and* DBP ≥60 and <80mmHg.
[c]Elevated: SBP 120 to 130mmHg *and* DBP <80mmHg.
[d]Stage 1: SBP 130 to 140mmHg *or* DBP 80 to 90mmHg.
[e]Stage 2: SBP ≥140 and ≤180mmHg *or* DBP ≥90 and ≤120mmHg.
[f]Hypertensive crisis: SBP >180mmHg *and/or* DBP >120mmHg.
Source: ISS Table 8.1.3

Table 7. Adjudicated MACE with Fatal Outcome, HS0003, 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/45	HS0003/ S3	MTP	BKZ 320 mg Q2W	255	US	Cardiac failure congestive	Subject died (natural death) due to CHF; Prior to the fatal outcome, the subject experienced 1 nonserious event of heart failure exacerbation (at 5 days following first dose of bimekizumab; treated with furosemide) and 1 heart failure hospitalization (89 days following the first dose of bimekizumab; treated with furosemide and metoprolol). Non-adherence to heart failure medications was reported in narrative. Multiple comorbidities: CHF, cardiac ventricular thrombosis, myocardial infarction, ischemic cardiomyopathy, and left ventricular hypertrophy. CV risk factors: diabetes, hypertension, pacemaker, and ongoing tobacco use

BKZ=bimekizumab, CHF = congestive heart failure, MACE=major adverse cardiac event, MTP = maintenance treatment period, US=United States
Source: Subject Narrative CSR HS0003

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/s/

SELENA D DECONTI
07/16/2024 08:24:04 AM

MARY R SOUTHWORTH
07/16/2024 08:34:07 AM

NORMAN L STOCKBRIDGE
07/16/2024 09:11:16 AM

Division of Hepatology and Nutrition Consultation

Drug-induced Liver Injury Team

BLA	761151[1] S010 (S165) / INDs134700, 128707
Consultation Issue	Drug-induced liver injury (DILI)
Drug Product	Bimekizumab (BKZ)
Indication	Hidradenitis suppurativa
Applicant	UCB, Inc
Requesting Division	Division of Dermatology and Dentistry (DDD) Dixon, Strother RPM, Kevin Clark MO, Melinda McCord TL
Primary Reviewer	Eileen Navarro Almario, MD Lead Physician, OND/DHN
Secondary Reviewer	Paul H. Hayashi, MD, MPH DILI Team Lead, OND/DHN
Pharmacology and Non-clinical Reviewer	Edwige Chiogo Vouffo, PharmD, PhD Non-clinical analyst, OND/DHN
Clinical Data Scientist Reviewer	Aaron Waddell, PhD, Expert Consultant, DRT Strategies, Inc., OND/CDER
Reviewer Office of Pharmacoepidemiology	Mark Avigan, MD, CM Associate Director, OPE/OSE
Signatory Authority	Joseph Toerner, MD, MPH Director, OND/DHN
Assessment Date	May 30, 2024

Context: Bimekizumab (BKZ) is a humanized monoclonal IgG antibody that binds and inhibits interleukin (IL)-17A and 17F. It is delivered subcutaneously (SC). IL-17 is a pro-inflammatory cytokine released from T-helper (TH) 17 cells causing neutrophil recruitment and upregulation of the innate immune response. BKZ, 320 mg every four to eight weeks, was approved in 2023 for the plaque psoriasis (PSO) therapy, and the Sponsor is seeking approval for the treatment of hidradenitis suppurativa (HS) in this supplemental NDA. The proposed HS dose is the same 320 mg but given every two to four weeks. The DILI Team consulted on the psoriasis BLA (see **Attachment**). For that initial BLA, we concluded that BKZ could lead to hepatocellular and mixed liver injury but did not identify any probable Hy's Law cases. The BKZ label for the psoriasis includes liver analyte elevations discussed in the highlighted Warnings and Precautions. Liver blood tests are recommended at baseline and as clinically indicated thereafter. The Division of Dermatology and Dentistry (DDD) noted elevation in liver enzymes in the HS trials and asked the Division of Hepatology and Nutrition DILI Team to assess these events and need for labeling updates.

Executive Summary: We did not detect a liver injury risk that would preclude approval of BKZ for HS treatment. The liver injury signal was less in this supplemental BLA compared to the original BLA for PSO. While there were more aminotransferase (AT) elevations in the BKZ treated arms compared to placebo, we often did not attribute the elevations to BKZ on

[1] \\CDSESUB1\evsprod\IND139803\0042

Reference ID: 5390131

case level assessments. There were no Hy's Law or cholestatic jaundice cases. However, the number exposed in HS trials was only half as many as those in the PSO trials, so underpowering is a possible explanation for less liver injury seen. Nevertheless, the liver injuries in the HS trials tended to be modest and resolved quickly. In many cases resolution occurred while continuing BKZ. Therefore, the current label's highlighted Warnings and Precautions section regarding "Liver Biochemical Abnormalities" is sufficient. Additional liver analyte data from the HS trials will need to be added in the non-highlighted sections of the label. Our full assessment and recommendations are in Section 5.0 of this consult.

Consultation Sections:

Section 1.0 Target Disease and Rationale
Section 2.0 ADME pertinent to DILI risk
Section 3.0 Non-clinical Data
Section 4.0 Clinical data
Section 5.0 Assessment & Recommendations
Attachment: DILI Team consult for bimekizumab psoriasis BLA

Abbreviations:
ADA: anti-drug antibody
ADME: absorption, distribution, metabolism, excretion
ALP or AP: alkaline phosphatase
ALT: alanine aminotransferase
AP: alkaline phosphatase
AST: aspartate aminotransferase
AT: aminotransferase (ALT and/or AST)
BMI: body mass index
BKZ: bimekizumab
CPK or CK: creatine phosphokinase
CYP: cytochrome P450
DB: direct bilirubin
DDI: drug-drug interaction
DILI: drug-induced liver injury
GGT: gamma-glutamyl transferase
HS: hidradenitis suppurative
IP: investigational product
mAb: monoclonal antibody
MRI: magnetic resonance imaging
NCTR: National Center for Toxicological Research
PsO: plaque psoriasis
R-value: ALT/ULN ÷ ALP/ULN
RPCT: randomized placebo controlled trial
SC: subcutaneous
TB: total bilirubin
US: ultrasound
ULN: upper limit of normal

Section 1.0 Disease and Rationale:

1.1 Hidradenitis suppurativa (HS): HS is a chronic Th1/Th17- driven inflammatory skin disease marked by follicular occlusion leading to papulonodular abscesses and draining sinuses in the

interdigital areas of the skin. Bystander CD4 cells undergo differentiation to TH1 or TH17 cells in the follicle, resulting in more inflammatory cell recruitment (**Figure 1**). HS prevalence is about 1% in the US and is more common in women. Keratin plugs in hair follicles leads to rupture of the dilated follicles and immunologic response to the release of their contents into the dermis. Environmental factors may also contribute to HS (e.g., tight occlusive dressing, smoking, obesity, deodorant use, shaving, excessive sweating). Genetic studies suggest monogenic deficiency in g secretase or polygenic defects lead to proliferation of the follicular epithelium and immune dysregulation in HS. Up to 40% of HS patients have a family history of HS.

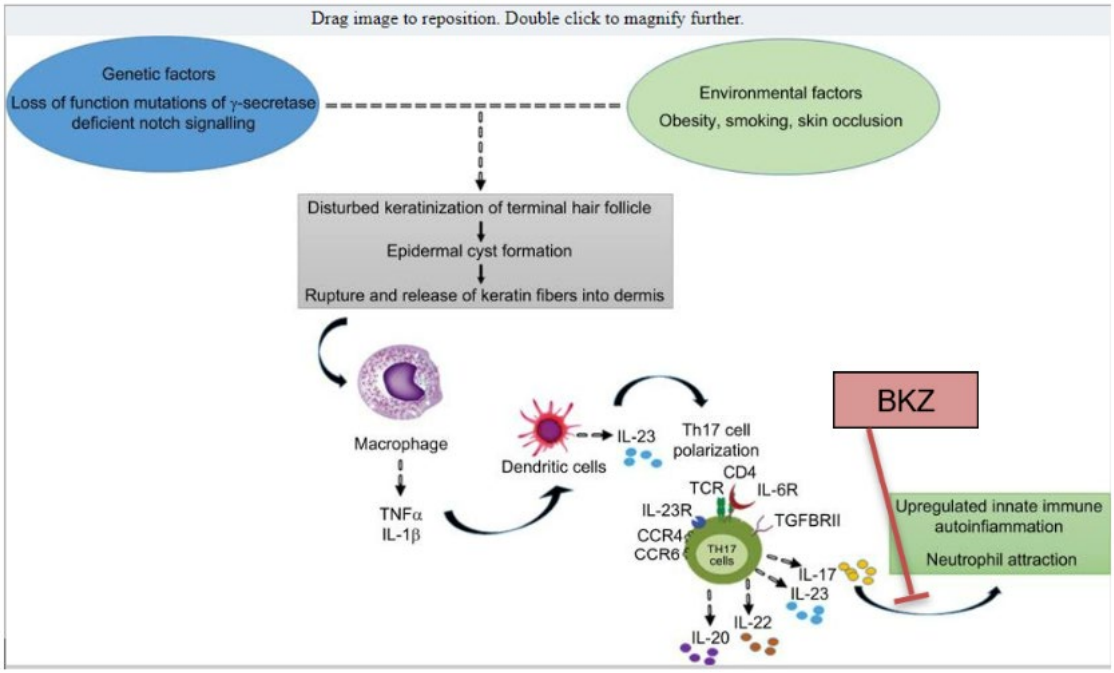


Figure 1: Hidradenitis suppurativa pathophysiology[2]

There are two FDA approved medications for HS: adalimumab (anti-tumor necrosis factor) approved in 2015 and secukinumab (anti-IL17) approved in 2023.Topical keratinolytics (resorcinol) and immunomodulators (e.g., intralesional corticosteroids) have been used with limited success. Systemic antibiotics such as clindamycin, tetracycline, dapsone and rifampin are also used. Oral cyclosporine and systemic corticosteroids are used in flares, and other immunosuppressants are used off label.

1.2 Rationale for Drug Use: Bimekizumab (BKZ) is a humanized IgG1/k monoclonal antibody that binds and inhibits IL-17A, IL-17F, and IL-17AF cytokines from interacting with the IL-17RA/IL-17RC receptor (**Figures 1 & 2**). It's derived from a rat model immunized with recombinant human IL-17A. The antibody is then humanized with human IgG protein sections. The levels of IL-17A and IL-17F are elevated in many immune-mediated inflammatory disorders leading to chronic inflammation.[8] A BKZ solution of 160 mg/mL is injected subcutaneously.[10]

[2] Modified from Napolitano M, et al. Hidradenitis suppurativa: from pathogenesis to diagnosis and treatment. *Clin Cosmet Investig Dermatol*. 2017;10:105-115. doi: 10.2147/CCID.S111019

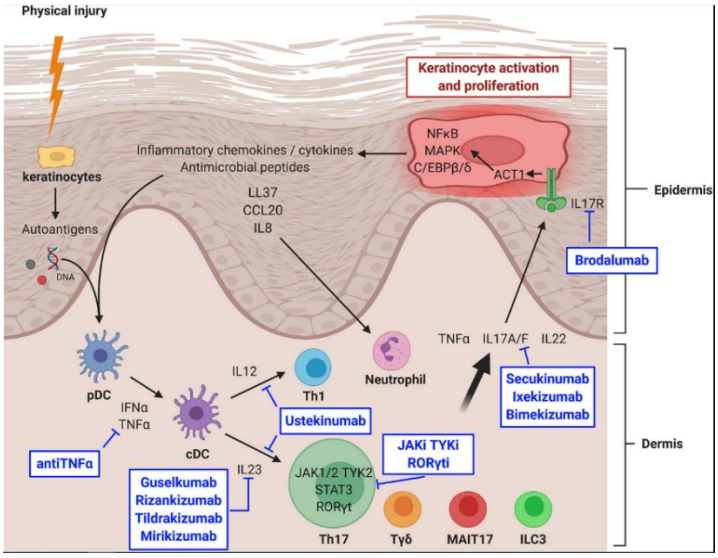
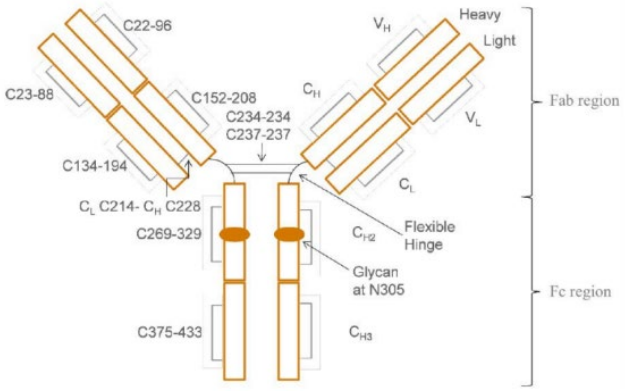


Figure 2: Bimekizumab and other drugs mechanism of action in the dermis[11]

2.0 ADME and DDI data pertinent to DILI



2.1 General Structure: See **Figure 3**.

Figure 3: Schematic of BKZ protein structure[3]

2.2 Absorption: Peak plasma concentration of BKZ after SC dosing in monkeys was about 2 days. BKZ bioavailability was 60-90%. In both healthy volunteers and patients with mild to moderate plaque psoriasis, bioavailability was 70%. Exposure was proportional to dose and there was accumulation following repeat dosing up to 26-week in monkeys. Hence, BKZ is slowly absorbed with good bioavailability.

2.3 Distribution: BKZ distribution is like other IgG1s. The mean volume of distribution in monkeys was 93.9-97.4 mL/kg. Convective extravasation might be the main distribution process for monoclonal antibodies (mAb). Following extravasation, mAb depends on diffusion, convection, and affinity to target antigens within the interstitial space or on cell surfaces in specific tissues. Without any target antigens for the mAb to bind to, or if the target is in the plasma, the distribution will be expected to be limited. For large proteins such as IgG molecules, the tissue distribution is further hindered by extravascular matrix. Thus, BKZ is distributed via extravasation and level of distribution expected to depend on distribution of the target antigen.

2.4 Metabolism: BKZ's catabolism is mediated by non-specific cell uptake throughout the body. Thereafter lysosomal degradation via proteases occurs. Typical cytochrome metabolism is not

[3] BLA761151 (761151 - 5076 - (213) - 2024-04-10 - MARKETING-77 /Marketing/2253 Consumer) - Introduction - PSO (#4)

involved. Reactive metabolite formation is not expected, though neoantigen and anti-drug (ADA) formation are possible.

2.5 Excretion: Monoclonal antibodies, like other IgG antibodies, are too large to be filtered by the kidneys, and therefore, not eliminated via urine, nor do IgG antibodies show up in bile. BKZ's mean clearance was 4.8 to 5.1 mL/kg/day similar to other IgG antibodies. BKZ lysosomal degradation to amino acids prevents parent drug excretion by the liver or kidney. Following single and repeat dosing in monkeys, there was slow clearance with a terminal $T_{1/2}$ of 10 to 14 days. ADAs appeared in pregnant monkey plasma and their newborn infants. Thus, bimekizumab is excreted slowly by lysosomal degradation, but ADA formation may occur.

2.6 Human pharmacology relevant to the patient population:[4] The mean steady state trough concentration in HS is 40% lower than that of PSO subjects and the Vd 18% higher than in subjects with HS. Moreover, apparent clearance in subjects with HS is estimated to be higher than PSO patients by 31%. The proposed dose for HS is 320 mg q2 weekly vs the q4 weekly dosing from PsO. During the 48-week treatment period in the randomized placebo-controlled HS studies, 59% had anti BKZ ADA and 37% had neutralizing ADA.

ADME summary findings are in **Table 1**.

Table 1: ADME summary table[5]

Item	Finding
Absorption	Slow absorption, Tmax: ~2 days
Distribution	Limited, mean volume of distribution in monkeys was 93.9-97.4 mL/kg
Metabolism	Catabolism followed by lysosomal degradation diffusely
Elimination	Diffuse protein degradation; $T_{1/2}$:10-14 days in monkeys

2.6 Drug-Drug Interactions (DDI): No DDI studies were done for BKZ. Monoclonal antibodies are not expected to cause DDI because their catabolism to peptides that does not overlap with small molecule metabolism pathways using enzymes such as the CYPs and uridine-5'-diphosphate glycosyltransferase. In animal studies, adalimumab led to a slight decrease in BKZ exposure by unknown mechanism, but ADAs against both drugs formed which may have had a role. Some cytokines including IL-1β, IL-6, TNFα, and IFN are known to influence the formation and the activity of some CYPs; therefore, blocking or enhancing such cytokines may lead to DDIs.

3.0 Non-clinical data

3.1 In vitro data: There were no in vitro data suggestive of DILI risk.

3.1 Animal data: Following weekly IV/SC administration at 200 mg/kg/week for eight weeks in monkeys NOAEL was 64.5 mg/kg/week in humans. In comparison, BKZ's maximum clinical dose is 320 mg/week, or 3.5 mg/kg/week and 4.1 mg/kg/week an average adult US male

[4] BLA761151 (761151 - 0116 - (165) - 2024-01-19 - SUPPL-10 (Efficacy) /Multiple Categories/Subcategories) - Summary of Clinical Efficacy - HS (#5)
[5] Table made by DILI Team

(average weight, 91 kg) and female (average weight, 78 kg).[6] No liver histopathology or liver enzyme changes occurred in animal studies.

