CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761151Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

IND 128707

MEETING MINUTES

UCB, Inc.
Attention: Leo DiNapoli, PhD, RAC
Director, Regulatory Affairs
1950 Lake Park Drive, Building 2100
Smyrna, Georgia 30080

Dear Dr. DiNapoli:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for bimekizumab injection, 160mg/mL.

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2019. The purpose of the meeting was to reach agreement on the nonclinical, clinical, clinical pharmacology, and administrative content and format of the planned BLA for bimekizumab for the treatment of PSO.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Strother D. Dixon, Senior Regulatory Project Manager at (301) 796-1015.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

[1] 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.

Enclosure:

- Meeting Minutes
- Sponsor Response to Preliminary

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	December 9, 2019; 11:00 AM EST
Meeting Location:	FDA, White Oak, Building 22
Application Number:	IND 128707
Product Name:	bimekizumab injection, 160mg/mL
Proposed Indication:	For the treatment of adult patients with moderate to severe chronic plaque psoriasis who are candidates for systemic therapy or phototherapy
Sponsor Name:	UCB, Inc.
Meeting Chair:	Kendall A. Marcus, MD
Meeting Recorder:	Strother D. Dixon

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Kevin Clark, MD, Clinical Reviewer, DDDP
Carmen Booker, PhD, Pharmacology Reviewer, DDDP
Chinmay Shukla, PhD, Clinical Pharmacology Scientific Lead, Division of Clinical Pharmacology (DCP) 3
Cindy (Liping) Pan, PhD, Senior Staff Fellow, DCP 3
Mohamed Alosh, PhD, Biometrics Team Leader, Division of Biometrics III
Carin Kim, PhD, Biometrics Reviewer, DB III
Serge Beaucage, PhD, CMC Team Lead, Office of Biotechnology Products (OBP)
Mayumi Takahashi, PhD, CMC Reviewer, OBP
Madhuri R. Patel, PharmD, Safety Evaluator, Division of Medication Error Prevention & Analysis
Yasmeen Abou-Sayed, PharmD, Risk Management Analyst, Division of Risk Evaluation
Qianyiren Song, PharmD, Regulatory Health Project Manager, DDDP
Kimberle P. Searcy, MPH, Regulatory Health Project Manager, DDDP
Strother D. Dixon, Senior Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Christopher Cioffi, PhD, Clinical Development Lead
Delphine Deherder, MS, Safety Scientist

Leo DiNapoli, PhD, RAC, Director, Regulatory Affairs
Cynthia Madden, MD, MPH, Lead Clinical Development Physician
Tom Meeusen, PhD, PharmD, Global Regulatory Lead, bimekizumab
Jason Morgan, PhD, Regulatory Scientist
Martin Nemansky, PhD, Bioanalytical Scientist
Luke Peterson, MS, Principal Biostatistician
Pavan Vajjah, Ph.D., Senior Principal Scientist, Quantitative Clinical Pharmacology
Veerle Vanvoorden, MSc, Associate Clinical Program Director

1.0 BACKGROUND

Purpose

The purpose of the meeting is to reach agreement on the nonclinical, clinical, clinical pharmacology, and administrative content and format of the planned BLA for bimekizumab for the treatment of PSO.

Regulatory Correspondence History

We have had the following meetings:

- September 24, 2019 – CMC PreBLA
- August 20, 2018 – Written Responses Only
- May 23, 2018 – Written Responses Only
- August 8, 2017 – Written Responses Only
- April 18, 2017 – Written Responses Only
- May 2, 2016 – Type B/Pre-IND

We have sent the following correspondences:

- December 3, 2019 – Advice
- November 22, 2019 – Advice
- May 31, 2019 – Advice
- March 29, 2019 – Advice
- March 19, 2019 – Advice
- October 26, 2018 – Advice
- September 19, 2018 – Advice
- July 20, 2018 – Advice
- July 19, 2018 – Agreed Initial Pediatric Study Plan – Agreement
- June 27, 2018 – Advice
- June 22, 2018 – Advice
- March 29, 2018 – Advice
- March 23, 2018 – Pediatric Study Plan – Other
- February 27, 2018 – Advice
- February 3, 2018 – Advice
- November 7, 2017 – Initial Pediatric Study Plan – Written Response
- June 22, 2017 – Advice

- November 2, 2016 – Advice
- August 17, 2016 – IRB Waiver Granted
- August 16, 2016 – Study May Proceed
- June 30, 2016 – Information Request

FDA sent Preliminary Comments to UCB, Inc. on December 5, 2019.

