CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761262Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 118701

MEETING MINUTES

AbbVie Inc.
Attention: Tony Freeney, MBA, BSC, PMP
Sr. Manager, Regulatory Affairs
Global Regulatory Strategy, US & Canada
1 N. Waukegan Road
Dept. PA72, Bldg. AP30-4
North Chicago, IL 60064

Dear Mr. Freeney:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for risankizumab.

We also refer to the teleconference between representatives of your firm and the FDA on May 10, 2021. The purpose of the meeting was to discuss the proposed content and format of the planned non-NME original BLA for the IV induction dosing regimen and a sBLA to risankizumab BLA 761105 for the SC maintenance dosing regimen for the treatment of moderately to severely active Crohn's disease (CD) in patients aged 16 years and older.

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 me at (301) 796-9007 or email me at jay.fajiculay@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Jay R. Fajiculay, Pharm.D.
Regulatory Health Project Manager
Gastroenterology
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	May 10, 2021, 2:00 p.m. – 3:00 p.m. ET
Meeting Location:	Teleconference
Application Number:	IND 118701
Product Name:	Risankizumab
Indication:	Crohn's Disease
Sponsor Name:	Abbvie
Regulatory Pathway:	351(a) of the Public Health Service Act
Meeting Chair:	Tara Altepeter, MD
Meeting Recorder:	Jay Fajiculay, PharmD

FDA ATTENDEES

Division of Gastroenterology, Office of Immunology and Inflammation
Jessica J. Lee, MD, MMSc, Director
Juli Tomaino, MD, MS, Deputy Director
Tara Altepeter, MD, Associate Director for Therapeutic Review
Marjorie Dannis, MD, Medical Officer

Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Kelly Richards, RN, MSN, RAC, Senior Regulatory Health Project Manager
Jay Fajiculay, PharmD, Regulatory Health Project Manager

Division of Pharmacology and Toxicology for Immunology and Inflammation
Sushanta Chakder, RPh, PhD, Supervisory Pharmacologist
Dinesh Gautam, PhD, Pharmacologist

Division of Inflammation and Immune Pharmacology
Office of Clinical Pharmacology, Office of Translational Science
Insook Kim, PhD, Clinical Pharmacology Team Leader
Liping Pan, PhD, Clinical Pharmacology Reviewer

Division of Biostatistics III, Office of Biostatistics
David Petullo, MS, Statistical Team Leader
Ling Lan, PhD, Statistical Reviewer

Division of Biotechnology Review and Research I
Office of Biotechnology Products, Office of Pharmaceutical Quality
Riley Myers, PhD, Team Leader
Milos Dokmanovic, PhD, RAC, CMC Reviewer

Division of Biotechnology Manufacturing, Office of Pharmaceutical Manufacturing Assessment, Office of Pharmaceutical Quality
Thuy Thanh Nguyen, DHSc, MPH, BSN, CAPT, USPHS
Zhong Li, Ph.D. Senior Pharmaceutical Quality Assessor

Division of Medication Error Prevention and Analysis, Office of Surveillance and Epidemiology
Idalia Rychlik, PharmD, Team Leader
Sherly Abraham, RPh, Safety Evaluator
Alvis Dunson, MScIH, Health Scientist-Safety Regulatory Project Management Staff

Division of Risk Management, Office of Surveillance and Epidemiology
Laura Zendel, PharmD, Team Leader
Mona Patel, PharmD, RAC, Risk Management Analyst

Office of Medication Error Prevention and Risk Management, OSE
Lubna Merchant, M.S., PharmD, Deputy Director

Office of Combination Products, Office of Clinical Policy and Programs
Office of the Commissioner
Patricia Love, MD, Deputy Director

Office of Therapeutic Biologics and Biosimilars, Office of New Drugs
Leila Hann, Science Policy Analyst

Office of Scientific Investigations, Office of Compliance
Min Lu, MD, MPH, Team Leader
Zana H. Marks, MD, MPH, Medical Officer

Division of Biomedical Informatics, Research, and Biomarker Development
Office of Drug Evaluation Sciences
Y. Veronica Pei, MD, MEd, MPH, Associate Director for Biomedical Informatics (Acting)

Office of Product Evaluation and Quality, Office of Gastrorenal, ObGyn, General Hospital, and Urology Devices, Center for Devices and Radiological Health
Rumi Young, MS