Summary of non-clinical findings related to DILI risk is in **Table 2.** Overall, non-clinical data do not suggest a DILI risk with BKZ. Overall, non-clinical data do not suggest a significant DILI risk.

Table 2: Summary of non-clinical data pertaining to DILI risk [4]

Item	Finding
In Vitro Studies	
Major CYPs or UGTs	N/A
Reactive metabolites (i.e., glutathione trapping)	N/A
Mitochondria studies/inhibition	N/A
Time dependent inhibition	N/A
LogP (lipophilicity) values >3 associated with increased DILI risk	N/A
Covalent binding	N/A
Transporter (BSEP or MRP2 inhibition)	N/A
Animal Studies	
Elevation in liver analytes (e.g., ALT, AP, TB)	No changes
Liver histopathology findings (animal species)	No changes

4.0 Clinical data:

4.1 In class or near class data: There are at least four monoclonal, anti-IL17 drugs approved. BKZ was already approved for psoriasis (PSO) in 2023. The DILI Team consulted on that BLA application (**Attachment**). Labeling and LiverTox information are in **Table 3** and FAERS data in **Table 4**.

Table 3: Approved anti-IL 17 monoclonal antibodies with DILI information by label and LiverTox®[20]

Drug (Brand)	**Mechanism of action**	**Approval year (s), Target Disease(s)**	**Labeling regarding DILI in** • Box Warning (BW) • Warnings/Precautions, Highlights (W/P, HL) • Adverse Reactions, Highlights (AR, HL) • Sections 5 & 6 (S5 & S6)	**LiverTox® category**[21]
Bimekizumab (Bimzelx®)	Monoclonal Anti-IL17A 17F	2023 PSO	• **BW**: No • W/P, HL: Yes; baseline liver tests to be checked & as needed thereafter. • AR, HL: No • S5: No • S6: Yes, elevated liver enzymes, hepatitis	Not available

[6] https://www.cdc.gov/nchs/fastats/body-measurements.htm

Secukinumab (Cosentyx®)	Monoclonal, anti-IL17	2015 PSO 2016 AS 2020 AxS 2021 ERA 2023 HS	• **BW**: No • W/P, No • AR, HL: No • S5: No • S6: No	E: unlikely cause of clinically apparent liver injury
Ixekizumab	Monoclonal, anti-IL17	2016 (PSO) 2017 (PSA) 2019 (AS) 2020 (NRAS)	• **BW**: No • W/P, HL: No • AR, HL: No • S5: No • S6: No	E: unlikely cause of DILI
Brodalumab	Monoclonal, anti-IL17	2017 (PSO)	• **BW**: No • W/P, HL: No • AR, HL: No • S5: No • S6: No	E: unlikely cause of DILI

AR = Adverse Reactions; AS: ankylosing spondylitis, AxS: axial spondylarthritis; BW = box warning; , CD: Crohn's disease, ERA: enthesitis related arthritis; HL = highlighted (page 1 of label); HS: hidradenitis suppurativa; NA = not available; RA: rheumatoid arthritis; S5 = Label Section 5; S6 = Label Section 6; W/P = Warnings and Precautions; PSA: psoriatic arthritis, PSO: psoriasis; .

Table 4: Results of FAERS and PubMed Searches related to DILI for xx marketed anti-IL17 monoclonal antibodies.

Drug (Initial approval year)	FAERS Total hepatobiliary reports (DILI, hepatotoxicity)[7]	Metys®[22] based rate of total reports per patients prescribed drug (%)[8]
Secukinumab (2015)	3180 (328, 70)	0.07% (n = 432,800)
Bimekizumab (2023)	3 (0, 0)	0.10% (n = 2857)
Ixekizumab	217 (17, 14)	0.09% (n = 248,342)
Brodalumab	56 (0, 0)	0.98% (n = 5740)

PubMed search using two different search syntaxes yielded no cases of hepatotoxicity for Bimekizumab. One publication indicates the rates of "severe" transaminase elevations were similar to comparators.[9]

4.2 Clinical Studies

4.2.1 Overview of Studies: The DILI Team focused on one phase 2 and three phase 3 studies (**Table 5**). In collaboration with our Clinical Data Scientist (CDS) colleagues, we did three grouped analyses (**Figure 4**). Only analyses 1 and 2a have placebo arms, but 1 has fewer

[7] https://fis.fda.gov/sense/app/95239e26-e0be-42d9-a960-9a5f7f1c25ee/sheet/8eef7d83-7945-4091-b349-e5c41ed49f99/state/analysis
[8] https://metys.symphonyhealth.com/metys/#/home/prescriptionQuery
[9] Lebwohl M, et al. Bimekizumab safety in moderate to severe plaque psoriasis: Rates of hepatic events and changes in liver parameters over 2 years in randomized phase 3/3b trials. *J Am Acad Dermatol*. 2024 Apr 6:S0190-9622(24)00568-1. doi: 10.1016/j.jaad.2024.03.041. Epub ahead of print. PMID: 38588819.DOI: 10.1016/j.jaad.2024.03.041

patients.

Table 5: Table of Clinical Studies Reviewed by DILI Team.

Study	Trial Population	Trial Design	Treatment Duration	Planned Patients #	Study Status
HS0001	Adults moderate/severe HS	Phase 2, MC, R, investigator/patient blind, PC, AC	12 wks	BKZ n = 46 Adalimumab n = 21 PBO n = 21	Complete
HS0003	Adults w/ moderate/severe HS	Phase 3, MC, R, DB, PC w/ MP	48 wks	**Based on initial period** BKZ 320mg Q2W n = 289 BKZ 320mg Q4W n = 144 PBO n = 72	Ongoing
HS0004	Adults w/ moderate/severe HS	Phase 3, MC, R, DB, PC w/ MP	48 wks	**Based on initial period** BKZ 320mg Q2W n = 291 BKZ 320mg Q4W n = 144 PBO n = 74	Complete
HS0005	Adults w/ moderate/severe HS	Phase 3, OL, MC	100 wks	BKZ n = 653	Ongoing

Modified from CDS report.

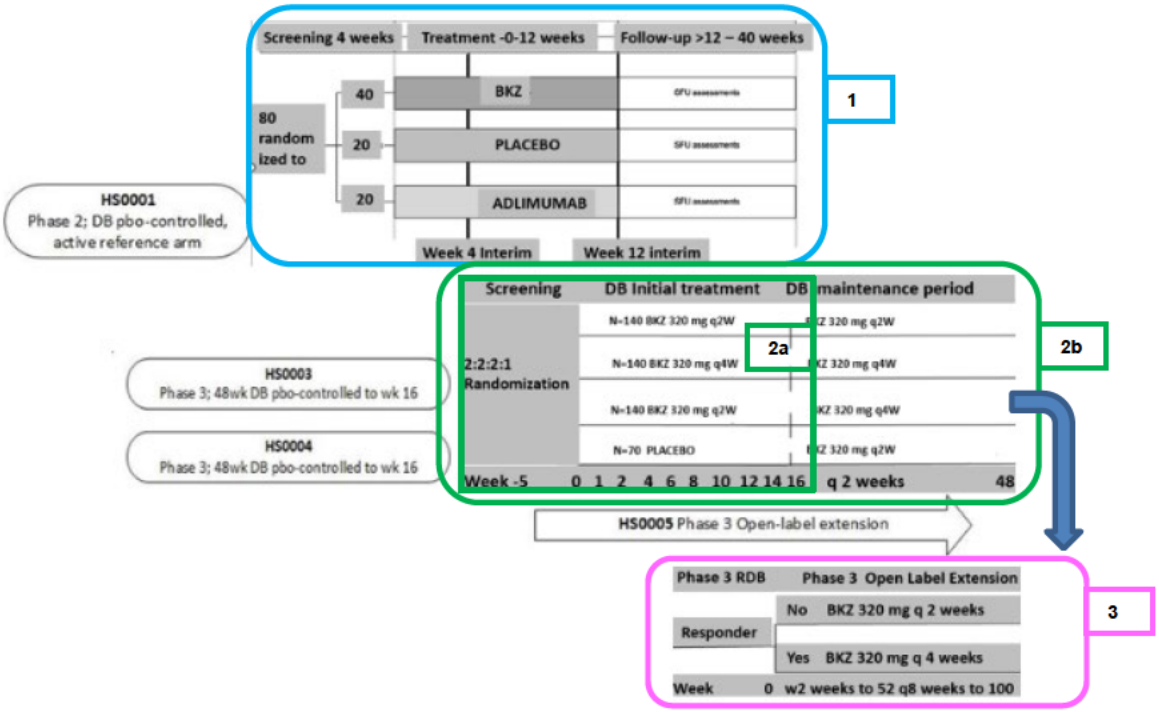


Figure 4: Schematics for four studies of focus and CDS analyses 1, 2 (2b includes 2a) and 3. HS0005 enrolls from HS0003 and HS0004, hence analysis 3 includes data from 2).

Enrollment numbers by study arms and pooling are shown in **Table 6**. Overall, 1041 subjects were exposed to BKZ.

Reference ID: 5390131

Table 6: Number of subjects by pool, study arm and CDS analyses in BKZ Trials[10]

Pooling[11]	16-week treatment Pool 1 (CDS analysis 2a)		48-week treatment Pool 2 (CDS analysis 2b)		Pool 3[12]	
ARM Dose	BKZ	Placebo	BKZ	BKZ	Phase 3 (CDS Analyses 2 & 3)	Phase 2/3 (CDS Analyses 1, 2, & 3)
320 q2	576	146				
320Q4	285					
320Q2W/Q2W			286			
320Q2W/Q4W				291		
320Q4W/Q4W				285		
ALL Doses					995	1041

4.2.2 CDS Analysis #1: This analysis included only HS0001. Just 46 subjects were exposed to BKZ in this study. There were no liver enzyme (excluding GGT) or bilirubin elevations, nor liver related AEs in subjects taking BKZ.

4.2.3 CDS Analysis #2: This analysis included two phase 3 studies HS0003 and HS0004, each of which enrolled 6:1, BKZ to placebo. The BKZ arms were split evenly across three dosing arms: 320 mg SQ/Q2 weeks followed by the same in maintenance (Q2/Q2), 320 mg SQ/Q4 weeks followed by the same in maintenance (Q4/Q4), and 320 mg SQ/Q2 weeks followed by Q4 week dosing in maintenance (Q2/Q4).

4.2.3.1 Analysis 2a: This CDS analysis included the 16-week randomized, placebo-controlled trial (RPCT) data of HS0003 and HS0004. The hepatocellular DILI screening plot (eDISH) had no subjects in the potential Hy's Law quadrant, but there were ten subjects on BKZ in Temple's and one on placebo (**Figure 5**). The three with AT elevations >5x ULN met criteria for concerning for clinically important DILI, but we assessed all three as unlikely DILI due to BKZ. There were four subjects in the cholestasis quadrant on BKZ and none on placebo (Figure not shown). None of these four moved to the right upper quadrant of the cholestatic DILI screening plot. Therefore, none of these four jaundiced subjects had ALP levels >2x ULN or AT >3x ULN making DILI unlikely in a non-cirrhotic population of subjects.

[10] Made by DILI Team
[11] BLA761151 (761151 - 0116 - (165) - 2024-01-19 - SUPPL-10 (Efficacy) /Multiple Categories/Subcategories) - Clinical Overview - HS (#90)
[12] BLA761151 (761151 - 0116 - (165) - 2024-01-19 - SUPPL-10 (Efficacy) /Multiple Categories/Subcategories) - Clinical Overview - HS (#61)

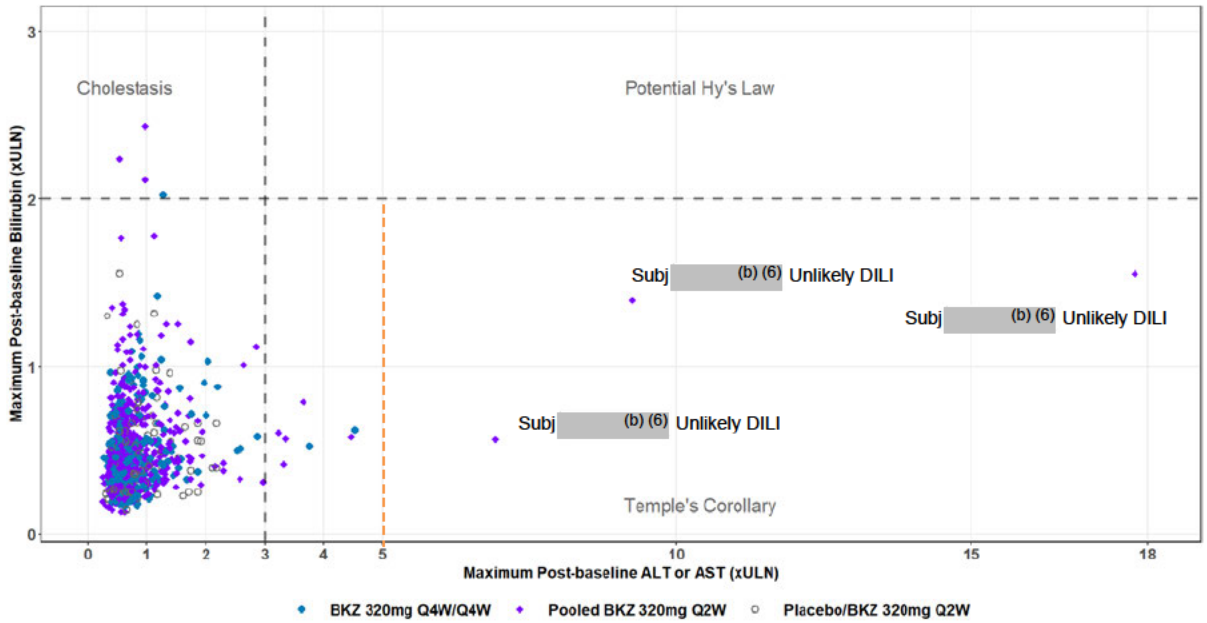


Figure 5: Hepatocellular DILI screening plot (eDISH) for Analysis 2a (HS0003 and HS0004 during the 16-week randomized, placebo-controlled portion.[13] The 320 mg Q2W arm combines those assigned to continue Q2 week dosing and those assigned to Q4 week dosing in maintenance, after 16-week portion of the studies.

Liver analyte elevations at varying cut-off values recapitulate the eDISH plot for AT (AST or ALT) elevations, but AST accounted for most the AT elevations (**Table 7**).

[13] Made by CDS

Table 7: Liver analyte elevations by set cut-off criteria between study arms in HS0003 and HS0004 during the 16-week randomized placebo-controlled period.[14]

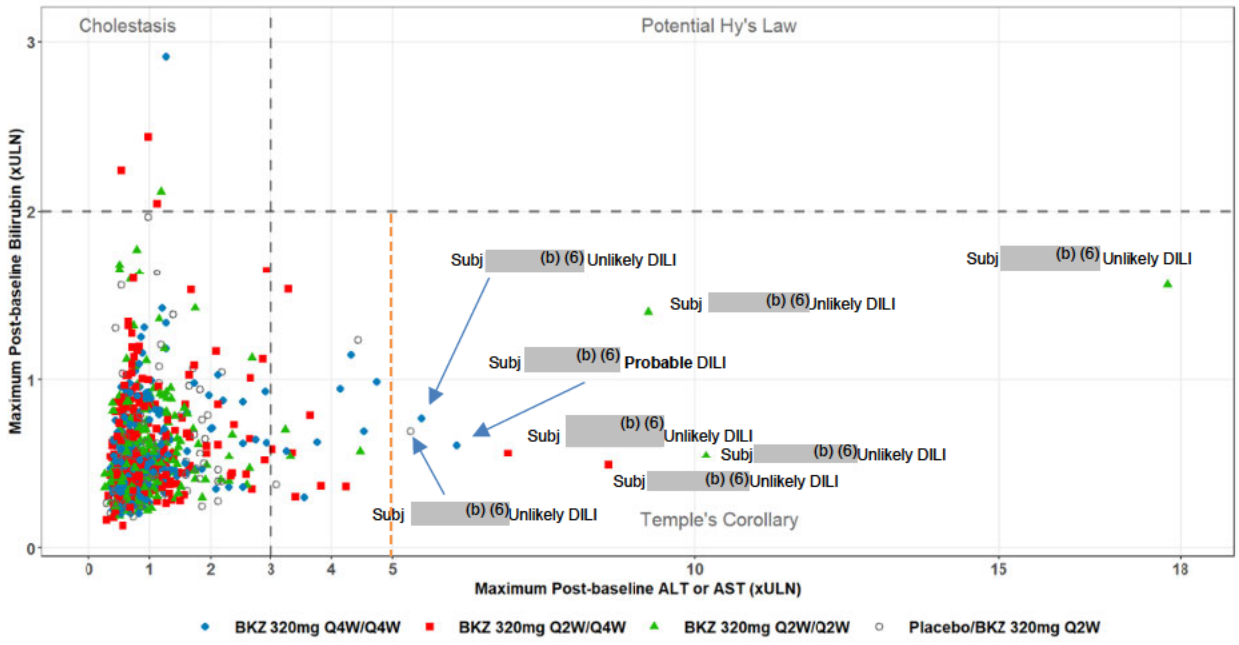
Laboratory Abnormality	BKZ 320mg Q4W/Q4W N=285 n (%)	Pooled BKZ 320mg Q2W N=576 n (%)	Placebo/BKZ 320mg Q2W N=146 n (%)	Q2W vs Placebo/BKZ 320mg Q2W Risk Difference (%) (95% CI)
ALT				
>=1X ULN	27/282 (9.6)	68/572 (11.9)	15/144 (10.4)	1.5 (-5.0, 6.5)
>=3X ULN	0/282 (0)	3/572 (0.5)	0/144 (0)	0.5 (-2.1, 1.5)
>=5X ULN	0/282 (0)	1/572 (0.2)	0/144 (0)	0.2 (-2.4, 1.0)
>=10X ULN	0/282 (0)	1/572 (0.2)	0/144 (0)	0.2 (-2.4, 1.0)
>=20X ULN	0/282 (0)	0/572 (0)	0/144 (0)	0.0 (-2.6, 0.7)
AST				
>=1X ULN	37/282 (13.1)	85/572 (14.9)	24/144 (16.7)	-1.8 (-9.2, 4.3)
>=3X ULN	2/282 (0.7)	8/572 (1.4)	0/144 (0)	1.4 (-1.2, 2.7)
>=5X ULN	0/282 (0)	3/572 (0.5)	0/144 (0)	0.5 (-2.1, 1.5)
>=10X ULN	0/282 (0)	1/572 (0.2)	0/144 (0)	0.2 (-2.4, 1.0)
>=20X ULN	0/282 (0)	0/572 (0)	0/144 (0)	0.0 (-2.6, 0.7)
ALP				
>=2X ULN	0/282 (0)	0/572 (0)	0/144 (0)	0.0 (-2.6, 0.7)
>=3X ULN	0/282 (0)	0/572 (0)	0/144 (0)	0.0 (-2.6, 0.7)
Total Bilirubin				
>=2X ULN	1/282 (0.4)	3/572 (0.5)	0/144 (0)	0.5 (-2.1, 1.5)
>=5X ULN	0/282 (0)	0/572 (0)	0/144 (0)	0.0 (-2.6, 0.7)
>=8X ULN	0/282 (0)	0/572 (0)	0/144 (0)	0.0 (-2.6, 0.7)
Direct Bilirubin				
>=2X ULN	0/8 (0)	1/31 (3.2)	0/4 (0)	3.2 (-46.8, 16.5)
>=5X ULN	0/8 (0)	0/31 (0)	0/4 (0)	0.0 (-49.7, 11.3)
GGT				
>=2X ULN	19/282 (6.7)	36/572 (6.3)	7/144 (4.9)	1.4 (-3.7, 4.9)