2.0 DISCUSSION

2.1. Regulatory

Question 13:
For the purposes of providing Investigator financial disclosure information, UCB proposes that the Phase 2 dose-ranging study (PS0010), the Phase 2 pharmacodynamic study (PS0016), and the three Phase 3 pivotal studies (PS0008, PS0009, and PS0013) be considered the "covered clinical studies" for the BLA per 21 CFR 54.2(e).
Does the Agency agree that providing financial disclosure information for PS0010, PS0016, PS0008, PS0009, and PS0013 is sufficient for filing and review?

FDA Response to Question 13:
Your proposal appears reasonable.

Question 14:
UCB proposes to provide transfer of sponsor obligation information in the BLA for the proposed "covered clinical studies" (ie, PS0010, PS0016, PS0008, PS0009, and PS0013).

Does the Agency agree that providing transfer of sponsor obligation information for PS0010, PS0016, PS0008, PS0009, and PS0013 is sufficient for filing and review?

FDA Response to Question 14:
Your proposal appears reasonable.

Question 15:
UCB is aware of the need to submit foreign data supporting information for non-US, non-IND study sites to satisfy the 21 CFR 312.120 requirement. A large majority of non-US study sites involved in the bimekizumab PSO program signed Form FDA 1572s and thus conducted the study under bimekizumab's PSO IND. UCB proposes to submit foreign data supporting information for non-US sites that did not sign 1572s for PS0010, PS0016, PS0008, PS0009, and PS0013 to satisfy this requirement.

Does the Agency agree that providing foreign data supporting information, as applicable, for PS0010, PS0016, PS0008, PS0009, and PS0013 is sufficient for filing and review?

FDA Response to Question 15:
Your proposal appears reasonable.

Question 16:
It is UCB's understanding that the proprietary name review request for a BLA should be provided separately from the BLA submission. Thus, UCB proposes to submit proprietary name review supporting information with the BLA and then soon after (ie, within a few days) submit a request for review of the submitted proposed proprietary name to the BLA (ie, a separate cover letter that refers to the information within the BLA).

Does the Agency agree with submission of the supporting information in the BLA followed by a subsequent request for review of the proposed proprietary name?

FDA Response to Question 16:
Your approach is reasonable. However, we would encourage you to submit the proposed proprietary name review request and the supporting materials together.

Please follow the procedure below to ensure that the document room accurately codes for a "Proprietary Name/Request for Review" and opens an OSE PDUFA clock for your BLA name review.

When submitting a proprietary name request for review to the Agency, it is crucial to:

- Check "Request for Proprietary Name Review" in Box 21 of FDA form 356h.
- Include the statement **"REQUEST FOR PROPRIETARY NAME REVIEW"** in bold capital letters, at the **top** of your cover letter **and** at the **top** of the first page of the main submission document (refer to the complete submission guidance link below).
- Please clearly state in the cover letter and supporting documentation the exact name you are requesting for review and include the phonetic spelling of the name.
- If you have already submitted draft labels & labeling, please add a link to them in the cover letter.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022,

(https://www.fda.gov/downloads/forindustry/userfees/prescriptiondruguserfee/ucm511438.pdf)

Question 17:
The proposed content for Modules 1, 2, 4, and 5 are provided in the BLA Table of Contents. A Device Presentation Reviewer's Guide is also included to outline UCB's plans for device data organization within the BLA. Note: Only CTD sections that are planned to have documents are included in the Tables of Contents.

Does the Agency agree with the proposed overall content and format of the BLA as described in this package?

FDA Response to Question 17:
Yes. From technical perspective (and not content related), the proposed table of content for the planned submission is acceptable.

Question 18:
A separate CMC-focused pre-BLA meeting was held with the Agency on 24 Sep 2019, thus CMC/Quality topics are out of scope for this briefing package and question.

Does the Agency agree that the overall BLA, as described in this package in terms of nonclinical, clinical, clinical pharmacology, and regulatory content, appears sufficient to support filing and review for the indication of treatment of adults with moderate to severe plaque psoriasis who are candidates for systemic therapy or phototherapy?

FDA Response to Question 18:
In general, the content appears sufficient to support filing and review of your BLA. See responses to Questions 3 and 4.

2.2. Nonclinical

Question 1:
The nonclinical program is summarized in Section 12 with extended details available in Section 4 of the IB.

Does the Agency agree that the nonclinical package appears sufficient for filing and review of the BLA?