SPONSOR ATTENDEES

Doina Cosma-Roman, MD, Executive Medical Director, Immunology, Pharmaceutical Development
Rachel Duan, MD, PhD, Medical Director, Pharmacovigilance and Patient Safety, Pharmaceutical Development
Tony Freeney, MBA, BSc, Senior Manager, Global Regulatory Strategy, Regulatory Affairs
Yihua Gu, MS, Senior Director, Statistics, Pharmaceutical Development
Martin King, PhD, Senior Director, Global Regulatory Strategy, Regulatory Affairs
Jamie Legg, Asset Strategy Leader, Immunology, Pharmaceutical Development
Aditya Lele, MS, Director, Statistical Programming
Xiaomei Liao, PhD, Senior Manager, Statistics, Pharmaceutical Development
Yinuo Pang, PhD, Director, Clinical Pharmacology and Pharmacometrics, Pharmaceutical Development
Anne Robinson, PharmD, Vice President, Global Regulatory Strategy, Regulatory Affairs
Lei Shu, PhD, Director, Statistics, Pharmaceutical Development
Kori Wallace, MD, PhD, Senior Medical Director, Immunology, Pharmaceutical Development
Troy ZumBrunnen, PharmD, Senior Director, Global Regulatory Strategy, Regulatory Affairs

1.0 BACKGROUND

Skyrizi (risankizumab) is a humanized monoclonal antibody that is directed against the p19 subunit of IL-23. BLA 761105 was approved on April 23, 2019 for the treatment of moderate-to-severe plaque psoriasis in adults who are candidates for systemic therapy of phototherapy. Risankizumab is currently being investigated under (b) (4) (b) (4) IND 118701 for the treatment of Crohn's disease (CD).

The Sponsor submitted the initial IND for the CD indication on September 27, 2013, and a type B end-of-phase 2 meeting was held on January 31, 2017. On February 22, 2021, the Sponsor submitted a type B pre-biologics license application (BLA) meeting request to discuss the proposed content and format of their planned separate original BLA for the IV induction dosing regimen and a supplemental BLA (sBLA) to risankizumab BLA 761105 for the SC maintenance dosing regimen for the treatment of moderately to severely active CD in patients aged 16 years and older.

FDA sent Preliminary Comments to Abbvie on May 4, 2021.

2.0 DISCUSSION

*Note: Questions 8-15 were answered in a separate meeting via written responses only issued on May 4, 2021.

FDA Introductory Comments:

We note that you requested this Pre-BLA meeting prior to completion of the phase 3 maintenance trial (M16-000 Sub-study 1), and that per the meeting background package, you have not finalized selection of the to-be-marketed dose(s). We have provided responses to your submitted questions where possible; however, some responses are preliminary because you have not provided adequate detail on the doses that you will propose for marketing.

We acknowledge that you propose to submit the data to support a proposed indication of "Treatment of moderately to severely active CD in patients aged 16 years and older" in two separate submissions, submitted at the same time: a separate BLA for the IV induction dosing regimen, and a supplemental BLA (sBLA) to existing BLA 761105 for the SC maintenance dosing regimen to be administered via on-body delivery system (OBDS). We remind you, as previously communicated in the Type C Guidance meeting held on October 20, 2020 (minutes dated November 12, 2020), as well as in the advice letter dated December 23, 2020, that we do not agree with this approach and recommend the IV formulation be submitted in a supplement rather than in a separate BLA.

As communicated previously, in general, the Division considers "treatment of Crohn's disease" to be a single indication, as the management of this chronic disease requires both induction and maintenance treatment regimens. Moreover, the evaluation of both efficacy and safety of the product for the proposed indication will focus on the 52-week treatment regimen as evaluated in the phase 3 program. Therefore, we recommend that all the data on both formulations needed to support the proposed treatment regimen (IV induction, followed by SC maintenance dosing, intended for chronic administration) are submitted in a single application. Accordingly, for these reasons and the reasons communicated previously, we continue to recommend that you submit both formulations in a supplemental BLA. However, if you choose to not follow this recommendation and the principles outlined in the guidance for industry, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* and submit a separate BLA, we recommend that you consider an alternate approach, submitting all of the necessary data and information for the proposed CD indication (*i.e.*, both formulations) to that separate BLA.

As acknowledged previously, submission of a separate BLA for the proposed new IV formulation will not affect the filing of the application if it is otherwise suitable for filing, or its review, if it is otherwise ready for review. However, we remind you that in order to support an indication for the treatment of moderately

to severely active CD, your program must demonstrate a clinical benefit in both induction and maintenance periods. Our evaluation will focus on the efficacy and safety of the to-be-marketed dosing regimen (selected IV induction dose followed by selected SC maintenance dose). Because CD is a chronic disease requiring long-term treatment, a short-term only indication is not appropriate. In the event that a review issue is identified that results in a determination that the benefit-risk profile of either the IV induction regimen, or the SC maintenance regimen is not favorable, it could impact the approvability of both applications. We reiterate that we strongly recommend all the necessary data and information on both formulations intended for use in CD patients are included in a single submission.