Source: adlb.xpt; Software: R

4.2.3.1 Analysis 2b: CDS Analysis 2b includes data from 2a but extends into the maintenance phases of studies HS0003 and HS0004 which include 48 weeks of therapy. In the maintenance phases (i.e., after the first 16 weeks), the placebo arm is lost with all placebo subjects switching to BKZ treatment. The hepatocellular DILI screening plot (eDISH) had no subjects in the potential Hy's Law quadrant but 27 subjects in Temple's quadrant, eight of which had ATs >5x ULN (**Figure 6**). Of these eight we assessed just one as probable DILI due to BKZ. Five subjects in the cholestasis quadrant (scatterplot not shown), did not move to the right upper quadrant in the cholestatic DILI scatterplot, suggesting no cholestatic DILI with jaundice occurred. Indeed, there were no cases in the right lower quadrant of the cholestatic screening plot either.

[14] Made by CDS

Reference ID: 5390131



Source: adlb.xpt; Software: R

Figure 6: Hepatocellular DILI screening plot (eDISH) for analysis 2b which included randomized controlled trial and maintenance parts of studies HS0003 and HS0004.[15]

Like the 16-week RPCT data in analysis 2a, AST elevations were more frequent compared to ALT (**Table 8**).

[15] Made by CDS

Reference ID: 5390131

Table 8: Liver analyte elevations by set cut-off criteria between study arms in HS0003 and HS0004 during the 16-week randomized placebo-controlled period and maintenance phase (up to 48 weeks).[16]

Laboratory Abnormality	BKZ 320mg Q4W/Q4W N=285 n (%)	BKZ 320mg Q2W/Q4W N=291 n (%)	BKZ 320mg Q2W/Q2W N=285 n (%)	Placebo/BKZ 320mg Q2W N=146 n (%)
ALT				
>=1X ULN	45/282 (16.0)	50/289 (17.3)	49/283 (17.3)	28/144 (19.4)
>=3X ULN	2/282 (0.7)	3/289 (1.0)	2/283 (0.7)	0/144 (0)
>=5X ULN	1/282 (0.4)	0/289 (0)	1/283 (0.4)	0/144 (0)
>=10X ULN	0/282 (0)	0/289 (0)	1/283 (0.4)	0/144 (0)
>=20X ULN	0/282 (0)	0/289 (0)	0/283 (0)	0/144 (0)
AST				
>=1X ULN	67/282 (23.8)	71/289 (24.6)	68/283 (24.0)	42/144 (29.2)
>=3X ULN	8/282 (2.8)	7/289 (2.4)	6/283 (2.1)	3/144 (2.1)
>=5X ULN	1/282 (0.4)	2/289 (0.7)	3/283 (1.1)	1/144 (0.7)
>=10X ULN	0/282 (0)	0/289 (0)	2/283 (0.7)	0/144 (0)
>=20X ULN	0/282 (0)	0/289 (0)	0/283 (0)	0/144 (0)
ALP				
>=2X ULN	0/282 (0)	0/289 (0)	0/283 (0)	0/144 (0)
>=3X ULN	0/282 (0)	0/289 (0)	0/283 (0)	0/144 (0)
Total Bilirubin				
>=2X ULN	1/282 (0.4)	3/289 (1.0)	1/283 (0.4)	0/144 (0)
>=5X ULN	0/282 (0)	0/289 (0)	0/283 (0)	0/144 (0)
>=8X ULN	0/282 (0)	0/289 (0)	0/283 (0)	0/144 (0)
Direct Bilirubin				
>=2X ULN	0/12 (0)	1/24 (4.2)	0/17 (0)	0/10 (0)
>=5X ULN	0/12 (0)	0/24 (0)	0/17 (0)	0/10 (0)
GGT				
>=2X ULN	28/282 (9.9)	34/289 (11.8)	20/283 (7.1)	9/144 (6.2)

Source: adlb.xpt; Software: R

4.4 CDS Analysis #3: This analysis extends the data from Analyses 2a and 2b to include longer-term data from the phase 3 OLE study, HS00005. The analysis yielded one more case in Temple's with ATs >5x ULN (Subject (b) (6). We assessed it as unlikely DILI due to a latency of 1.85 years, rapid resolution while still taking BKZ, and a competing diagnosis of mononucleosis with liver enzyme elevation. Cholestatic plots had two subjects on BKZ in the right lower quadrant (i.e., peak ALP>2x ULN). Both subjects were adjudicated as unlikely DILI. One subject was the same one identified in Temple's on eDISH discussed above (Subject (b) (6)). The other subject (b) (6)) also had a long latency at 1.27 years and with resolution too quick for DILI (6 days) particularly if immune mediated.

4.5 Case level analyses: We assessed cases across the HS0001, HS0003, HS0004 and HS0005 with any of the following criterion:

- Sponsor identified potential Hy's law case
- ALT or AST >3x ULN with TB >2x ULN
- ALT or AST >5x ULN
- ALP> 2x ULN
- AEs under the Hepatic Failure Subgrouping in the Hepatobiliary System Organ Class.

Overall, we assessed 17 subjects for potential DILI. We considered one as probable DILI due to BKZ and three as possible. We assessed the rest as unlikely. There were no subjects with jaundice (TB >2x ULN) and thus no Hy's Law cases. We agreed with the sponsor that Subject 40286-18096 is the one probable case of DILI due BKZ. This subject is discussed in detail

[16] Made by CDS

Reference ID: 5390131

below (Section 4.5.1). The three possible DILI cases had confounding alternative diagnoses (**Table 9**).

Table 9: Four subjects with at least possible DILI due to BKZ[17]

#	ID	Causality Score*	Alternate diagnosis	Age (y)	Sex	Race	Latency from start drug (d)	Latency from stop drug (d)~	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	NA	24	F	White	129	[98]	243	82	104	0.41	7.15	2.41
2		4	Alcohol	41	F	Black	449	[13]	186	163	104	0.41	5.47	4.79
3		4	Cocaine/stone	18	F	White	448	0	325	166	NA	NA	NA	NA
4		4	Isoniazid	29	M	White	14	[76]	226	152	104	0.47	6.65	4.47
			Average	*28*			*[47]*	*[132]*	*245*	*141*	*104*	*0.43*	*6.4*	*3.9*
			Std dev	*8.46*			*41*	*149*	*51*	*34*	*0*	*0.03*	*0.7*	*1.1*
			Median	*26.5*			*[45]*	*[87]*	*235*	*158*	*104*	*0.41*	*6.6*	*4.5*
			Min	*18*			*[98]*	*[476]*	*186*	*82*	*104*	*0.41*	*5.5*	*2.4*
			Max	*41*			*0*	*14*	*325*	*166*	*104*	*0.47*	*7.1*	*4.8*

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

~Bracketed [ ] day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

The unlikely cases are shown in **Table 10**. Overall, most of these injuries had long latencies and often resolved rapidly without stopping BKZ. Such an injury pattern would be inconsistent with DILI particularly because monoclonal antibodies are expected to have a substantial immune component to liver injury if it does occur. Such immune mediated DILI is expected to resolve more slowly. They were two subjects with probable myopathy along with several others we suspect had myopathy but did not have CK levels checked. These cases are noteworthy because they might explain some of the preponderance of AST elevations over ALT; AST is generally higher than ALT in myopathies. The subject with the highest AT values (Subject 40249-17257) had a history of widely fluctuating liver enzymes and her ALT had already increased 10-fold from her baseline on the day she started BKZ, making DILI unlikely, and autoimmune hepatitis (AIH) more likely. She also received COVID-19 vaccination just before the liver injury and rare cases of post-vaccination liver injury are reported.

[17] Made by DILI Team

Table 10: Thirteen subjects with unlikely DILI to BKZ[18].

#	ID	Causality Score*	Alternate diagnosis	Age (y)	Sex	Race	Latency from start drug (d)	Latency from stop drug (d)~	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)	5	Myopathy	24	M	White	28	[476]	88	180	104	0.47	2.59	5.29
2		5	Myopathy	41	M	Black	393	[277]	59	177	104	1.05	1.74	5.21
3		5	?myopathy	21	F	Black	333	[114]	102	291	104	0.35	3.00	8.56
4		5	?myopathy	25	M	White	83	[277]	159	314	104	1.29	4.68	9.24
5		5	?myopathy	23	M	White	224	[14]	143	346	104	0.64	4.21	10.18
6		5	?myopathy	31	M	White	113	[117]	90	235	104	0.7	2.65	6.91
7		5	Alcohol	25	M	White	448	[224]	145	235	104	1.29	4.26	6.91
8		5	Alcohol	51	M	White	399	[401]	166	238	104	0.58	4.88	7.00
9		5	Fatty liver	40	F	White	126	14	239	167	104	0.53	7.03	4.91
10		5	AIH; Covid vaccine	18	F	White	0	[14]	978	514	104	1.17	28.76	15.12
11		5	Unknown	47	F	Black	448	0	NA	700	345	0.58	NA	6.21
12		5	Unknown	18	M	White	283	[27]	148	161	104	0.58	4.35	4.74
13		5	EBV	21	F	White	653	[75]	272	192	269	0.76	3.09	2.18

*1=definite, 2=highly likely, 3=probable, 4=possible, 5=unlikely, 6=indeterminate

^For purposes of R-value calculations, the ULNs were imputed if ALT, AST or AP did rise above the ULN

~Bracketed [ ] day values mean the drug continued for that many days after injury onset.

R-value = (ALT/ULN) ÷ (AP/ULN) or (AST/ULN) ÷ (AP/ULN); hepatocellular: R-values ≥ 5; mixed: 2-5; cholestatic: R-value < 5

ULNs used for R-values: ALT 34 U/L, AST 34 U/L, AP 104 U/L, TB 1.2 mg/dL

NA = not available or not applicable

4.5.1 Case of interest:

1. Subject (b) (6) (HS0004): probable DILI due to BKZ.

Summary: This is a 24-year-old female, white, with HS, who developed elevated aminotransferases approximately 129 days after starting BKZ. Initial dose was 320 mg SC q4 weeks.

At baseline, the subject's BMI was 32 kg/m^2. Relevant medical history, besides the target disease, included obesity, chronic diarrhea, chronic nausea and vomiting, and Cushing's syndrome. Alcohol history was described as "no alcohol intoxication." Concurrent medications relevant to DILI risk were ethinylestradiol with levonorgestrel. The subject's ALT, AST, AP, and TB were 24 U/L, 21 U/L, 85 U/L, and 0.5 mg/dL, respectively.

The subject started BKZ at 320 mg subcutaneously (SC) q4 weeks on (b) (6) (Day 1). On (b) (6) (Day 129), ALT, AST, AP, and TB were 73 U/L, 31 U/L, 86 U/L and 0.6 mg/dL, respectively. The study drug continued without change. The subject had ongoing issues with diarrhea, nausea, and vomiting which were evaluated extensively during the trial. Thereafter, her ALT and AST gradually increased further (**Figure 7**), and study drug was stopped with last dose on (b) (6) (Day 227). Liver enzymes continued rise to last documented (peak) levels on (b) (6) (Day 253), were ALT, AST, AP, and TB of 253 U/L, 81 U/L, 79 U/L and 0.76 mg/dL, respectively. No further lab values were provided, but the narrative says the "liver function tests were almost normal" by (b) (6) (Day 281). Evaluation testing results were not mentioned. Liver imaging by ultrasound was normal. However, the narrative states that "after discussion with the hepatologist, the Investigator considered hepatic cytolysis as related to the study drug by the elimination of other plausible

[18] Made by DILI Team

causes."

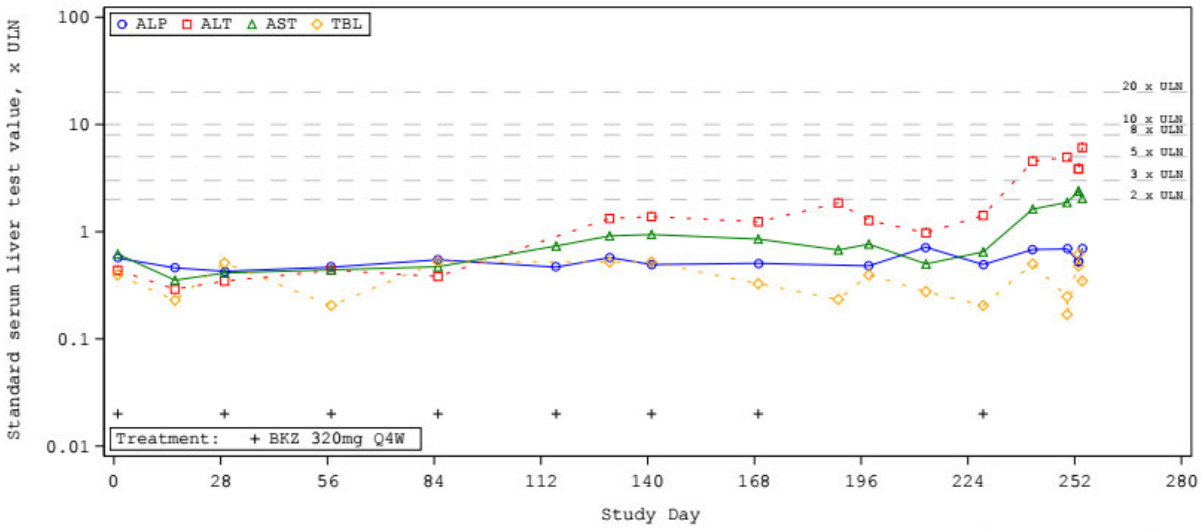


Figure 7: Liver analytes and BKZ dosing (+ signs) by study day for Subject (b) (6).[19]

Assessment: We assessed this case as probable DILI due to BKZ. Latency is consistent; dechallenge washout (by narrative; not graphed) would also be consistent with a long-acting drug and potential immune mediated liver injury. Evaluation testing was not well-documented, but the narrative suggests evaluation was done to the satisfaction of the on-site hepatologist such that the investigator implicated BKZ.

5.0 Assessment and Recommendations

5.1 Assessment: Bimekizumab (BKZ) is a humanized monoclonal IgG antibody that binds and inhibits interleukin (IL)-17A and 17F. IL-17 is a pro-inflammatory cytokine that causes neutrophil recruitment and upregulation of the innate immune response. BKZ was approved in 2023 for psoriasis (PSO) at 320 mg SC every four to eight weeks, and the Sponsor is seeking approval for a hidradenitis suppurativa (HS) indication (320 mg every two to four weeks). The DILI Team consulted on the PSO BLA (**Attachment**) and concluded that BKZ could cause hepatocellular and mixed liver injury but did not identify any Hy's Law cases. Current BKZ labeling discusses liver analyte elevations in the highlighted Warnings and Precautions. The Division of Dermatology and Dentistry (DDD) noted elevations in liver enzymes in the HS trials and asked the Division of Hepatology and Nutrition (DHN), DILI Team to assess these events and need for labeling updates.