FDA Response to Question 1:
We agree that the nonclinical program appears adequate to support submission of your BLA. Provide an updated carcinogenicity risk assessment for bimekizumab in the BLA submission.

2.3. Clinical Pharmacology

Question 3:
Assessment of anti-bimekizumab/anti-drug antibody (ADAb) status is discussed in Section 13.4.2.3. Time points at which blood samples for plasma concentrations of bimekizumab and ADAb will be collected across PS0008, PS0009, and PS0013 are provided in Table 13–6 and Table 13–7, respectively.

An interim clinical database data cut will be taken based on all available data through the last scheduled study visit (ie, Week 52 or Week 56 depending on the study). For BLA submission, PK data for all available visits and ADAb results for visits through Week 52/56 will be provided within the respective interim CSRs. In addition, the ADAb results will be evaluated within the Integrated Summary of Immunogenicity. The bioanalytical reports supporting the validity of the PK and ADAb data will be interim (QA audited) reports as study samples from ongoing study participants in the SFU (ie, who have not entered PS0014) will not be available by BLA submission. After all study samples, including any pending SFU samples, have been analyzed, PK and ADAb result files will be provided for inclusion into the final CSRs and final bioanalytical reports will be created and submitted to the IND when available.
Does the Agency agree that submission of the data cut immunogenicity data (ie, without pending SFU data) and interim (QA-audited) bioanalytical reports is sufficient for filing and review of the BLA?

FDA Response to Question 3:
The immunogenicity assays used for the detection and confirmation of anti-drug binding and neutralizing antibodies should be adequately validated prior to analysis of Phase 3 clinical samples. Be advised that clinical serum samples should be appropriately stored until suitable immunogenicity assays are developed and fully validated. It is strongly recommended to discuss with the FDA any issues you may have on assay validation prior to testing clinical serum samples from pivotal trials. Data supporting full validation of the assays for PK assessment and immunogenicity assessment should be submitted in the license application. Your proposal of submitting QA audited interim bioanalysis reports at the time of BLA submission will not be acceptable. We recommend you finalize the bioanalysis reports and submit with your BLA. Additional PK and immunogenicity data that you obtain during the open label extension phase can be added as an addendum to your original bioanalysis reports.

2.4. Clinical/Biostatistics

Question 2:
The Phase 2 studies (PS0010 and PS0016 and their respective OLE studies PS0011 and PS0018) will be complete and final CSRs will be submitted with the BLA.

The Phase 3 bimekizumab studies PS0008, PS0009, and PS0013 will be ongoing, but clinically complete at the time of BLA submission (ie, the last study participant will have received their last maintenance dose of bimekizumab in each of these studies).

At the time of the interim clinical database data cut, PS0008, PS0009 and PS0013 study participants who do not enter the OLE study PS0014 may still be going through the SFU Period, which monitors safety up to 20 weeks after the last dose of bimekizumab. This means that the clean interim data cuts used as a basis for the interim CSRs will contain all data up to and including the last study participant's Week 52 visit (for PS0009) and the last study participant's Week 56 visit (for PS0008 and PS0013), including all SFU data available at the time of the data cut.

Since most study participants in PS0008, PS0009, and PS0013 will be enrolled in the PS0014 OLE study, only a limited amount of SFU data from PS0008, PS0009, and PS0013 will be unavailable when these interim clinical database data cuts are taken. While that pending SFU data will not be in the interim CSRs or in the BLA, it will be included in the final CSRs, which will be submitted to the IND when available.

In order to provide comprehensive pooled data for safety and exposure to bimekizumab, an interim clinical data cut of PS0014 will be performed at a pre-determined cut-off date (approximately 6 months prior to submission) and clinical safety narratives will be provided (see also Question 6, Section 11.2.5).

For Agency reference, the Phase 3b study PS0015 will be ongoing and blinded at the time of the data cut-off for the BLA.

Does the Agency agree that submission of the interim CSRs for PS0008, PS0009, and PS0013 and the interim data cut of PS0014, is sufficient to support filing and review?

FDA Response to Question 2:
Your proposal appears reasonable. As discussed in your Meeting Package, Phase 3 Trial PS0015 is expected to be ongoing and blinded at the time of the data cut-off date for the BLA submission and thus is not planned for inclusion in the application.

Question 4:
UCB is developing a competitive ligand binding assay (CLBA) to assess neutralizing antibodies (NAbs) to bimekizumab, as agreed to by the Agency (for reference, see Briefing Package submitted 29 June 2017 [SN0025] and 08 Aug 2017 Agency responses). UCB will follow a tiered approach for immunogenicity testing. Consecutive screening, confirmatory, and titration ADAb methods will be applied. All confirmed ADAb-positive samples will be tested in the CLBA NAb method. The CLBA assay is currently being validated and consequently the Nab results are not expected to be available for the BLA. Thus, UCB proposes to submit the Nab results by the time of the 120-Day Safety Update (120-DSU) (see Table 11–1); this would be provided as an addendum to the Integrated Summary of Immunogenicity.

Table 11–1: Proposed data to be provided with the BLA and later by the time of the 120-Day Safety Update

	PS0008, PS0009, and PS0013 SFU data	PS0008, PS0009, and PS0013 ADAb data	PS0008, PS0009, and PS0013 NAb data
Included in the BLA	Interim clinical data cut up to LPLV for PS0008, PS0009, and PS0013, including all SFU data available at the time of the data cut	All ADAb data for PS0008, PS0009, and PS0013 study participants in the pivotal studies, available at the time of the interim clinical data cut, excluding all SFU ADAb data.	No NAb data proposed to be provided at the initial BLA submission
Data outstanding at BLA submission	SFU data for study participants still ongoing and/or for which data was not available at the time of the interim clinical data cut	ADAb data that is outstanding at the time of the interim clinical data cut (all SFU samples)	All PS0008, PS0009, and PS0013 NAb data
Submitted by the time of the 120-Day Safety Update	Any and all outstanding SFU data for pivotal studies not provided at initial submission	All SFU ADAb data for pivotal studies	All PS0008, PS0009, and PS0013 NAb data will be provided, including SFU samples

ADAb=anti-drug antibody; LPLV=last patient last visit; NAb=neutralizing antibody; SFU=Safety Follow-Up

Understanding that the data will be a review issue, does the Agency agree with UCB's proposal to provide the NAb data by the time of the 120-DSU?

FDA Response to Question 4:
As stated in the FDA response to Question 3, the neutralizing antibody assay should be adequately validated prior to analysis of pivotal trial serum samples. We recommend you assess the effect on neutralizing antibody on PK, safety and efficacy and submit this information in the BLA for review.

Meeting Discussion:
The sponsor inquired whether submission of NAb data with the 120 day safety report would be acceptable. The Agency responded that this would not be acceptable and recommended the sponsor to submit NAb data with the original BLA submission.

Question 5:
On 06 May 2019, UCB submitted a request for advice (IND 128707, SN 0131) on the ISAP (Amendment 1). As of the date of this briefing package, UCB has not received feedback, but has revised some elements of the plan for integrated analyses to align with current submission planning. Included with this briefing package is ISAP A2. To facilitate Agency review, the changes from the previous version are summarized in Section 13.3 and described in ISAP A2 Section 7.2. Additionally, a tracked changes version is included with this package. Details on the analysis methods for efficacy and safety can be found in ISAP A2 Section 4.3 and ISAP A2 Section 4.4, respectively.

Does the Agency agree that the proposed efficacy and safety analyses within the ISAP A2 appear sufficient to support filing and review of the BLA?

FDA Response to Question 5:

To characterize the safety profile of bimekizumab, you propose to summarize safety information from the following pools of data, summarized in the table below:

Pool name	Studies included in pool	Treatment groups included in pool	Treatment Periods included in pool	Purpose of pool
S1	PS0009, PS0013	Subjects exposed to: BKZ 320mg Q4W PBO	Initial Treatment Period (Weeks 0-16)	Primary safety pool; Investigate subgroups; Summarize safety of BKZ vs PBO through Week 16 in Phase 3 PBO-controlled studies
S2	PS0010, PS0011, PS0016, PS0018 PS0008, PS0009, PS0013, PS0014	Subjects exposed to: Phase 3 BKZ 320mg Q4W Phase 3 BKZ 320mg Q8W Phase 3 BKZ Total Phase 2/3 BKZ Total Ustekinumab [a] Adalimumab [a]	Initial Treatment Period, Maintenance Treatment Period, OLE Treatment Period	Provide most comprehensive overview of BKZ safety by including all Phase 2/3 data from studies in PSO
S3	PS0010, PS0016, PS0008, PS0009, PS0013	Subjects exposed to: BKZ 320mg Q4W	Initial Treatment Period (Weeks 0-16) for Phase 3 data, Weeks 0-12 for PS0010, and Weeks 0-8 for PS0016	Summarize PK and immunogenicity during Initial Treatment Period
S4	DV0002, DV0006	Subjects exposed to: BKZ 320mg Q4W BKZ 320mg Q8W	16-week Treatment Period	Summarize PK and immunogenicity data for DV0002 and DV0006 to allow for pooled assessment by dose regimen and device type (auto-injector and safety syringe)

[a] Data for active comparators (ustekinumab, adalimumab) will be included in a subset of outputs produced for Pool S2.