Non-clinical data do not support a substantial DILI risk for BKZ. Post-market data include just three reports to FAERS for hepatobiliary adverse events so far; none are specifically labeled as DILI or hepatotoxicity. The estimated rates hepatobiliary reports per patient are low (<1%) for all four marketed monoclonal anti-IL17 antibodies. The three other marketed anti-IL17 monoclonal antibodies are not labeled for liver injury and considered low risk for DILI by LiverTox®.

[19] BLA761151 (761151 - 0116 - (165) - 2024-01-19 - SUPPL-10 (Efficacy) /Multiple Categories/Subcategories) - Integrated Summary of Safety - HS - Figures (#102)

eDISH plots for the two phase 3, randomized placebo-controlled trials, which exposed 861 HS subjects to BKZ, did not have subjects in the potential Hy's Law quadrant, but several were in Temple's. Accordingly, the BKZ arms had higher rates of elevated aminotransferases (AT; ALT or AST) compared to placebo during the first 16-weeks of treatment with some correlation with q2 week dosing over q4 weeks. The differences in AT elevations were mainly due to AST. The rates of AST ≥3x ULN were 0.7% and 1.4% in the q4 week and q2 week dosing arms versus 0% in the placebo arms. The respective rates for ALT≥3x ULN were 0%, 0.5% and 0%. The rates increase when the maintenance phase data (48 weeks) are included, but AST elevations were still more common than ALT elevations.

We considered only one subject in Temple's quadrant as probable DILI due to BKZ. The injury had a latency of 129 days, gradual onset, gradual resolution, modest peak enzymes (ALT 243 U/L, AST 82 U/L) without hyperbilirubinemia, and mixed pattern injury (R-value 2 to 5). Enzymes returned to near normal with holding BKZ. There were three subjects with possible DILI, but they all had competing alternative diagnoses. The remaining cases we assessed as unlikely DILI.

There is a disconnect between more AT elevations in the BKZ arms compared to placebo and the lack of attribution to DILI on case level analyses. The liver enzyme elevations occurring in the 48-week maintenance were similar in pattern, and the only case we assessed as probable DILI appeared in the maintenance phase. Also, BKZ associated AT elevations occurred in the PSO trials. So, we believe the imbalance during the first 16-weeks is due to BKZ. Lack of attribution to DILI may be partly explained if some of the AT elevations are due to non-DILI events that are linked to BKZ. Myopathy and hemolysis would explain more AST over ALT elevations. At least two of twelve unlikely DILI cases had myopathy. There were four more that had similar patterns of AST > ALT with low GGT suggesting non-liver events. CK levels were not checked in these cases. Whether BKZ makes subjects more suspectable to myopathy or AST elevations due to other causes (e.g., alcohol use) is speculative. Indeed, there were no other data to support BKZ associated myopathy or hemolysis.[20] Thus, the BKZ associated AT elevations without attribution to BKZ liver injury remains unexplained.

Compared to the PSO trials, the liver injury signal was less prominent. The rate of ALT >5x ULN was up to 4.7% in the PSO trials while only 0.4% in the HS trials. Thus, the enzyme elevations were modest, and they typically resolved rapidly in the HS trials. There were no hyperbilirubinemia cases assessed as possible or probable DILI in the HS trials, compared to four in the PSO trials. Only one subject in HS trials had a prolonged DILI course compared to at least four in the PSO trials with enzyme elevations lasting several weeks. The difference in liver injury signal may be due to lower trough levels and higher clearance in HS patients compared to PSO patients. The number of subjects exposed was smaller in the HS trials compared to PSO (861 for HS; approximately 1700 for PSO) so underpowering to detect a similar signal is also possible.

Overall, we do not see a substantial DILI risk with this supplemental BLA. The signal for liver injury is less in the HS trials compared to PSO trials. The current labeling for PSO does not need substantial changes, other than description of liver analyte changes in the HS trial.

[20] Personal communication from the DDD clinical reviewer, Kevin Clark, MD.

5.2 Recommendations

1. DILI concerns should not preclude approval.
2. Labeling recommendations should BKZ be approved for HS
    a. Would not change wording on Liver Biochemical Abnormalities in the Highlights for Warnings and Precautions
    b. In section 5.0, point out imbalance in AT elevations during the randomized control trial portion, but no appearance of jaundice. Consider describing the one subject with slow onset and slow resolution liver injury.
    c. In section 6.0, describe the percentages of AT elevations across treatment and placebo arms.

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Eileen Navarro, MD
DILI Team Lead, DHN
CDER/OND

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Paul H. Hayashi, MD, MPH
DILI Team Lead, DHN
CDER/OND

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Joseph Toerner, MD, MPH
Director, DHN
CDER/OND

Reference ID: 5390131

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PAUL H HAYASHI
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CONSULTATIVE REVIEW AND EVALUATION OF CLINICAL DATA
CONSULT #12026

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/S-010; IND 134700 Bimekizumab subcutaneous injection for the treatment of hidradenitis suppurativa (HS)
Date of Request:	2/2/2024
Date Received:	2/2/2024
Desired Completion Date:	5/2/2024

I. Executive Summary

Bimekizumab, a humanized, monoclonal antibody that selectively binds and neutralizes human interleukin-17A (IL-17A) and interlukin-17F (IL-17F), is FDA-approved for the treatment of moderate-to-severe plaque psoriasis (PsO) in adults. On January 19, 2024, the Applicant, UCB Inc., submitted a supplemental biological licensing application (sBLA) for bimekizumab for the indication of treatment of moderate-to-severe hidradenitis suppurativa (HS) in adults. The sBLA submission is currently under review by the Division of Dermatology and Dentistry (DDD).

Given concerns for increased risk of psychiatric events, including worsening depression and emergence of suicidal ideation and behavior (SI/B), DDD instructed the Applicant to include appropriate neuropsychiatric eligibility criteria, subject- and study-specific stopping criteria, and prospective safety monitoring for SI/B and depression. Similar to protocols submitted to support the approval of the PsO development program, DDD consulted the Division of Psychiatry (DP) to evaluate the adequacy of the proposed eligibility and stopping criteria, and safety monitoring. In all study protocols evaluating bimekizumab for HS, the Applicant included reasonable eligibility and withdrawal criteria and evaluation of changes in depression, anxiety, and SI/B.

DDD has consulted DP again to review from the submitted BLA and to opine on the clinical relevance of psychiatric adverse events (AEs) and changes in depression and SI/B, and to determine the adequacy of the Applicant's proposed labeling changes. The presented analysis included pooled data from two phase 3 studies (HS0003 and HS0004), and an independent description of study results from one phase 2 study (HS0001) and one open-label extension safety study (HS0005). Similar to the PsO development program, the results of the pooled analysis confirmed an increased risk for SI/B among subjects treated with bimekizumab relative to placebo (relative risk: 2.7). The Applicant also reported three suicidal attempts that occurred 1 to 2 years after treatment initiation. Although a casual association between treatment with bimekizumab and increased risk for SI/B cannot be definitely established, the consistent signal between the PsO and HS development program does support the Applicant's proposal to communicate the SI/B risk as a Warning and Precaution statement in the product label.

Reference ID: 5374356

II. Background

Bimekizumab is a humanized, monoclonal antibody of the immunoglobulin G1 (IgG1) subclass that selectively binds and neutralizes human IL-17A and IL-17F. Nonclinical 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. On January 19, 2024, the Applicant, UCB Inc., submitted a sBLA for bimekizumab for the treatment of moderate-to-severe HS in adults. The Applicant proposes to administer bimekizumab subcutaneously with a dosing regimen of 320 mg every 2 weeks for 16 weeks, followed by a maintenance dose of 320 mg every 4 weeks.

Bimekizumab is currently FDA-approved for the treatment of moderate-to-severe PsO in adults (BLA 761151; October 17, 2023). The Applicant is also developing parallel programs for psoriatic arthritis and ankylosing/axial spondylarthritis (IND 128708). Adalimumab (BLA 125057) and secukinumab (BLA 125504) are the only FDA-approved treatment for moderate-to-severe HS in patients 12 years of age and older and in adults, respectively. Current clinical guidelines suggest that treatment, typically consisting of corticosteroids, antibiotics, and biologics, is based on individual subjective impact and objective severity. Given the limited number of approved treatment options, the Applicant considers bimekizumab a potential individualized treatment option that could improve quality of life for patients with HS.

Patients with HS and other similar autoimmune conditions are at higher risk for depression, anxiety, and suicide than the general public. In a systematic review of epidemiological studies, the prevalence of patients with HS and co-morbid depression and anxiety is 26% and 5%, respectively. Notably, the odds for depression and anxiety among HS was approximately two- to three-folds higher than that of controlled individuals without HS and was correlated with disease severity. The prevalence of suicidal ideation (7.9%) and behavior (4.2%) also appears to be greater than the general population. Data from European national registries suggest that the hazard for completed suicides was approximately three times higher in patients with HS relative to the general population.[1]

It is unclear if the psychiatric risk is due to an immune-mediated cause, high psychosocial burden of the illness, or a combination of both factors. 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) have also been associated with downstream psychiatric effects and are theorized to modulate neurotransmission. However, a clear mechanism explaining the relationship between biological inflammatory markers and psychiatric events is not established.

Due to concerns for adverse psychiatric events, including worsening symptoms of depression and suicidal ideation and behavior (SI/B), associated with IL-17 products, DDD previously consulted DP to review data from the Applicant's PsO development program to recommend appropriate product labeling and risk mitigation strategies. The analysis revealed a three-fold

[1] Garg A, Malviya N, Strunk A, et al. Comorbidity screening in hidradenitis suppurativa: evidence-based recommendations from the US and Canadian Hidradenitis Suppurativa Foundations. *J Am Acad Dermatol*. 2022;86(5):1092-1101.

higher risk for suicidal ideation and several cases of suicidal behavior (including one completed suicide) during the open-label treatment period. Although there was much uncertainty with regard to the strength of the SI/B signal and no established causal association due to the nature and rarity of events, DP and DDD agreed to describe the risk of SI/B in Section 5 (Warnings and Precautions) of the product label. Because of similar background risk for psychiatric events among patients with HS and PsO, DDD has consulted DP again to evaluate data from the Applicant's HS development program and to determine the adequacy of the Applicant's proposed updates to the product label.

III. Review of Clinical Data: Methods

To support their HS development program, the Applicant conducted one phase 2 study (HS0001), two phase 3 efficacy studies (HS0003 and HS0004), and one long-term safety study (HS0005) under IND 134700. Refer to Table 1 for a description of trial design characteristics, sample size, relevant psychiatric eligibility criteria, and psychiatric safety monitoring assessments. The Applicant used HS0001 as a proof-of-concept study to evaluate the efficacy and safety profile of bimekizumab relative to adalimumab (the only study with an active control arm) and to inform the designs of Studies HS0003 and HS004. Of note, the Applicant initiated HS0001 approximately 2.5 years prior to the initiation of Studies HS0003 and HS0004. Differences in the psychiatric eligibility criteria and monitoring were likely based on the need to align studies across other development programs (PsO) and the evolving recommendations from the Agency to allow subjects with mild-to-moderate depression and recent SI/B history for enhanced generalizability and potential signal detection. To determine whether patients with HS and PsO share a similar psychiatric safety profile and to assess the adequacy of the Applicant's proposed labeling updates, this review will analyze psychiatric AEs (including case narratives), SI/B data collected using the Columbia Suicide Severity Rating Scale (C-SSRS), and changes in symptoms of depression using the Hospital Anxiety and Depression Scale (HADS) and Patient Health Questionnaire–9 items (PHQ-9).

Pooling strategy

Due to differences in trial durations, eligibility criteria, and safety assessments, this review will only include a pooled analysis of combined data from Studies HS0003 and HS0004. Each analysis will also include an evaluation of the 16-week initial period and 48-weeks of the combined initial and maintenance treatment periods. This review will also descriptively evaluate data from Studies HS0001 and HS0005 (open-label extension for Studies HS0003 and HS0004) for each subsequent analysis. Of note, changes in depression was prospectively monitored using the HADS in Study HS0001 and the PHQ-9 in Studies HS0003, HS0004, and HS0005.

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Table 1: Listing of Clinical Trials to Support Applicant's HS Development Program

Trial[1]	Trial Design	Trial Duration	Treatment Groups/ Sample Size	Relevant Psychiatric Eligibility Criteria	Relevant Psychiatric Safety Assessments	Relevant Psychiatric Withdrawal Criteria
Completed Efficacy and Safety Studies						
HS0001	Phase 2, randomized, double-blind, placebo-controlled, active-controlled study	12 weeks	BKZ: 46 ADA: 22 PBO: 22	• Presence of active SI, or positive SB using the "Screening" version of the C-SSRS and the HADS with either of the following criteria: - Lifetime history of suicide attempt (including an actual attempt, interrupted attempt, or aborted attempt), or had SI in the past 6 months as indicated by a positive response to either questions 4 or 5 of the C-SSRS at Screening - HADS-D score ≥ 10 and HADS-A score ≥ 15	• HADS and C-SSRS: Screening, Baseline, and Weeks 2, 4,6, 8, 10, 12, and 30 (safety follow-up visit)	• HADS-D score ≥ 15 (any subject with a HADS-D score ≥ 10 was to be referred immediately to a mental healthcare professional) • Active SI as indicated by a positive response to question 4 or 5 or SB using the "Since to Last Visit" version of the C-SSRS
HS0003	Phase 3, randomized, double-blind, placebo-controlled study	48 weeks total (16-week ITP + 32-week MTP)	DB ITP BKZ 320 mg Q2W: 289 BKZ 320 mg Q4W: 144 PBO: 72 DB MTP BKZ 320 mg Q4W/Q4W: 125 BKZ 320 mg Q2W/Q4W: 129	• Presence of active SI or positive SB using the "Screening" version of the eC-SSRS and with either of the following criteria: - History of suicide attempt within the past 5 years prior to screening (subjects with a history of	• PHQ-9 and eC-SSRS: Screening, Baseline, and Weeks 4, 8, 12, 16, 20, 24, 28, 30, 36, 40, 44, 48, and at the safety follow-up visit (20 weeks	• Subjects must be referred immediately to a mental healthcare professional and must be withdrawn from the study in the case of: - Active SI as indicated by a positive response to Question 5 on the "Since Last Visit" version of the eC-SSRS

			BKZ 320 mg Q2W/Q2W: 129 PBO/BKZ 320 mg Q2W: 65	suicide attempt more than 5 years should be evaluated by a mental healthcare practitioner prior to enrolling) - SI in the past month prior to screening based on a positive response to either question 4 or 5 of the "Screening" version of the eC-SSRS • Moderately severe major depression or severe depression indicated by a PHQ-9 total score ≥ 15 at screening • Medications used to treatment depression should be stable for 8 weeks prior to baseline	after last dose of study medication)	- Any SB since last visit - Severe major depression as indicated by PHQ-9 total score ≥ 20 • Subjects must be referred immediately to a mental healthcare professional and may be withdrawn from the study based on Investigator's judgement for: - Active SI as indicated by a positive response to Question 4 on the "Since Last Visit" version of the eC-SSRS - Moderately severe major depression as indicated by PHQ-9 total score between 15 to 19, if this represents an increase of at least 3 points compared to last visit
HS0004	Phase 3, randomized, double-blind, placebo-controlled study	48 weeks total (16-week ITP + 32-week MTP)	DB ITP BKZ 320 mg Q2W: 291 BKZ 320 mg Q4W: 144 PBO: 74 DB MTP BKZ 320 mg Q4W/Q4W: 133 BKZ 320 mg Q2W/Q4W: 130 BKZ 320 mg Q2W/Q2W: 131 PBO/BKZ 320 mg Q2W: 69			
Ongoing Studies						
HS00052	Phase 3, open-label, long-term extension study	52 weeks	BKZ 320 mg Q2W or Q4W: 653	Subjects who completed the MTP through Week 48 in HS0003 and HS0004 and did not meet any withdrawal criteria	• PHQ-9 and eC-SSRS: Baseline, and Weeks 2, 4, 8, 12, 16, 29, 24, 28, 32, 36, 40, 44, 48, and 52	Same as HS0003 and HS0004

Source: Reviewer's table
Abbreviations: ADA = adalimumab; BKZ = bimekizumab; C-SSRS = Columbia Suicide Severity Rating Scale; DB = double-blind; HADS = Hospital Anxiety and Depression Scale; HADS-A = HADS-Anxiety Subscale; HADS-D = HADS-Depression Subscale; ITP = initial treatment period; MTP = maintenance treatment period; PBO = placebo; PHQ-9 = Patient Health Questionnaire-9 items; Q2W = every 2 weeks; Q4W = every 4 weeks; SB = suicidal behavior; SI = suicidal ideation
[1]NCT hyperlinked for each study
[2]Sample size reflects clinical-data cutoff date of November 15, 2022

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IV. Review of Clinical Data: Analysis

Baseline Characteristics

In general, the average age of subjects participating in Studies HS0003 and HS0004 was 36 years. Approximately 60% of subjects were female, 80% of subjects were white, and 35% of subjects were enrolled in U.S. study sites. Table 2 provides a summary of relevant baseline psychiatric characteristics, including prior or ongoing psychiatric conditions and concomitant psychotropic medication use, for subjects that participated during the initial treatment period in Studies HS0003 and HS0004. The proportion of subjects with prior or ongoing co-morbid psychiatric conditions were generally similar between treatment arms. The observed incidences of SI/B, depression, and anxiety (SI/B: 7%; depression: 7%; anxiety: 5%) were also within range of the background incidences reported for subjects with HS (SI/B: 12 to 20%; depression: 15 to 28%; anxiety: 10 to 18%);[2] however, incidences were lower relative to subjects that participated in the prior PsO development program .

Table 2: Psychiatric Baseline Symptoms, Co-morbid History, and Concomitant Medications among Subjects Participating in the Initial Treatment Period (Pooled Studies HS0003 and HS0004)

Baseline Characteristics	Placebo (N=144)	BKZ 320 mg Q4W (N=285)	BZK 320 mg Q2W (N=576)	BKZ Total (N=861)
Baseline PHQ-9 Total Score, mean (SD)	3.7 (3.8)	3.6 (3.9)	3.1 (3.4)	3.2 (3.6)
total score < 5	96 (66)	196 (69)	441 (77)	637 (74)
total score ≥5 and ≤ 9	36 (25)	58 (20)	101 (18)	159 (19)
total score ≥10 and ≤ 14	12 (8.2)	25 (8.8)	28 (4.9)	53 (6.2)
Lifetime history of SI/B based on the C-SSRS, n (%)	18 (12)	44 (15)	71 (12)	115 (13)
Co-morbid Psychiatric Conditions, n (%)[1]	34 (23)	70 (25)	139 (24)	209 (24)
Anxiety	17 (12)	37 (13)	64 (11)	101 (12)
ADHD	2 (1.4)	4 (1.4)	10 (1.7)	14 (1.6)
Depression	23 (16)	43 (15)	78 (14)	121 (14)
Sleep disorder	4 (2.7)	11 (3.9)	28 (4.9)	39 (4.5)
Stress disorder	1 (0.7)	4 (1.4)	5 (0.9)	9 (1.0)
Substance-related disorders	2 (1.4)	1 (0.4)	10 (1.7)	11 (1.3)
SI/B and self-injury	1 (0.7)	4 (1.4)	7 (1.2)	11 (1.3)
Concomitant Medications				
Antidepressants	16 (11)	33 (12)	65 (11)	98 (11)
Antiepileptics	2 (1.4)	2 (0.7)	7 (1.2)	9 (1.0)
Antipsychotics	3 (2.1)	7 (2.5)	13 (2.3)	20 (2.3)
Anxiolytics	8 (5.5)	17 (6.0)	36 (6.3)	53 (6.2)
Hypnotics/sedatives	3 (2.1)	5 (1.8)	16 (2.8)	21 (2.4)
Pain management	7 (4.8)	9 (3.2)	18 (3.1)	27 (3.1)
Psychostimulants	2 (1.4)	4 (1.4)	8 (1.4)	12 (1.4)

[1]Occuring in at least 1% of patients
Note: Anxiolytics include antidepressants and benzodiazepines

[2] Caccavale S, Tancredi V, Boccellino MP, et al. Hidradenitis suppurativa burdens on mental health: a literature review of associated psychiatric disorders and their pathogenesis. *Life (Basel).* 2023;13(1):189.

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Although the percentage of patients receiving psychotropic medications was low, the Applicant reported that percentages were similar across all treatment arms and reflect similar incidences to baseline psychiatric comorbidity across 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 50%).

Similarly, the average age of subjects participating in HS0001 was 37 years and the majority were female (70%), White (70%), and enrolled in U.S. study sites (50%). Approximately 20% of subjects reported a prior or ongoing psychiatric condition; depression (13%) and anxiety (5%) were the most frequently reported conditions. Only three subjects in the adalimumab treatment reported a lifetime history of SI/B (all cases of SI).

DP Reviewer's Comment: *In general, the treatment arms from Studies HS0003 and HS0004 were well-balanced with respect to psychiatric co-morbidities and concomitant psychotropic medication use and reflect the overall population of patients with HS. Given Study HS0001's conservative SI/B eligibility criteria (i.e., exclusion of subjects with lifetime history of SB, SI within the past 6 months, and severe anxiety), the lower background rate of anxiety and SI/B history relative to Studies HS0003 and HS0004 is expected. Although psychiatric-relevant eligibility criteria for Studies HS0003 and HS0004 were identical relative to phase 3 studies supporting the PsO development program, differences in the proportion of subjects with a history of SI/B, depression, and anxiety are likely due to differences in background risk between patients with HS and PsO.*

Psychiatric Adverse Events

The Applicant assessed for adverse events (AE) at each study visit throughout the treatment period and categorized AEs by system organ class and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA; version 19.0). Coding accuracy between observed events and preferred terms was adequate from a psychiatric AE perspective. AEs listed under the Injury, Poisoning, and Procedural Complications system organ classifications suggested no obvious miscoding of hidden psychiatric events. Of note, there were 61 cases coded under fatigue or tiredness (several due to post-covid vaccination or post-study drug administration). These events were not included in this analysis due to difficulties in determining the etiology from both the underlying medical condition of HS and possible systemic drug effects versus any depressive etiology.

Table 3 provides the incidence of psychiatric AEs among subjects participating in Studies HS0003 and HS0004 during the initial treatment period. The incidence rate (per 100 person-years) for psychiatric AEs was approximately 1.7 times higher in the total bimekizumab treatment group vs. placebo (placebo = 9.1; BKZ total = 15.2). The Mantel Haenszel (MH) risk difference for psychiatric AEs comparing bimekizumab to placebo in these two trials is 1.63%. During the initial treatment period, none of the AEs were serious or resulted in any deaths and four psychiatric AEs (depression, alcohol abuse, adjustment disorder, and suicidal ideation) occurring among subjects receiving bimekizumab led to study discontinuation.

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Table 3: Incidence of Psychiatric Adverse Events during the Initial Treatment Period (Pooled Studies HS0003 and HS0004)

Adverse events, n (%)	Placebo (N=144)	BKZ 320 mg Q4W (N=285)	BZK 320 mg Q2W (N=576)	BKZ Total (N=861)
Subjects with at least one Psychiatric AE	4 (2.7)	16 (5.6)	23 (4.0)	39 (4.5)
Adjustment disorder	-	-	2 (0.3)	2 (0.2)
Alcohol abuse	-	2 (0.7)	-	2 (0.2)
Anxiety	1 (0.7)	4 (1.4)	6 (1.0)	10 (1.2)
Confusion	-	-	1 (0.2)	1 (0.2)
Depression	2 (1.4)	5 (1.8)	9 (1.6)	14 (1.6)
Insomnia	1 (0.7)	2 (0.7)	3 (0.5)	5 (0.6)
Irritability	-	1 (0.4)	1 (0.2)	2 (0.2)
Panic attacks	-	-	1 (0.2)	1 (0.2)
Sleep disorder	-	1 (0.4)	2 (0.3)	3 (0.3)
Stress disorder	-	-	1 (0.2)	1 (0.1)
Suicidal ideation	-	1 (0.4)	-	1 (0.1)

Source: Reviewer-created using iss adae.xpt dataset
Abbreviations: BKZ = bimekizumab
Notes: Adjustment disorder includes preferred terms for adjustment disorder and adjustment disorder with depressed mood; Anxiety includes preferred terms of anxiety and nervousness; Irritability includes preferred terms of irritability and emotional distress; Depression includes preferred terms of depression and depressed mood

Table 4: Incidence of Psychiatric Adverse Events during the Initial and Maintenance Treatment Period (Pooled Studies HS0003 and HS0004)

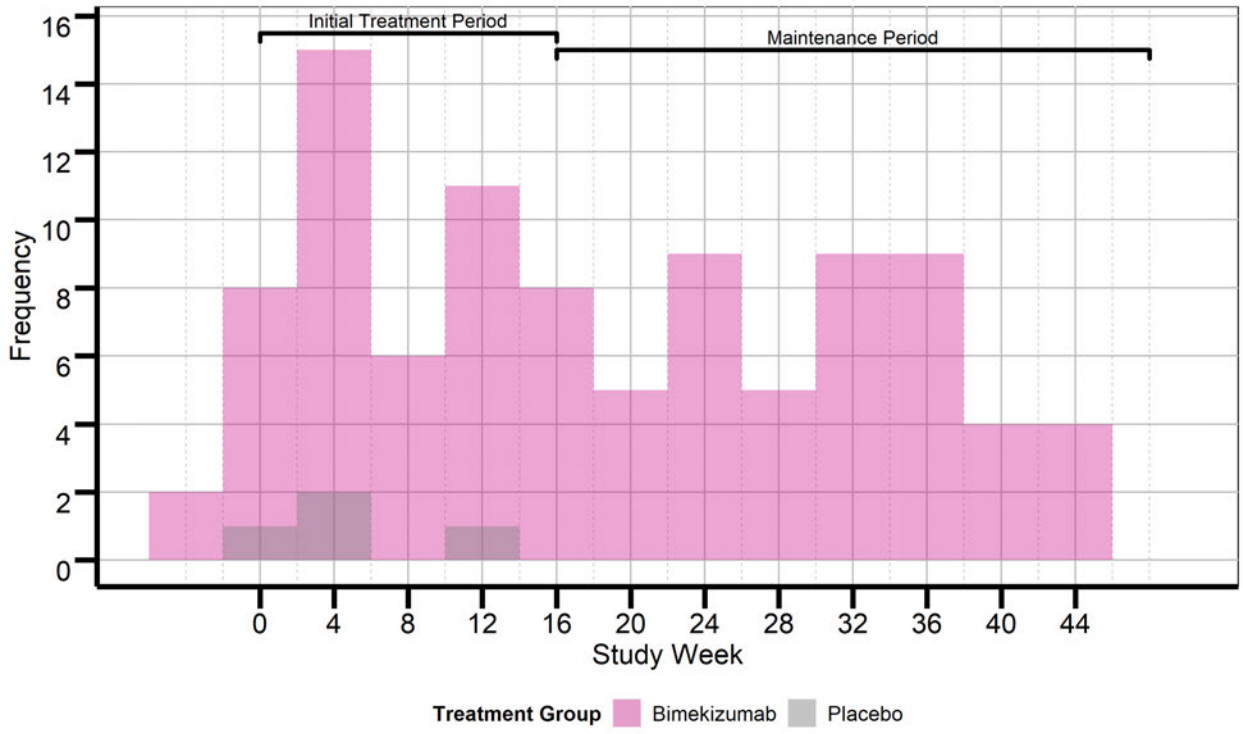
Adverse events, n (%)	Placebo/BKZ 320 mg Q2W (N=65)	BKZ 320 mg Q4W/Q4W (N=143)	BKZ 320 mg Q2W/Q4W (N=145)	BKZ 320 mg Q2W/Q2W (N=141)
Subjects with at least one Psychiatric AE	6 (4.5)	25 (8.8)	23 (7.9)	21 (7.4)
Adjustment disorder	-	1 (0.4)	1 (0.3)	2 (0.7)
Alcohol abuse	-	2 (0.7)	-	-
Anxiety	2 (1.5)	7 (2.5)	9 (3.1)	8 (2.8)
Confusion	-	-	-	1 (0.4)
Depression	2 (3.1)	8 (5.6)	8 (5.5)	6 (4.3)
Insomnia	-	3 (1.1)	5 (1.7)	4 (1.4)
Irritability	-	1 (0.4)	1 (0.3)	-
Obsessive compulsive disorder	-	-	-	1 (0.4)
Panic attacks	1 (0.7)	-	-	1 (0.4)
Sleep disorder	-	1 (0.4)	1 (0.3)	1 (0.4)
Stress disorder	-	-	-	1 (0.4)
Suicidal ideation	2 (1.5)	2 (0.7)	-	1 (0.4)

Source: Reviewer-created using iss adae.xpt dataset
Abbreviations: BKZ = bimekizumab
Notes: Adjustment disorder includes preferred terms for adjustment disorder and adjustment disorder with depressed mood; Anxiety includes preferred terms of anxiety, nervousness, stress, and tension; Irritability includes preferred terms of irritability and emotional distress; Depression includes preferred terms of depression and depressed mood

Table 4 provides the incidence of psychiatric AEs among subjects participating in Studies HS0003 and HS0004 during the combined initial and maintenance treatment period. During the maintenance treatment, the incidence rate (per 100 subject-years) for psychiatric AEs suggested

that subjects switching from placebo to bimekizumab did not experience incidence rates greater than subjects initiating treatment with bimekizumab (placebo/BKZ 320 mg Q2W = 7.5). Subjects who continued with bimekizumab treatment for an additional 32 weeks also did not experience a greater incidence rate (BKZ 320 mg Q4W/Q4W = 11.0; BKZ 320 mg Q2W/Q4W = 9.8; BKZ 320 mg Q2W/Q2W = 9.0) relative to the initial 16-week period. This may suggest that the risk for psychiatric AEs does not increase with increased exposure. Two subjects also discontinued treatment due to AEs of worsening depression and adjustment disorder (no serious AEs or AEs resulting in deaths). 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 across treatment arms.

Figure 1: Frequency of Psychiatric Adverse Events by Treatment Arm and Study Visit across the Initial and Maintenance Treatment Periods (Pooled Studies HS0003 and HS0004)



Source: Reviewer-created using iss adea.xpt dataset

During the open-label extension (OLE) study (HS0005), the incidence of psychiatric AEs was 2.6% (N=17). There were no new psychiatric AEs that were not captured during the initial or maintenance treatment periods. Psychiatric AEs reported in the OLE study (HS0005) included: anxiety (0.5%), confusion (0.2%), depression (0.8%), insomnia (0.9%), irritability (0.5%), and suicidal ideation (0.3%; n =2). Among subjects participating in HS0001, the Applicant reported only one psychiatric AE (insomnia) in a subject randomized to the bimekizumab treatment arm.

DP Reviewer's Comment: *In double-blind, placebo-controlled trials evaluating subjects with PsO, 12 out of 670 subjects (1.8%) receiving placebo and 0 out of 83 subjects receiving placebo experienced psychiatric AEs (most common AEs included anxiety and depression). Although the*

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absolute risk differences for psychiatric AEs in the PsO (1.8%) and HS (1.6%) development program were similar, the percentage of subjects receiving bimekizumab and experiencing a psychiatric AE was three-fold higher in the HS development program. Because the incidence of psychiatric AEs in the placebo group was also higher in subjects with HS vs. PsO (2.7% vs. 0%), greater AE reporting in HS subject could be attributed to the higher background rates of co-morbid psychiatric conditions in subjects with HS.

Given that the Applicant did not identify any new psychiatric AEs and the relatively low overall occurrence (<2%) of AEs related to depression and anxiety, DP does not recommend any additional descriptions of psychiatric AEs in product labeling.

Suicidal Ideation and Behavior (SI/B) Events per C-SSRS

All studies prospectively monitored for SI/B using the C-SSRS (electronic version used for HS0003 and HS0004) throughout the entire treatment period. Table 5 and Table 6 describes the incidence of suicidal ideation (SI), suicidal behavior (SB), and SI/B for each treatment arm while on-treatment (i.e., post-baseline) during the initial and combined initial and maintenance treatment periods. Because a subject could experience multiple SI/B events during study participation, categorization into each of Columbia Classification Algorithm of Suicide Assessment (C-CASA) categorizes was based on the maximum severity of SI/B observed in the treatment period. Refer to Appendix Figure 1 for a visual timeline of SI/B events occuring in Studies HS0003 and HS0004.

Pooled analysis of C-SSRS data from the 16-week initial treatment period of Studies HS0003 and HS0004 indicated that 1.9% bimekizumab-treated subjects and 0.7% placebo-treated subjects reported SI/B with an estimated relative risk of 2.70 (95% CI: 0.36, 20.12). Most of the subjects (12 out of 17) reported passive SI; all five cases of active SI during the initial treatment period occurred in the bimekizumab treatment group. There were no cases of SB. When restricted to only new-onset positive C-SSRS events, the incidence for any positive SI/B response was 0% (0/146) for the placebo group and 0.9% (8/861) for the bimekizumab treatment group with a relative risk of 2.90 (95% CI: 0.17, 49.96). Among the eight bimekizumab-treated subjects who had new-onset SI/B during the first 16 weeks, only one subject had a positive response more than once throughout the treatment period.

Among subjects participating in the maintenance treatment period, seven subjects reported an SI/B event. Six subjects reported passive SI and one subject endorsed active SI with intent. None of the subjects that switched from placebo to bimekizumab reported a positive response to the C-SSRS. The Applicant also noted that there were also two serious AEs of SI (one that occurred during a follow-up period after study discontinuation) that were adjudicated as suicide attempts (Subject IDs: HS0003-50175-17314 and HS0003-40342-17026). Both subjects appeared to endorse SI approximately 300 days after receiving their first dose and denied endorsing any SB. Based on the case summaries (see below), the Neuropsychiatric Adjudication Committee (NAC) adjudicated these event conservatively as a suicide attempt.

During the open-label treatment period, 11 subjects experienced SI (Wish to be dead = 6; nonspecific thoughts = 2; some intent to act, no plan = 3). Five out of the 11 subjects reported SI

during initial and maintenance treatment periods. Two subjects reported SB; one subject (HS0004-[redacted] (b) (6) reported an actual attempt on Day 701 (Week 52 visit) and one subject (HS0004-[redacted] (b) (6) reported an interrupted/aborted attempt on Day 655 (Week 44 visit). The Applicant also reported no positive cases of SI/B in subjects participating in Study HS0001.