For the set of safety analyses based on Pool S2, you propose that four safety treatment groups will be considered and will include only those subjects who were exposed to bimekizumab. Treatment groups will be defined as 'Phase 3 bimekizumab (BKZ) 320mg Q4W', 'Phase 3 BKZ 320mg Q8W', 'Phase 3 BKZ Total', and 'Phase 2/3 BKZ Total'.

You also propose supportive analyses of interest using subsets of Pool S2. The proposed analyses and your rationale for each are as follows:

A. Pool S2 data collected while on blinded bimekizumab, excluding open-label studies and Escape Period data from PS0013. Rationale: This allows for a comparison between a pool that excludes unblinded data versus a pool that does not exclude unblinded data to determine if that has an impact on the AE profile.

B. Data from PS0009 and PS0013 during the Maintenance Period only. Rationale: This provides a direct comparison of Pool S1 between the Initial and Maintenance Period to evaluate whether the AE profile changes with prolonged exposure.

C. Data from PS0008 and PS0013 during the Maintenance Period only. Rationale: Compare the bimekizumab 320mg Q4W and 320mg Q8W dosing regimens during the Maintenance Period of PS0008 and PS0013 among subjects who were treated with bimekizumab 320mg Q4W during the Initial Period of these 2 studies.

D. Pool S2 data where subjects with <=4 weeks of bimekizumab 320mg Q8W dosing after treatment switch in PS0014 will have their Q8W data excluded. Rationale: Because PS0014 will be ongoing, including Q8W subjects with <=4 weeks of data will increase the number of Q8W exposures that are not yet differentiated from the Q4W subjects. This supportive analysis will help to understand if this has an impact on the AE profile.

Regarding your proposed pooling strategy for safety data, we have the following comments:

- Your proposed pooling strategy for Pools S1 and S3 appears reasonable. For Pool S1, provide raw incidence rates for adverse events (≥1%) by treatment group. For Pool S2 analyses involving the Maintenance and Open-Label Extension study periods, provide raw incidence rates for adverse events (≥1%) by treatment group as well as the exposure-adjusted rates (in subject-years) by treatment group.
- Regarding Pool S2, the safety data from different dosing regimens in your Phase 2 trials may provide supportive safety data, and you may investigate AEs by conducting the additional exploratory pooled analyses you have proposed.

  However, we note there are some limitations that may affect the interpretation of results from these pooled analyses. For example, the doses in your Phase 2 trials were different from those in your Phase 3 trials:

  - PS0010 (12-week treatment period) and PS0011 (extension period) included 9 combinations of doses excluding the placebo that varied in BKZ doses of 64mg Q4W, 160 mg Q4W, 320 mg loading dose at baseline and 160 mg Q4W, 320 mg Q4W; 480 mg Q4W which then further varied after Week 12 depending on their PASI 90 response at Week 12.

- PS0016 was a Phase 2a PK/PD study where BKZ 320 mg was only administered at baseline, Weeks 4 and 12 only (i.e., no Week 8 administration)
- PS0018 was an open-label study that included 160 mg Q4W at first, and at the investigator's discretion, subjects received BKZ 320 mg Q4W from Weeks 12 to 48.

By pooling the different doses (concentration, treatment duration, frequency of dose) in the above Phase 2 trials, it would make it difficult to attribute a safety signal to a specific dose. In addition, for your Phase 3 trials, BKZ 320 mg Q8W is not a true Q8W regimen but a mixture of a Q4W (for the first 16 weeks) followed by a Q8W regimen.

Because the dosing regimens in your Phase 2 trials were different from those in your Phase 3 trials, which may impact the safety profiles, we recommend that you pool long- term safety data from all of your Phase 3 trials. Additionally, you may consider an additional exploratory safety analysis by pooling the 48-week 320 mg Q4W data from your Phase 2 studies (PS0010, PS0011) along with your Phase 3 data.