Table 5: Incidence of Suicidal Ideation and Behavior Using the eC-SSRS during the Initial Treatment Period until End of Week 16 (Pooled Studies HS0003 and HS0004)

	Placebo (N=146)		BKZ 320 mg Q4W (N=285)		BZK 320 mg Q2W (N=576)		BKZ Total (N=861)	
C-CASA Category	Lifetime[1]	Study[2]	Lifetime[1]	Study[2]	Lifetime[1]	Study[2]	Lifetime[1]	Study[2]
Suicidal Ideation, n (%)	18 (12)	1 (0.7)	42 (15)	6 (2.1)	71 (12)	10 (1.7)	113 (13)	16 (1.9)
Wish to be dead	8 (5.5)	1 (0.7)	22 (7.7)	5 (1.8)	28 (4.9)	6 (1.0)	50 (5.8)	11 (1.3)
Non-specific active suicidal thoughts	4 (2.7)	-	11 (3.9)	1 (0.4)	3 (0.5)	2 (0.3)	14 (1.6)	3 (3.5)
Active SI with any methods and without intent or plan	5 (3.4)	-	5 (1.8)	-	14 (2.4)	2 (0.3)	19 (2.2)	2 (2.3)
Active SI with some intent to act, without specific plan	1 (0.7)	-	2 (0.7)	-	7 (1.2)	-	9 (1.0)	-
Active SI with specific plan and intent	-	-	2 (0.7)	-	3 (0.5)	-	5 (0.6)	-
Suicidal Behavior, n (%)	4 (2.7)	-	8 (2.8)	-	7 (1.2)	-	15 (1.7)	-
Preparatory acts	2 (1.4)	-	2 (0.7)	-	-	-	2 (0.2)	-
Aborted attempt	1 (0.7)	-	1 (0.4)	-	2 (0.3)	-	3 (0.3)	-
Interrupted attempt	-	-	-	-	-	-	-	-
Actual Attempt	1 (0.7)	-	5 (1.8)	-	5 (0.9)	-	10 (1.1)	-
Suicidal Ideation or Behavior, Risk (95% CI)[3]	18 (12)	1 (0.7)	44 (15)	6 (2.1)	71 (12)	10 (1.7)	115 (13)	16 (1.9)
MH Relative Risk							**2.70 (0.36, 20.12)**	
MH Risk Difference							1.17 (-0.44, 2.79)	

Source: Reviewer-created using adcssrs.xpt datasets for HS0003 and HS0004
Abbreviations: eC-SSRS = electronic Columbia Suicide Severity Rating Scale; C-CASA = Columbia Classification Algorithm of Suicide Assessment; CI = confidence interval; MH = Cochran Mantel Haenszel test; SI = suicidal ideation
[1]Incidence for lifetime history is based on most severe suicidal ideation and behavior category reported on the screening eC-SSRS assessment.
[2]Incidence within each C-CASA category represents the most severe SI or SB event during the on-treatment initial and maintenance study periods.
[3]Comparison between total bimekizumab group vs. placebo (reference), stratified by study

Table 6: Incidence of Suicidal Ideation and Behavior Using the eC-SSRS during the Initial and Maintenance Treatment Period until End of Week 48 (Pooled Studies HS0003 and HS0004)

C-CASA Category[1]	Placebo/BKZ 320 mg Q2W (N=65)	BKZ 320 mg Q4W/Q4W (N=143)	BKZ 320 mg Q2W/Q4W (N=145)	BKZ 320 mg Q2W/Q2W (N=141)
Suicidal Ideation, n (%)	1 (1.5)	10 (7.0)	7 (4.8)	6 (4.3)
Wish to be dead	1 (1.5)	8 (5.6)	5 (3.4)	4 (2.8)
Non-specific active suicidal thoughts	-	1 (0.7)	-	2 (1.4)
Active SI with any methods and without intent or plan	-	-	2 (1.4)	-
Active SI with some intent to act, without specific plan	-	1 (0.7)	-	-
Active SI with specific plan and intent	-	-	-	-
Suicidal Behavior, n (%)	-	1 (0.7)	-	-
Preparatory acts	-	-	-	-
Aborted attempt	-	-	-	-
Interrupted attempt[3]	-	1 (0.7)	-	-
Actual Attempt	-	-	-	-

Source: Reviewer-created using adcssrs.xpt datasets for HS0003 and HS0004
Abbreviations: eC-SSRS = electronic Columbia Suicide Severity Rating Scale; C-CASA = Columbia Classification Algorithm of Suicide Assessment; SI = suicidal ideation
[2]Incidence within each C-CASA category represents the most severe SI or SB event during the on-treatment initial and maintenance study periods.
[3]Subject ID: HS0003-(b) (6)(subject HS0003-(b) (6)not included due to event occurring after study discontinuation)

DP Reviewer's Comment: *Because of the low sample size in the placebo arm and the biased 6:1 randomization ratio between bimekizumab and placebo treatment arms, the estimated relative risk may not represent the true underlying risk in the population. Given that the Applicant excluded subjects with a lifetime history of SB and SI occurring within 6 months of study enrollment (more conservative criteria relative to Studies HS0003 and HS0004), it is also not surprising to see zero SI/B events in Study HS0001.*

Pooled analysis of C-SSRS data from two 16-week placebo-controlled studies in subjects with PsO indicated that 12/670 (1.8%) bimekizumab-treated subjects and 1/169 (0.6%) placebo-treated subjects reported SI. The estimated relative risk for SI/B in the PsO development program was 3.0 (95% CI: 0.39, 22.74). Similar to the HS development program, there were no cases of SB reported during the initial treatment period.

Evaluation of the case narratives (summarized below) suggest that several cases were confounded by background psychiatric history and external psychosocial stressors. It is also important to note that the three SB cases (not including the one suspected case during the follow-up period after treatment discontinuation) also occurred 1 to 2 years after treatment initiation and that the majority of events were passive SI that did not lead to SB. It may be the case that a drug effect on SI/B is to make SI/B more likely when an individual experiences an unstable or worsening mental state due to an external psychosocial stressor.

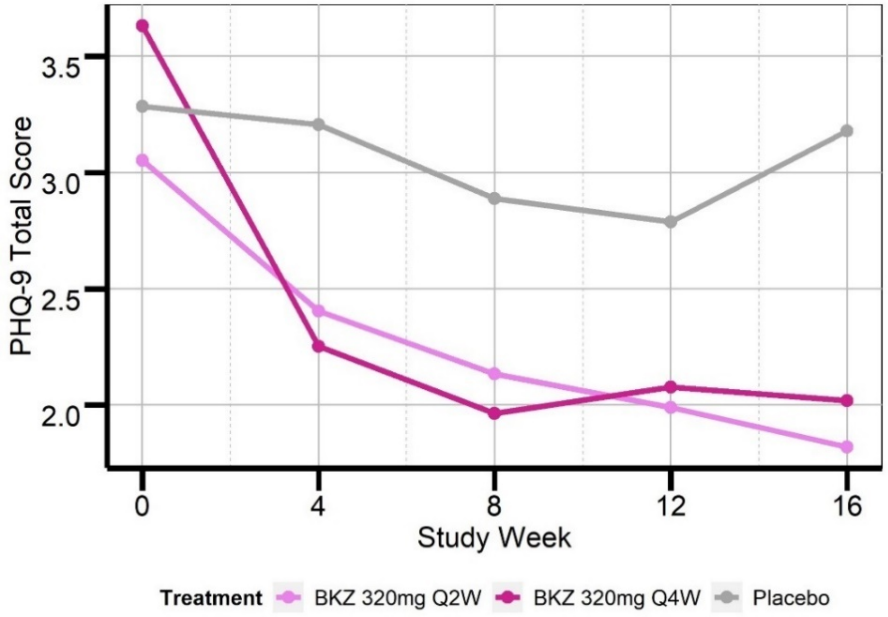
Although a casual association between treatment with bimekizumab and increased risk for SI/B cannot be definitively established, the consistent signal between the PsO and HS development programs does support communicating the risk to prescribers and patients. The Applicant's proposal to communicate the risk as a Warning and Precaution statement in the product label (similar to C-SSRS data described for the PsO studies) is acceptable.

Changes in Depressive Symptoms

For reference, the PHQ-9 is a self-report screening instrument for depression severity. 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 2 provides a visual summary of the average PHQ-9 total score during the initial treatment period for subjects participating in Studies HS0003 and HS0004.

At Baseline, mean PHQ-9 total scores were low and similar in the bimekizumab treatment groups (BKZ 320 mg Q2W: 3.1; BKZ 320 mg Q4W: 3.6) and the placebo group (3.7). Two study participants (0.2%) in the bimekizumab total group had a PHQ-9 Total Score of ≥20 points at any post-baseline visit during the initial treatment period and were adjudicated; the Applicant adjudicated one of those cases as an SI/B event (Subject HS0003- (b) (6) stated that positive responses on questionnaires were inadvertent and was lost to follow-up). Of the 17 subjects treated with placebo or bimekizumab who endorsed SI in the initial treatment period, seven answered Question 9 of the PHQ-9 with a response higher than 0 at corresponding visit.

Figure 2: **Mean PHQ-9 Total Score by Treatment Arm during the Initial Treatment Period (Pooled Studies HS0003 and HS0004)**



Source: Reviewer-created using iss adphq9.xpt dataset

At Week 16, mean PHQ-9 change from baseline scores were low in the bimekizumab total group (-1.1 points) and in the placebo group (-0.4 points). Table 7 also describes the percentage of subjects with moderately-severe or severe depression, shifts in total score of at least 5 points, and abnormal scores on PHQ-9 Question 9. Although the percentages across each PHQ-9 metric were numerically greater in the bimekizumab treatment arms vs. placebo, the difference was minimal and not clinically significant. Among subjects that received bimekizumab and participated in the maintenance phase and open-label extension phase, an additional 33 subjects (53 total; 5.4%) and 11 subjects (13 total; 1.3%) exhibited an PHQ-9 total score ≥15 and ≥20, respectively.

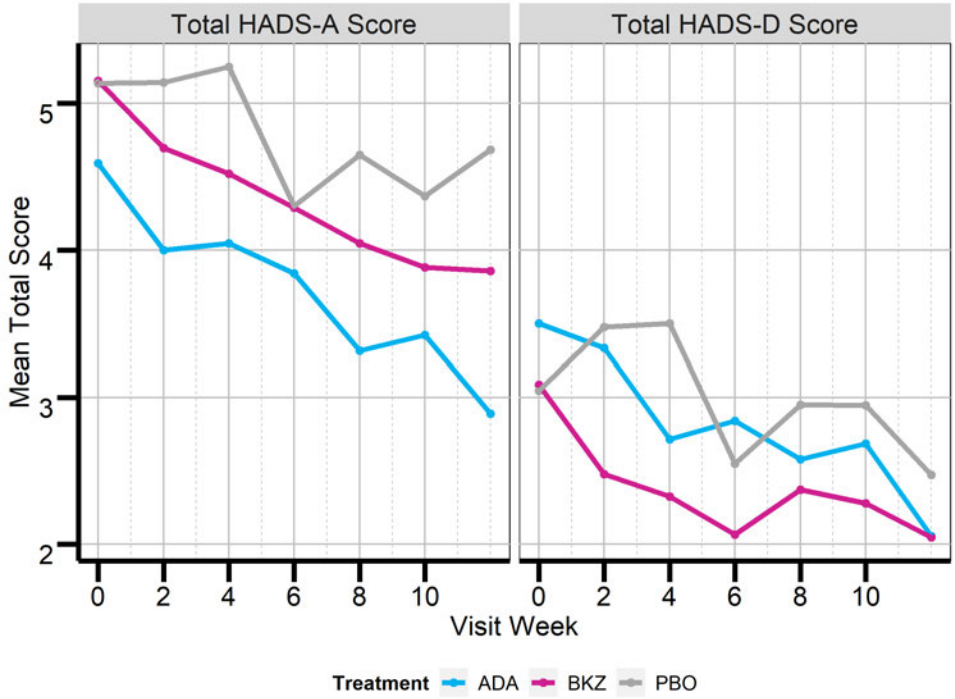
Table 7: Evaluation of PHQ-9 Assessment during the Initial Treatment Period (Pooled Studies HS0003 and HS0004)

Parameter	Placebo (N=144)	BKZ 320 mg Q4W (N=285)	BZK 320 mg Q2W (N=576)	BKZ Total (N=861)
PHQ-9 Total Score[1]				
Baseline, mean (SD)	3.7 (3.8)	3.6 (3.9)	3.1 (3.4)	3.2 (3.6)
Post-baseline score ≥ 15, n (%)	4 (2.8)	9 (3.2)	11 (1.9)	20 (2.4)
Post-baseline score ≥ 20, n (%)	-		2 (0.4)	2 (0.2)
Increase from baseline > 5, n (%)	11 (7.6)	27 (9.6)	48 (8.5)	75 (8.8)
PHQ-9 Question 9[2]				
Post-baseline score > 0, n (%)	4 (2.7)	11 (3.9)	8 19.4)	19 (2.2)
Post-baseline new onset response > 0, n (%)	2 (1.4)	10 (3.5)	6 (1.0)	16 (1.9)

Source: Reviewer-created using adphq9.xpt datasets for HS0003 and HS0004
Abbreviations: BKZ = bimekizumab; PHQ-9 = Patient Health Questionnaire – 9 items
[1]Total score ranges from 0 to 27 with higher scores indicating a worse state. Scores ranging between 5 to 9, 10 to 14, 15 to 19, and ≥ 20 indicates minimal symptoms of depression, minor/mild depression, moderately-severe depression, and severe major depression, respectively.
[2]PHQ-9 Question 9 is "Thoughts that you would be better off dead, or of hurting yourself." A response of 0 reflects "Not at all." A response >0 reflects "Several days" (numeric response=1), "More than half the days" (numeric response=2), or "Nearly every day" (numeric response=3).

Figure 3 describes the changes in the HADS-Anxiety (HADS-A) and HADS-Depression (HADS-D) total scores during the 12-week initial treatment period in Study HS0001. At Week 12, the mean change from baseline in the total HADS-A score was -1.2 in the bimekizumab group and -0.7 in the placebo group, and the mean change from baseline in the total HADS-D score was -0.9 in both treatment groups. Two subjects in the placebo group and one subject in the bimekizumab group had an abnormal shift (change from <8 to >10) in the HADS-A total score. One subject in the placebo group also had an abnormal shift in the HADS-D total score. None of the subjects met the HADS-D withdrawal criteria (HADS-D total score ≥15).

Figure 3: Mean HADS-A and HADS-D Total Score by Treatment Arm during the 12-Week Double Blind Period in Study HS0001



Abbreviations: ADA = adalimumab; BKZ = bimekizumab; HADS-A = Hospital Anxiety and Depression Scale – Anxiety subscale; HADS-D = Hospital Anxiety and Depression Scale – Depression subscale; PBO = placebo

***DP Reviewer's Comment**: Among subjects who participated in Studies PS0008, PS0009, and PS0013 under the PsO development program, 15 subjects (1.5%) in the bimekizumab treatment group and seven subjects (4.1%) in the placebo group reported PHQ-9 total scores ≥15. Only one subject reported a total score ≥20 and also reported positive SI. Similarly, the percentage of subjects with a positive response for Question 9 on the PHQ-9 was higher in the placebo group (3%) vs. bimekizumab (0.3%). Although the results between item 9 on the PHQ-9 and the C-SSRS were inconsistent in PsO subjects, DP acknowledged that the C-SSRS is a more in-depth rating of SI/B and that the PHQ-9 item is "double-barreled" and asks about both SI "thoughts that you would be better off dead…" and SB or self-injury ("…or thoughts of hurting yourself in some way"). DP previously concluded that the lack of finding on the PHQ-9 Question 9 item does not negate the finding on the C-SSRS and does not rule out an underlying risk for SI/B.*

In contrast, the PHQ-9 total scores and Question 9 item scores in subjects with HS were relatively similar across treatment arms. Given that the Applicant administered both the PHQ-9 and the C-SSRS during the same visits, it is unclear why there was no imbalance of abnormal PHQ-9 scores during the treatment period. Because the C-SSRS results suggested an increased risk for SI/B with bimekizumab, DP similarly concludes that the estimation of SI/B and depression using the PHQ-9 should be interpreted with caution.

Summary of Case Narratives

The Applicant used an independent NAC to comprehensively review potential cases of SI/B and worsening depression. Table 8 includes a summary of cases narratives based on subjects in Studies HS0003, HS0004, and HS0005 that experienced an abnormal rating on the C-SSRS or PHQ-9, serious AEs, psychiatric AE of special interest, and AEs that led to study discontinuation. Of note, the Applicant did not report any psychiatric events in Study HS0001.