- Your proposed supportive analyses of interest for Pool S2 appear reasonable.
- You proposed to pool PK and immunogenicity data from Phase 3 studies (PS0008, PS0009, and PS0013) for PK and immunogenicity analysis in addition to providing data for each study in the CSRs. Your proposal appears reasonable. Additionally, we recommend that you pool data from your Phase 2 (PS0010 and PS0016) along with your Phase 3 data for PK and immunogenicity analysis as well.

Include the following in your pooled analyses (Trials PS0008, PS0009, and PS0013)

- Line listings for all abnormal safety findings (e.g., adverse events, vital signs, laboratory values.)
- Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate; and
- Shift tables for all vital signs. Provide the normal range of values for all parameters.

Additional Comments

For PS0008 and PS0009, you plan to test for superiority of your product against an active comparator (adalimumab and ustekinumab, respectively) at the α level of 0.05 (two-sided). We remind you of the Agency's previous comments that in general, to support a superiority claim against an active comparator, replication of study findings from two adequate and well-controlled trials are needed (2/3/2018; 7/20/2018;

3/19/2019). In addition, we previously made reference to the Agency's guidance for a single study submission (4/18/2017; 2/3/2018; 7/20/2018; 3/19/2019).

It should be noted that a comparative claim would be based on efficacy and safety consideration and the database for safety should be sufficient in terms of sample size and study duration (e.g. one year) to demonstrate favorable benefit risk. It is not clear whether your trials would be adequate to reliably compare the benefit-risk of your product against each comparator.

You are also reminded of the Agency's previous comments (4/18/2017; 7/20/2018; 3/19/2019) concerning the need for an adequate scientific bridge between EU-approved and US-licensed active comparator to justify the relevance of these data.

Meeting Discussion:
The sponsor proposed to pool only Phase 3 trial immunogenicity data and not include Phase 2 study immunogenicity data due to difference in assay sensitivity. The Agency responded this approach is reasonable.

The sponsor proposed to provide shift tables for biochemistry and hematology labs based on CTCAE grade. The Agency responded that their proposal is acceptable. However, shift tables including the raw values should be provided along with the normal reference range. The sponsor also proposed to provide shift tables for blood pressure "markedly abnormal criteria for blood pressure." The Agency recommended the sponsor define abnormal blood pressure based on specific criteria.

Question 6:
UCB proposes to provide the following clinical safety narratives, regardless of treatment (placebo or active):

- For PSO studies that will have interim or final CSRs at the time of submission, individual clinical safety narratives for deaths, premature termination adverse events (PTAEs), serious adverse events (SAEs), AEs that have been identified for special monitoring, and pregnancies will be provided.
- For the clinical data cut from the ongoing OLE study, PS0014, clinical safety narratives for deaths, PTAEs, SAEs, AEs that have been identified for special monitoring, and pregnancies will be provided.

The events pre-specified to be of special monitoring for which clinical safety narratives will be provided include:

- serious infections
- neutropenia (for events meeting protocol withdrawal criteria)
- anaphylaxis

- suicidal ideation and behavior, depression (for events meeting protocol-defined withdrawal criteria related to suicidality and depression)
- Major Adverse Cardiac Events (MACE) (as adjudicated by the Cardiovascular Adjudication Committee)
- liver function test (LFT) changes/enzyme elevations (for events meeting protocol-defined withdrawal criteria for LFT elevations, including any Hy's Law cases)
- malignancies
- inflammatory bowel diseases

Does the Agency agree that the proposal for clinical safety narratives is sufficient for filing and review of the BLA?

FDA Response to Question 6:
Your proposal appears reasonable. Of note, PTAEs should include all subjects who discontinued from the trials because of an AE, whether or not the AE was considered treatment-related.

Question 7:
UCB proposes to provide electronic Case Report Forms (eCRFs) for all study participants from PSO studies for whom a clinical safety narrative was written.

Does the Agency agree with this proposal?

FDA Response to Question 7:
Your proposal appears reasonable. However, other eCRFs should be readily available upon request.

Question 8:
The following table outlines the data sets and SAS programs that are proposed for inclusion in the BLA.

Data Source	Data Tabulations (SDTM)	Analysis data sets (ADaM)	SAS programs for analysis data sets	SAS programs for primary efficacy endpoint
PS0016	X	X		
PS0018	X	X		
PS0010	X	X		
PS0011	X	X		
PS0008	X	X	X	X
PS0009	X	X	X	X
PS0013	X	X	X	X
PS0014	X	X		
ISS		X	X	X
ISE		X	X	X

ADaM=Analysis Data Model; SDTM=Study Data Tabulation Model; ISE=Integrated Summary of Efficacy; ISS=Integrated Summary of Safety

Does the Agency agree that the data sets and SAS programs proposed above for inclusion in the application are sufficient to support filing and review of the BLA?

FDA Response to Question 8:
Your proposal appears reasonable.

Additional Comments
In your BLA submission, provide full details regarding how and when you discovered about the 24 subjects that received incorrect treatment assignments at Visit 20 for PS0008.

Question 9:
Summaries of studies in other indications are provided in the Clinical Attachment. UCB proposes to include the following safety data from other indications in the BLA:

Completed studies
PA0007, PA0008, AS0008, HS0001, UC0011, and RA0123 will have been completed and full CSRs will be submitted at the time of filing. CSRs from completed studies in healthy volunteers will also be submitted.

Ongoing open-label studies
A safety-cut for the ongoing OLE studies to the PsA and AS programs (ie, PA0009 and AS0009 [Phase 2] and PA0012 [Phase 3]) is planned and will include suspected unexpected serious adverse reactions (SUSARs) from the drug safety database (with a cut-off of approximately 6 months prior to submission, anticipated for early November 2019), provided in line listings.

Ongoing blinded studies
For the Phase 3 programs in other indications (PsA, axSpA, and HS, all of which will be ongoing and blinded at the time of BLA submission for PSO), SUSARs from the drug safety database (with a cut-off of approximately 6 months prior to submission, anticipated for early November 2019) will be provided in line listings. IND safety reports will continue to be submitted to the relevant INDs (PSO IND 128707, PsA and axSpA IND (b) (4), HS IND (b) (4)).

A summary of studies in other indications, along with status at filing, is included in Table 11–2.

Table 11–2: Summary of studies in other indications with bimekizumab

Study	Phase	Indication	Expected status at filing [a]
AS0013	2a	AS	Ongoing
AS0008	2b	AS	Complete
AS0009	2b	AS	Ongoing OLE
AS0010	3	nr-axSpA	Ongoing
AS0011	3	AS	Ongoing
HS0001	2	HS	Complete
HS0003	3	HS	Ongoing [b]
HS0004	3	HS	Ongoing [b]
PA0007	1b	PsA	Complete
PA0008	2b	PsA	Complete
PA0009	2b	PsA	Ongoing OLE
PA0010	3	PsA	Ongoing
PA0011	3	PsA	Ongoing
PA0012	3	PsA	Ongoing OLE
RA0123	2a	RA	Complete
UC0011	2a	UC	Complete

AS=ankylosing spondylitis; HS=hidradenitis suppurativa; nr-axSpA=nonradiographic axial spondyloarthritis; OLE=open-label extension; PsA=psoriatic arthritis; PSO=psoriasis; RA=rheumatoid arthritis; UC=ulcerative colitis
[a] This is based on the expected status at the initial filing of PSO and is subject to change. Completed studies will be included in the submission.
[b] Anticipated to initiate in Q1 of 2020.

Does the Agency agree that the proposed safety data from other indications is sufficient to support filing and review of the BLA?

FDA Response to Question 9:
As an exploratory analysis, you may investigate rare AEs by conducting a pooled analysis of data from other indications; however, interpretation of findings may be limited based on your proposed pooled analysis as different patient populations may be susceptible to different adverse events to result in a different safety profile. Furthermore, we do not have information concerning the doses used in the studies of other indications (psoriatic arthritis [PsA], ankylosing spondylitis [AS], non-radiographic axial spondyloarthritis [nr-axSpA], and hidradenitis suppurativa [HS]). We recommend that safety information from different indications also be presented separately.

Meeting Discussion.
Based on the Agency's comments provided the sponsor proposed to remove the pooled safety data analysis across indications. The Agency advised to conduct this safety analysis as originally proposed.

Question 10:
Regarding data and information to facilitate the Agency's planning of Bioresearch Monitoring (BIMO) inspections, UCB proposes to provide the following, per the 2018 guidance, from the Phase 3 pivotal studies (ie, PS0008, PS0009, PS0013) in the BLA:

- Clinical Study-Level Information
- Study participant-Level Data Line Listings by Clinical Site
- For the by-study participant, by-clinical site listings of tests performed for safety monitoring, data for the following domains will be provided: laboratory, electrocardiogram, and vital signs
- Summary-Level Clinical Site Datasets

Does the Agency agree that the proposed BIMO data sets (ie, from PS0008, PS0009, and PS0013) are sufficient for filing and review of the BLA?