Table 8: Case Narratives for Psychiatric Events Occurring in Studies HS0003, HS0004, and HS0005

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0003-(b) (6)	28/F/White	Depression/ Study discontinuation	BKZ 320 mg Q4W	225/1	Subject reported a PHQ-9 total score = 25 and AE of mild depression after having a bad week due to worsening underlying disease (HS flare). The subject had no medical history of depression or psychiatric illness. The subject was also not using any relevant concomitant medications at the time of AE. After psychology referral, the Applicant withdrew subject from the study. At the early termination visit, PHQ-9 total score decreased to 5.	Unclear, due to worsening underlying disease that is a known risk factor
HS0003-(b) (6)	58/M/White	Suicidal ideation/ SAE leading to study discontinuation	BKZ 329 mg Q4W	35/8	Subject reported that he grew up in a fairly strict environment and had several problems within his family (primary provider). Subject's father died of suicide and subject received psychological treatment (focusing on trauma) in 2014. After first administration, subject became irritated more quickly. Subject developed severe SI (urge to jump out of window) and anxiety. After transport to hospital, staff also suspected alcohol intoxication. Psychological assessment indicated that the combination of sudden diverse symptoms of agitation, motor restlessness, suspicion (partner cheating), and disorganization (no florid delusions or hallucinations) was most appropriate for a delirious condition in response to study drug.	Possible, due to timing of event relative drug administration and resolution of symptoms. However, assessment confounded by prior medical history and possible alcohol intoxication.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0003-(b) (6)	21/F/White	Suicidal ideation/SAE[1]	BKZ 320 mg Q2W	196/126	Subject reported an ongoing medical history of mild anxiety and depression (treated with duloxetine) and social history of stressful student life. Subject's parents were diagnosed with cancer and living in another country. The subject withdrew consent due to study burden; however, at the safety follow-up visit, the subject reported SI (2 weeks prior to visit) and indicated SB on the C-SSRS. During discussion with the Investigator, the subject denied SB. The event also resolved the same day.	Unlikely, due to having discontinued BKZ for several months before event, pre-existing psychiatric condition, and external social stressors.
HS0003-(b) (6)	33/F/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg QW	85/16	Subject reported no prior psychiatric history. The Investigator referred subject for further psychiatric evaluation after reporting a PHQ-9 total score of 21. Subject stated that she was "not in a good mood" when completing the PHQ-9 questionnaire and that her elevated score reflected frustrations with the status of her painful lesions in her genital areas. During the early termination visit, her PHQ-9 total score was 3 and she expressed disappointment for leaving the study.	Unclear, due to worsening underlying disease.
HS0003-(b) (6)	30/F/Black	Depression/ Study discontinuation	BKZ 320 mg Q4W	35/35	Subjects medical history includes depression and substance abuse. During the study, subject reported that she just moved, was having difficulty with work and with family, and recently terminated a relationship with her boyfriend. She was also stressed from going to the study site because of the distance. After experiencing a 9-point increase in the PHQ-9, she reported improvements in symptoms at the follow-up visit.	Unclear, due to pre-existing psychiatric condition and confounding external social stressors.

Reference ID: 5374356

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0003-(b) (6)	42/F/Black	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q2W	225/12	At the time of the abnormal psychiatric evaluation (PHQ-9 total score of 27), the subject was having a bad week due to worsening underlying disease. The subject reported trying to change her response to the PHQ-9 after realizing a potential data entry error. After medical referral, the psychologist noted the subject having mild depressive disorder and recommended professional psychological support would be necessary.	Unclear, due to possible data entry error and worsening underlying disease.
HS0003-(b) (6) -	50/F/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q4W	168/27	Prior to the abnormal PHQ-9 total score of 20, the subject had an SAE for adjustment disorder with depressed mood. Concomitant medications included trazodone. Prior to the event, her sibling was murdered, and she had been feeling depressed.	Unlikely, due to extreme external psychological stress.
HS0003-(b) (6)	29/M/Black	Suicidal ideation/SAE	BKZ 320 mg Q2W	245/8	Subject had a medical and family history of depression and substance use. The subject also reported being a victim of sexual abuse in childhood. After being hospitalized for a diabetic foot ulcer that resulted in a toe amputation, the subject visited the emergency department for psychiatric evaluation due to suicidal ideation (plans to overdose on pills) and homicidal ideations (wanting to harm family). He reported that he had a stressful event in his life that triggered these feelings, but they resolved quickly without recurrence.	Unclear, due to pre-existing psychiatric condition, family history, worsening of comorbid diabetes and confounding external social stressors.
HS0003-(b) (6)	25/F/White	Suicidal ideation and abnormal psychiatric evaluation/SAE leading to study discontinuation[1]	BKZ 320 mg Q4W	313/33	Subject has a psychiatric history of depression, stimulant abuse, and post-traumatic stress disorder. Per the Investigator, the subject had been going through an unexpected personal issue lately, and her mental and emotional feelings were not normal. She was admitted to the psychiatric unit due to severe SI and was withdrawn from the study. Although the subject claimed to cut her leg 1 week earlier, she denied SB. Due to positive SB based on the C-SSRS	Unclear, due to pre-existing psychiatric condition and confounding external social stressors.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
					and a PHQ-9 score of 25, the subject met study withdrawal criteria.	
HS0003-(b) (6)	52/M/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q4W	198/31	Subject has a psychiatric history of depression and continues treatment with bupropion and venlafaxine. He reported that he had filled out several questions in PHQ-9 questionnaire in error (PHQ-9 total score was 16) because he did not have his glasses and was rushing to attend his therapist appointment afterwards. His regular therapist indicated that he had been attending outpatient therapy and medication management sessions since 2021. Previously unknown to the site was the information that he was diagnosed with narcissistic personality disorder. In consultation with the subject's therapist, the Investigator decided to not restart BKZ treatment and withdraw the subject.	Unclear, due to pre-existing psychiatric condition and potential data entry error.
HS0004-(b) (6)	57/M/White	Adjustment disorder/ Study discontinuation	BKZ 320 mg Q2W	29/1	Subject reported an ongoing psychiatric condition of adjustment disorder with depressed mood. The subject also reported taking cannabis and dexamethasone when experiencing worsening symptoms. The Investigator treated the subject with escitalopram.	Unlikely, due to worsening of pre-existing condition and confounding cannabis use.
HS0004-(b) (6)	31/F/White	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q4W	115/1	The Investigator referred the subject to a mental health professional after recording an elevated PHQ-9 score of 18. The event was not resolved at the time of study withdrawal.	Unassessable, due to insufficient information.
HS0004-(b) (6)	26/F/White	Depression/SAE	BKZ 320 mg Q4W	138/20	Subject had a psychiatric history of depression and attention deficient/hyperactivity disorder. After experiencing an SAE of worsening depression due to personal reasons ongoing in her life, investigators referred her for psychiatric follow-up. There were no abnormal ratings on the C-SSRS or PHQ-9. Symptoms of depression resolved after 82 days after onset.	Unclear, due to worsening of pre-existing condition and external psychosocial stressors.

Subject ID	Age/ Gender/ Race	Event type/ Reason for narrative	Original Treatment Arm	Days since first BKZ dose/Days since last BKZ injection	Summary	Causality Assessment
HS0004-[redacted]	23/F/Black	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q2W	40/1	The Investigator withdrew the subject from the study after the reporting a PHQ-9 total score ≥20. During her Week 4 visit, the subject reported passive SI on the C-SSRS. On follow-up, the subject stated that the questionnaire answers were inadvertent.	Unassessable, due to insufficient information and possible data entry error.
HS0005-[redacted]	40/F/Black	Depression and suicidal ideation/SAE leading to study discontinuation	BKZ 320 mg Q4W	584/24	Subject had a psychiatric history of bipolar disorder, depression, and anxiety. One day after reporting an AE for back pain and SAEs for depression and SI, the subject was hospitalized and started treatment with olanzapine. Per the Investigator, the subject was withdrawn from the study due to depression and SI and not due to back pain. At the Week 36 follow-up visit, the subject discussed the hospitalization, prior history of mental issues, and she agreed to visit a mental health professional. Her PHQ-9 total score of 17 and endorsement of active SI on the C-SSRS corresponded to her SAEs and hospitalization.	Unclear, due to worsening of pre-existing condition.
HS0005-[redacted]	30/F/Black	Abnormal psychiatric evaluation/ Study discontinuation	BKZ 320 mg Q2W	435/15	After a reporting an elevated PHQ-9 score of 21, the Investigator referred the subject for mental health evaluation. Notes indicated that the subject had depressive symptoms for 7 years with no SI.	Unassessable, due to insufficient information and possibly unclear due to worsening underlying psychiatric condition.

Abbreviations: AE = adverse event; BKZ = bimekizumab; C-SSRS = Columbia Suicide Severity Rating Scale; F = female; M = male; PHQ-9 = Patient Health Questionnaire-9 items; Q2W = every 2 weeks; Q4W = every 4 weeks; SAE = serious adverse event; SB = suicidal behavior; SI = suicidal ideation

[1]Conservative adjudication as suicidal behavior, per the Neuropsychiatric Adjudication Committee

Note: The Applicant did not submit case narratives for Subjects HS005-4[redacted] (19-year-old white male) and HS0005-[redacted] 20-year-old while male). Both subjects endorsed suicidal behavior during the open-label extension period (> 600 days since first dose of study medication). Both cases were confounded by external psychosocial stressors (relationship problems with partner).

Reference ID: 5374356

DP Reviewer's Comment: *In general, assessment of case narratives did not demonstrate a clear signal for SI/B risk associated with bimekizumab (no cases were submitted for placebo-treated subjects). Thirteen out of the 17 cases were confounded by past psychiatric history and external social stressors. Although subgroup analyses of events by dose and demographic variables are limited, 10 out of the 17 cases involved subjects <35 years of age. Because younger adults are likely exposed to greater psychosocial stressors, it is unclear whether the risk for worsening depression and SI/B is truly different across different age groups.*

IV. Findings from Previous PsO Development Program and Rationale to Support Product Labeling

On October 17, 2023, FDA approved bimekizumab for the treatment of moderate-to-severe PsO in adults. To support their PsO development program, the Applicant conducted two phase 2 studies (PS0010 and PS0016), four phase 3 studies (PS0008, PS0009, PS0013, and PS0015), and three long-term extension safety studies (PS0011, PS0018, and PS00154). Refer to Dr. Shamir Kalaria's (December 18, 2020) and Dr. Jennifer Reid's (June 5, 2023) Clinical Consult Reviews for addition information regarding the aforementioned studies and relevant psychiatric data submitted to support product labeling.

During evaluation of the initial submission (July 15, 2020), DP's pooled analysis of phase 2 and phase 3 clinical trial data did not reveal a clinically meaningful signal for bimekizumab-associated psychiatric AEs, SI/B, or symptoms of depression and anxiety. Although the number of SI events was greater for bimekizumab (n=17; 1.7%) as compared to placebo (n=1; 0.6%), DP noted that the majority of subjects experienced passive SI and that use of the C-SSRS may increase SI ascertainment. Because of the low number of cases of SI/B and psychiatric AEs and the lack of a clear association between treatment and events, DP did not recommend any product labeling to describe psychiatric safety data. After DDD issued a complete response letter for the initial BLA submission, the Applicant re-submitted additional clinical safety data from one phase 3 study and an ongoing long-term safety study. Re-evaluation of the psychiatric safety data revealed a similar three-fold increase in positive C-SSRS responses in bimekizumab group compared to placebo; however, there was also one completed suicide in a subject with no prior psychiatric history. In the context of the completed suicide and three AE cases of suicide attempts, the C-SSRS differences are consistent with a possible signal for an association between SI/B and bimekizumab. Therefore, DP recommended that the product label reflect this potential association with SI/B, including a Boxed Warning, a Warning and Precaution statement, and a description of the completed suicide. Given that SI/B is a rare event that lacks any reliable definitive prognostic factors, DP did not believe a Risk Evaluation and Mitigation strategy (REMS) would mitigate the risk beyond what labeling would accomplish.

Because of the serious, potentially life-threatening risk of SI/B associated with treatment with bimekizumab, the clinical review team sought advice from the Medical Policy and Program Review Council (meeting held July 19, 2023) on the most effective strategy to address the potential risk of SI/B and ensure safe use of this product. The clinical team identified the following uncertainties with regards to the estimated SI/B signal:

- SI/B is a serious, but rare event that can occur in the general population.
- Studies were not powered or designed to reliably assess differences in the incidence of SI/B.
- It is unclear whether the estimated rate of SI/B surpasses the background rate of SI/B in the target population and could be confounded due to disease severity.
- The confidence intervals for the estimated relative risk for SI/B was wide due to the low number of events.
- Clinical trials did not include enough observations to evaluate whether there is a difference between SI/B risk with bimekizumab and other treatments.
- Results based on the PHQ-9 Question 9 score and the C-SSRS were inconsistent.
- Because of psychiatric stopping criteria and exclusion criteria implemented in clinical trials, the true risk of SI/B associated with the use of bimekizumab in the target population is not known.
- Bimekizumab is approved in 39 countries worldwide without labeling restrictions related to SI/B or neuropsychiatric events and there were no post-marketing international reports of completed suicides or suicide attempts.

As a result, the clinical team agreed that the potential risk of SI/B is justified by the potential benefit in adult patients with moderate-to-severe PsO. The review team also agreed that a Limitation of Use statement instructing healthcare professionals to avoid prescribing bimekizumab to patients with a psychiatric history would not reduce the risk of SI/B because a majority of subjects with positive responses on C-SSRS or suicide attempts/completed suicides had no prior psychiatric history. Given the uncertainties regarding the estimated SI/B signal and the lack of an established causal association, DDD and DP ultimately agreed with describing the risk of SI/B in the Warnings and Precautions section of product labeling and did not require a boxed warning.

Based on the data collected in their HS development program, the Applicant concluded that the risk of SI/B appears to be consistent with the signal identified in the original PsO development program. Therefore, the Applicant proposes the following relevant changes to the product label:

(b) (6)

Because the risk for SI/B associated with bimekizumab appears to be similar between patients with PsO and HS, DP agrees with the Applicants proposal to include language in Sections 5 (Warning and Precautions) and 6 (Adverse Drug Reactions) that parallels the description of the SI/B signal observed in the PsO development program. DP does not recommend any further labeling changes or additional risk mitigation strategies.

V. Conclusion and Recommendations

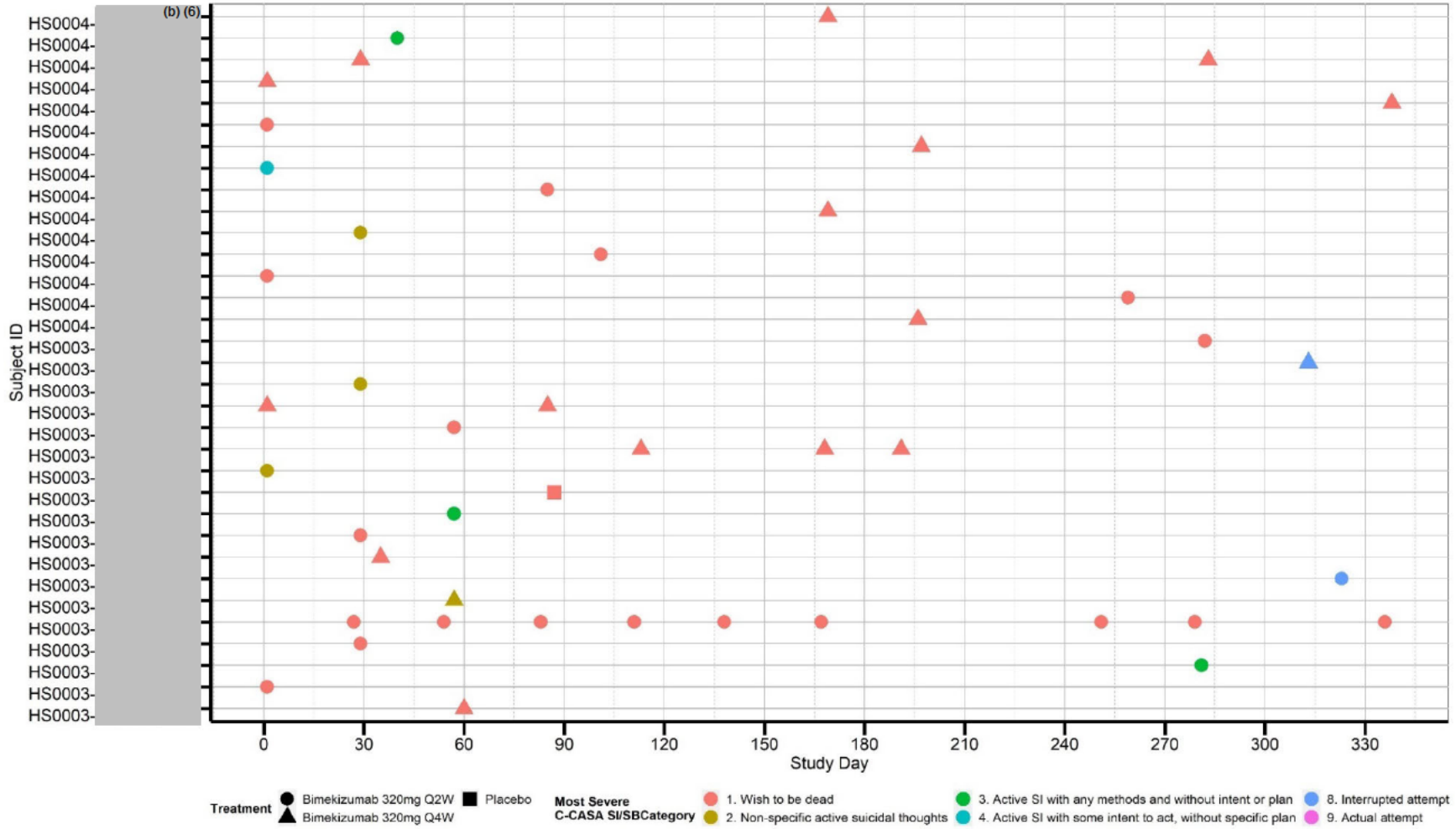
Based on the review of clinical data from phase 2 and 3 HS trials for bimekizumab, the risk for SI/B appears to be similar to the previous signal estimated in patients with PsO. Although there were no SI/B-related deaths, the Applicant's NAC conservatively adjudicated two cases of SB in two phase 3 studies and two suicidal attempts in the open-label extension study. AE reporting and prospective monitoring using the HADS and PHQ-9 questionnaires suggested no clinically meaningful differences in the risk of depression and anxiety with bimekizumab.