FDA Response to Question 10:
Your proposal appears reasonable.

Question 11:
UCB will submit a 120-DSU as a refresh of the Summary of Clinical Safety that summarizes safety results from updated data in ISAP A2 Pool S2 (long-term safety data) as described in Section 13.3.2. These updates will include additional SFU data from studies PS0008, PS0009, and PS0013, as well as additional data from the ongoing OLE study PS0014. For PS0014, this update will include safety data collected between the initial clinical data cut-off for the BLA (early November, see Section 13.6.3) and the cut-off for the 120-DSU.

Based on the current target for BLA submission in late Q2 2020, UCB proposes a clinical data cut-off for the 120-DSU of approximately 1 month before BLA submission. This provides approximately 6 months of additional safety data.

UCB proposes to provide the following in the 120-DSU:

- Study drug exposure
- Study participant disposition
- AEs, SAEs, PTAEs, deaths, AEs that have been identified for special monitoring, markedly abnormal laboratory values, and ADAb
- Clinical safety narratives for study participants with SAEs, PTAEs, safety topics of interest, and death

Does the Agency agree with the proposed content and data cut-off date (ie, approximately one month before BLA submission) for the 120-DSU?

FDA Response to Question 11:
Your proposal appears reasonable. In your 120-day safety update, include narratives for pregnancies as well.

Question 12:
Based on Agency feedback, UCB updated the secondary and "other" efficacy variables for the Patient Symptom Diary (PSD) items of pain, itch, and scaling from "change from Baseline" to "response." These changes are also reflected in the statistical hierarchical testing procedure in PS0009 and PS0013. These symptom response variables are based on clinically meaningful thresholds of treatment response (defined based on anchor-based methods) and are provided in the Phase 3 study SAPs for PS0009 (SAP Section 8.2.1.4) and PS0013 (SAP Section 8.2.1.4).

There was no change to the frequency of diary assessments or how the diary assessments were performed. The analyses are planned in the subset of study participants who have a Baseline score in the items above the responder threshold and are detailed in Section 13.5.

Does the Agency agree with the upgraded PSD symptom response endpoints and thresholds for defining response?

FDA Response to Question 12:
You propose thresholds for the PSD response score of itch, pain, and scaling are 2.39, 1.98, and 2.86, respectively. At this time, we cannot fully comment on the proposed thresholds in the absence of supportive evidence. Submit evidence to support these thresholds for review and comment.

Additional Comments:

- At the time of BLA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). Include the full text version of any referenced articles.

- Provide an analysis of ECG data (Trials PS0008, PS0009, and PS0013) and submit electronic links to the following information:

    - Copies of the study report(s) for any clinical assessments of the effect of product administration on the QT interval that have been performed
    - Electronic copy of the study report
    - Electronic copy of the clinical protocol
    - Electronic copy of the Investigator's Brochure
    - Annotated CRF
    - A data definition file which describes the contents of the electronic data sets
    - Electronic data sets as SAS.xpt transport files (in CDISC SDTM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses
    - Please make sure that the ECG raw data set includes at least the following: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, please also include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)
    - Dataset whose QT/QTc values are the average of the above replicates at each nominal time point
    - Narrative summaries and case report forms for any
        - Deaths
        - Serious adverse events
        - Episodes of ventricular tachycardia or fibrillation
        - Episodes of syncope
        - Episodes of seizure
        - Adverse events resulting in the subject discontinuing from the study
    - ECG waveforms to the ECG warehouse (www.ecgwarehouse.com)
    - A completed Highlights of Clinical Pharmacology Table

- In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan, all protocol amendments (with dates), generated

treatment assignment lists, and the actual treatment allocations (along with the date of enrollment).

Meeting Discussion:
The sponsor acknowledged that they do not have narratives for four subjects who experienced syncope which were adjudicated as vasovagal syncope. The Agency indicated that the sponsor could provide adjudication packets in lieu of narratives.

The sponsor also proposed not to include the exposure-response analyses for ECG data. The Agency agreed.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

PREA REQUIREMENTS

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of

[2] 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.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address

(1)				
(2)				

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[6]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar

[6] https://www.fda.gov/media/85061/download

biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ATTACHMENTS AND HANDOUTS

The sponsor's response to the Meeting Preliminary Comments is attached.

7 Pages have been Withheld in Full as B4(CCI/TS) Immediately Following this Page

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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/

KENDALL A MARCUS
12/12/2019 04:51:59 PM