Reviewer's Recommendation:

1. Although a causal association between bimekizumab and increased risk for SI/B is not clearly established, the signal appears consistent between the PsO and HS development programs. Therefore, DP agrees with the Applicant's proposal to communicate the risk in Sections 5 (Warning and Precautions) and 6 (Adverse Drug Reactions) of product label.

2. DP continues to recommend that any future bimekizumab 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. DP also continues to recommend a mental health professional (psychiatrist or clinical psychologist) be involved in the screening and prospective monitoring process.

VI. Appendix Figure 1: Timeline of Most Severe Suicidal Ideation and Behavior Events by Treatment Arm and Study Visit across Initial, Maintenance, and Follow-up Periods (Pooled Studies HS0003 and HS0004)



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/s/

SHAMIR N KALARIA
05/02/2024 09:26:51 AM

BERNARD A FISCHER
05/02/2024 09:28:47 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Division of Pediatrics and Maternal Health
Office of Rare Diseases, Pediatrics, Urologic and Reproductive Medicine
Office of New Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Silver Spring, MD 20993
Tel 301-796-2200
FAX 301-796-9744

Division of Pediatrics and Maternal Health Review

Date: 3/15/2024 **Date consulted:** 2/6/2024

From: Wenjie Sun, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH

Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Dermatology and Dentistry (DDD)

Drug: Bimzelx (bimekizumab) subcutaneous injection, 160mg/mL

BLA: 761151 (S-010)

Applicant: UCB, Inc.

Subject: Pregnancy labeling

Approved Indication: for the treatment of moderate to severe plaque psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy.

Proposed Indication: for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS)

Materials Reviewed:

- Applicant's submitted background package and proposed labeling for BLA 761151/S-010 on January 19, 2024
- DDD consult form for DPMH, DARRTS Reference ID: 5324264

- Prior DPMH Pregnancy and Lactation Labeling Rule (PLLR) labeling review for Bimzelx, BLA 761151, by Kristie Baisden, DO, on February 3, 2021, DARRTS Reference ID: 4741087
- Prior DPMH PLLR labeling and postmarketing requirement (PMR) review for Bimzelx, BLA 761151, by Kristie Baisden, DO, on April 25, 2023, DARRTS Reference ID: 5163918

Consult Question: DDD requests DPMH assistance with the submission and to update the Pregnancy section of labeling.

INTRODUCTION AND BACKGROUND

Regulatory History

- Bimzelx (bimekizumab-bkzx, hereafter referred to as BKZ) for subcutaneous administration is a humanized monoclonal antibody that binds IL-17A and 17F. BKZ was approved October 18, 2023, for the treatment of moderate to severe plaque psoriasis (PsO) in adult patients who are candidates for systemic therapy or phototherapy.
- DPMH participated in the development of labeling language for the Pregnancy, Lactation, and Females and Males of the Reproductive Potential subsections at the time of initial approval.
- At the time of the approval, postmarketing requirements (PMRs) for a pregnancy registry (PMR 4268-3) and a database study (PMR 4268-4) were issued.
- On January 19, 2024, the Applicant submitted an efficacy supplement seeking a new indication for the treatment of adult patients with moderate to severe hidradenitis suppurativa (HS).
- Data submitted with this sBLA include reports of eight pregnancies in seven subjects in the HS program. DDD consulted DPMH on February 6, 2024, to review the submission and to consider whether subsection 8.1 of labeling should be updated.

The reader is referred to the prior DPMH review of BLA 761151[1] for a summary of drug characteristics and Psoriasis and Pregnancy. The reader is referred to Appendix A for a summary of HS and Pregnancy.

Current state of labeling for BLA 761151[2]

- There is no Boxed Warning or contraindication of use.
- Serious Adverse Reactions include the following:
  - Suicidal ideation and behavior
  - Increased risk of infection
  - Avoid use in patients with active tuberculosis.
  - Elevation of serum transaminases
  - Inflammatory bowel disease
- Subsection 8.1 Pregnancy states that "Available data from case reports on Bimzelx use in pregnant women are insufficient to evaluate for a drug associated risk of major birth

[1] Prior DPMH Pregnancy and Lactation Labeling Rule (PLLR) labeling review for Bimzelx, BLA 761151, by Kristie Baisden, DO, on February 3, 2021, DARRTS Reference ID: 4741087
[2] Approved labeling for BLA 761152, Drugs@ FDA, last updated 10/17/2023, accessed 2/13/2024.

Reference ID: 5347693

defects, miscarriage, or other adverse maternal or fetal outcomes. Transport of human IgG antibody 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."

- There is a recommendation to delay live virus immunizations in infants exposed to BKZ in utero for a minimum of four months after birth.
- There are no known interactions between BKZ and hormonal contraception.

Refer to Appendix B for currently approved labeling for subsection 8.1 Pregnancy.

REVIEW

PREGNANACY

DPMH completed a PLLR labeling review of the BKZ on February 3, 2021[3] and reviewed updated pregnancy information on April 25, 2023. In those reviews, DPMH concluded that 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 BKZ was immediately discontinued) were insufficient to evaluate for a drug-associated risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes. Pregnant women were excluded from clinical trials with BKZ.

During this submission (data cut-off date November 15, 2022), the Applicant reports an additional eight BKZ exposed pregnancies in seven participants exposed to BKZ during their clinical development program for HD. See **Table 1**. No birth defects were reported. Pregnancies were followed to outcome, and not to infant's first year of life. During the study, all study medications were stopped upon the diagnosis of pregnancy as per protocol. All pregnant participants have the diagnosis of obesity (BMI $\geq$ 30kg/m^2).

Table 1. Reviewer's Table of BKZ Exposed Pregnancies

Pregnant Participant	Participant ID	Exposure according to timing of last dose of BKZ (half-life 23 days)*	Outcome	Pregnancy related complications
1	(b) (6)	1st trimester	Term Live birth	GDM, GHTN, Hashimoto thyroiditis, preeclampsia
2		Pre-pregnancy (last dose 71 days before DOC)	Term Live births	Twins
3		1st trimester	SAB (10^{+2} weeks)	Pregnant with progesterone implant[4]
4		Pre-pregnancy (2.5 weeks before DOC)	SAB (21^{+2} weeks)	COVID-19 diagnosis within two weeks of loss

[3] DPMH Pregnancy and Lactation Labeling Rule (PLLR) labeling review for Bimzelx, BLA 761151, by Kristie Baisden, DO, on February 3, 2021, DARRTS Reference ID: 4741087

[4] The Applicant did not specify what type of progesterone implant was used.

Reference ID: 5347693

5	(b) (6)	Pre-pregnancy (3 months before DOC)	Induced abortion (10 weeks) for unknown reasons	Pregnant with non-hormonal implant (coil) for contraceptive.[5]
6		1st trimester	Induced abortion for personal reasons	None reported
7		1st trimester	Ongoing	None reported
8		NA	Unknown	NA

Source: Applicant's Summary of Clinical Safety and case narratives for Study HS0003, HS0004, HS0005.
**This information is extracted by this reviewer based on reported EDC and date of last dose of BKZ.*
***The Applicant reported one case of exposed pregnancy in the Summary of Clinical Safety (participant ID not shared), however this reviewer was unable to locate a case narrative for this case.*
SAB=spontaneous abortion; DOC=date of conception; NA=not applicable; GDM=gestational diabetes mellitus; GHTN=gestational hypertension

Reviewer's comment:
This reviewer could not find the case narratives associated with pregnant participants (b) (6) (one case of BKZ exposed pregnancy with unknown outcome that was presented in the Summary of Clinical Safety) listed in the Table above.

The Applicant did not submit any additional cases of pregnancy from their pharmacovigilance database other than the ones listed above. The Applicant did not perform a review of the published literature. The protocols for bimekizumab pregnancy registry and database PMR studies are currently under review by FDA. The pregnancy registry has not started to enroll patients yet.

The Applicant did not submit any new data regarding use of BKZ in lactating women or females and males of reproductive potential.

DPMH performed a review of the published literature through an updated literature search in Embase and Pubmed (on Feburary13, 2024) using search team "bimekizumab" and "pregnancy". No relevant articles were identified.

DISCUSSION/CONCLUSION

There is a pregnancy registry and database study for use of BKZ in pregnant women.[6] However, the pregnancy registry has not initiated enrollment of patients at the time of this review. Results from additional eight BKZ exposed pregnancies to the 20 exposed pregnancies that were reviewed for the initial approval are not sufficient to change the approved labeling language at the current time. DPMH agrees with the previous conclusions on bimekizumab use during

[5] The Applicant did not specify what type of implant was used.
[6] Previous language for PMRs regarding the pregnancy registry and database study were non-specific regarding the indication of treatment.

pregnancy, which states there are insufficient data to evaluate for a drug associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. DPMH does not recommend labeling change at the current time. See Appendix B for subsection 8.1 of currently approved labeling.

Because bimekizumab will be used in females of reproductive potential with the diagnosis of HD and there are insufficient data to inform drug-associated effects on maternal and infant outcomes with bimekizumab *in utero* exposure, DPMH recommends issuing postmarketing requirements (PMRs) for a pregnancy registry and database study to obtain additional data for this population. Since there is an existing pregnancy registry and database study for bimekizumab, the Applicant may enroll patients taking bimekizumab for HD into the existing bimekizumab pregnancy registry that is enrolling patients with moderate to severe plaque psoriasis. Additionally, because many patients with HS are also obese, obesity should be included as a confounder in the study design.

Appendix A.

Hidradenitis Suppurativa and Pregnancy

HS is a chronic, painful, follicular, occlusive disease that affects the folliculopilosebaceous unit mainly, but not exclusively, in intertriginous axillary, groin, perianal, perineal, genital, and inframammary skin. The goal for treatment is to reduce new lesions, scarring, associated symptoms and minimize impact on quality of life.

Common therapies for reducing disease burden in mild HS include oral tetracyclines, oral antiandrogenic agents, metformin, and topical clindamycin. For moderate to severe disease that failed initial therapy, other treatments include biologics and surgical unroofing of skin tunnels and recurrent nodules. Biologics include tumor necrosis factor (TNF) inhibitors (adalimumab[7] and infliximab[8]), interleukin (IL) 17A inhibitor (secukinumab[9]) and oral acitretin (in patients of nonchildbearing potential).[10]

The majority of patients with HS experience no change or improvement during pregnancy. A minority of pregnant women will experience worsening disease.[11] HS may flare in the postpartum period.

[7] Available studies with use of adalimumab during pregnancy do not reliably establish an association between adalimumab and major birth defects. See approved labeling for Abrilada at Drugs@FDA, last updated 10/4/2023.
[8] Infliximab does not carry an indication for treatment of HS. Available observational studies in pregnant women exposed to Infliximab showed no increased risk of major malformations among live births as compared to those exposed to non-biologics. See Approved labeling for Remicade, Drugs@FDA, last updated 10/5/21.
[9] Limited available human data with Cosentyx use in pregnant women are insufficient to inform a drug-associated risk of adverse developmental outcomes. See approved labeling for Cosentyx, Drugs@FDA, last updated 11/21/23.
[10] Ingram JR. Hydradenitis suppurativa: management. UpToDate. Last updated 11/20/2023. Accessed 2/15/24.
[11] Vossen AR, van Straalen KR, Prens EP, van der Zee HH. Menses and pregnancy affect symptoms in hidradenitis suppurativa: A cross-sectional study. J Am Acad Dermatol. 2017;76(1):155.

Reference ID: 5347693

Appendix B.
Approved labeling for subsection 8.1 of BIMZELX (bimekizumab)

FULL PRESCRIBING INFORMATION

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Exposure Registry

There is a pregnancy exposure registry that monitors pregnancy outcomes in women exposed to BIMZELX during pregnancy. For more information, healthcare providers or patients can contact the Organization of Teratology Information Specialists (OTIS) AutoImmune Diseases Study at 1-877-3118972 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 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 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).

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/

WENJIE SUN
03/15/2024 04:23:31 PM

MIRIAM C DINATALE
03/15/2024 04:26:49 PM

LYNNE P YAO
03/20/2024 05:17:40 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

BLA761151Orig1s010

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

BLA 761151/S-010

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

UCB, Inc.
Attention: Susan Tegtmeyer
Associate Director
1950 Lake Park Drive
Building 2100
Smyrna, GA 30080

Dear Susan Tegtmeyer:

Please refer to your supplemental biologics license application (sBLA) dated and received January 19, 2024, under section 351(a) of the Public Health Service Act for Bimzelx (bimekizumab-bkzx) injection, for subcutaneous use.

We also refer to your amendments dated February 21 and March 8, 2024.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 601.2(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is November 19, 2024.

We are reviewing your application according to the processes described in the draft guidance for industry *Good Review Management Principles and Practices for New Drug Applications and Biologics License Applications*.[1] Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling by October 19, 2024, and, if necessary, any anticipated postmarketing requirements (PMRs) and postmarketing commitments (PMCs) by September 24, 2024.

[1] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

During our filing review of your application, we identified the following potential review issues:

BIOSTATISTICS:

The statistical analysis plans (SAPs) and clinical study report for the phase 3 trials (HS0003 and HS0004) state that "if participants undergo lesion interventions as specified in the study protocol, the affected lesions will be counted by the Investigator as permanently present, thus accounting for potential bias due to the intervention." Submit detailed information on the process (e.g., capturing, documentation, and tracking) for lesion intervention as it is not clear how these lesions were counted as permanently present. In addition, we have found at least one instance where a lesion that received lesion intervention was not counted as permanently present. Subject HS0003-(b) (6) had an abscess that received lesion intervention (i.e., "INCISION & DRAINAGE" according to ADHSLIT.xpt) at Week 2; however, the abscess count at Week 16 was 0 for this subject. Therefore, it is not clear whether lesions that received intervention were counted as permanently present. Provide clarification.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

We request that you submit the following information:

For safety and efficacy, submit analyses and discussion by ethnicity subgroups (Hispanic/Latino, Not Hispanic/Latino).

PRESCRIBING INFORMATION

Your proposed Prescribing Information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the Prescription Drug Labeling Resources[2] and Pregnancy and Lactation Labeling Rule[3] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

[2] Prescription Drug Labeling Resources website: https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources
[3] Pregnancy and Lactation Labeling Rule website: https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule

human drug and biological products

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential

- Regulations and related guidance documents

- A sample tool illustrating the format for Highlights of Prescribing Information and Contents

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

- Other prescription drug labeling resources for the Prescribing Information, patient labeling, and carton and container labeling.

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

Please respond only to the above requests for information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

NATIONAL DRUG CODE(s)

Prior to the action date of your sBLA, we recommend you:

- Review the regulations that describe the requirements for national drug code (NDC(s)) including the requirements for obtaining new NDC(s) and restrictions regarding the use of NDC(s) [see 21 CFR 207.33 and 21 CFR 207.35, respectively].

- Ensure that NDC(s) that appear on prescription drug labeling (e.g., Prescribing Information, outer packaging, carton labeling, container labeling) are assigned correctly per the above. CDER does not typically review the accuracy of NDC(s) on prescription drug labeling prior to approval.

- Optionally, reserve new NDC(s) by referring to the Drug Registration and Listing website[4] or contacting eDRLS@fda.hhs.gov. Include the required additional data

[4] https://www.fda.gov/drugs/guidance-compliance-regulatory-information/electronic-drug-registration-and-listing-system-edrls

elements when converting the NDC reservation submission to a drug registration and listing submission when a drug is approved.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed Prescribing Information (PI) and Medication Guide (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft guidance for industry *Providing Regulatory Submissions in Electronic and Non-Electronic Format-Promotional Labeling and Advertising Materials for Human Prescription Drugs* (June 2019).[5] Do not submit launch materials until you have received our proposed revisions to the Prescribing Information (PI), and Medication Guide (as applicable), and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see FDA.gov.[6] If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication in pediatric patients unless this requirement is waived, deferred, or inapplicable.

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[5] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[6] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/office-prescription-drug-promotion-opdp

We acknowledge receipt of your request for a partial waiver of pediatric studies in patients 0 to 12 years of age for this application. Once we have reviewed your request, we will notify you if the partial waiver request is denied.

We acknowledge receipt of your request for a partial deferral of pediatric studies in patients 12 to 18 years of age for this application. Once we have reviewed your request, we will notify you if the partial deferral request is denied.

If you have any questions, contact Strother D. Dixon, Senior Regulatory Project Manager at strother.dixon@fda.hhs.gov or (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Gordana Diglisic, MD
Associate Director for Therapeutic Review
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

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/

GORDANA DIGLISIC
04/02/2024 03:52:07 PM

See Labeling Review with
“Date of Submission: November 19, 1998”
for Labeling Comments

Copy of Reference Listed Drug labeling removed.

It is believed the Chemistry Reviews are misnumbered. Only three reviews were located in the archived volumes, numbered 1, 3, and 4.

THIS IS THE ORIGINAL UNREDACTED SBA, which was scanned and then redacted electronically. Please see the T:/ drive.

ANDA 74-726/013 and S-014

FOR

Name: Desoximetasone Ointment USP 0.25%

Sponsor: Clay-Park Labs, Inc.

Approval Date: July 1, 2003

This package is Not Redacted.

THIS MATERIAL IS NOT TO BE COPIED AND SENT OUT OF DIDP.