Meeting Discussion: ***Refer to the Sponsor's response document dated May 7, 2021.***

FDA reminded the Sponsor of the recommendation to submit the IV formulation in a supplement rather than in a separate original BLA, and restated that if the Sponsor chooses not to follow this recommendation and the principles outlined in the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees and submit a separate original BLA, that the Sponsor can submit all of the necessary data and information for the proposed CD indication (i.e., both formulations) to that separate original BLA. The FDA reiterated their position that a single submission is preferable, and strongly encouraged the Sponsor to consider this approach. The Sponsor thanked the Agency for the alternate proposal to submit all the data as a single original BLA, and stated that they are considering this as a possibility.

The Sponsor asked for clarification that if they chose this approach to submit all the data as a single original BLA, if FDA would collapse or convert the single new BLA into the existing BLA during the review period. FDA reiterated their response (similar to clarification to Question 6) that at the present time, FDA does not intend to collapse or combine a new BLA into the existing application during the review period.

FDA reminded the Sponsor that clinical benefit must be demonstrated in both induction and maintenance periods to support approval of a new product intended for the treatment of Crohn's disease. The Sponsor expressed their understanding and stated that they do not intend to pursue a split indication for either induction or maintenance alone. The Sponsor also expanded on their rationale for their proposed submission strategy (using two separate applications) citing CMS reimbursement issues and pricing as one consideration.

Question 1: *Does Agency agree with the proposal to delay submission of data from Study M19-974 (therapeutic protein drug interaction study)?*

FDA Response to Question 1:
It is premature to agree because you have not specified the timeline for the submission of the results of Study M19-974, though you stated that the study will not be completed in time for the 90-day safety update. Clarify if you plan to submit Study M19-974 by 120 days post initial submission as previously agreed. If the study results are submitted later than Day 120, the study results may not be reviewed during the BLA review cycle to inform labeling.

We do not agree that the drug interaction information included in labeling for the plaque psoriasis indication would be directly applicable for the proposed CD indication because of the differences in two populations, such as inflammation burden and the proposed higher doses for CD than the approved dose for plaque psoriasis.

Without adequate justification, the labeling should include language indicating potential for CYP/ transporter-mediated drug interaction. Refer to Draft Guidance for Industry Drug-Drug Interaction Assessment for Therapeutic Proteins Guidance for Industry https://www.fda.gov/media/140909/download

***Meeting Discussion:* Refer to the Sponsor's response document dated May 7, 2021. The Sponsor clarified that the study results will not be available during the review cycle, and that the Clinical Study Report for M19-974 is planned to be submitted (b) (4). No additional discussion occurred.**

Question 2: *Does the Agency agree that the safety and efficacy data described in the briefing package are adequate to support the review of risankizumab for the treatment of moderately to severely active Crohn's disease in patients aged 16 years and older?*

FDA Response to Question 2:
As you have not provided the efficacy data for the maintenance period, nor the final selection of the doses to be marketed, it is premature to agree.

Regarding safety, refer also to response to Question 3.

***Meeting Discussion:* Refer to the Sponsor's response document dated May 7, 2021. No additional discussion occurred.**

Question 3: *Does the Agency agree that the proposed number of subjects exposed to risankizumab and the duration of exposure is adequate to support the submission and review of risankizumab for the proposed indication in the treatment of moderately to severely active Crohn's disease in patients aged 16 years and older?*

FDA Response to Question 3:
The number of patients exposed to either 600 mg (n=662) or 1200 mg (n=740) for 12 weeks (proposed induction treatment duration) appears reasonable. However, since you have not yet identified the to-be-marketed induction or maintenance doses, it is premature to comment on whether the proposed number of patients exposed to risankizumab and the duration of exposure will be acceptable for submission/ review. We note that you estimate 366 patients will have been exposed to the 180mg maintenance dose, and 171 patients will have been exposure to the 360mg maintenance dose (both for 52 weeks). If known, please clarify the number of patients who received each maintenance dose (180mg vs 360mg) by induction dose level.

We remind you that our assessment of the safety of the product, and adequacy of the size of the safety database, will focus primarily on the number of patients who received the to-be-marketed dosing regimen (selected IV induction dose for 12 weeks, followed by selected SC maintenance dose through 52 weeks). Further, the necessary size of the safety database may be impacted by the types and frequency of adverse events identified in the study population.

Additionally, only 12 patients who are 16-17 years of age were enrolled. It is also unclear how many of these patients received the to-be-marketed dosing regimen. Thus, it is premature to agree that this small number of patients will be adequate to support inclusion of older adolescents in the initial approval (though we encourage you to submit the data for our consideration).

Meeting Discussion: Refer to the Sponsor's response document dated May 7, 2021. No additional discussion occurred.

Question 4: *Does the Agency agree with the proposed plan and cutoff date for the 90-day Safety Update?*

FDA Response to Question 4:
You have proposed a database lock for M16-000 Sub-study 1 (maintenance study) of May 10, 2021, and a database lock for the 90-day safety update of September 1, 2021. We agree that the proposed plan is reasonable.

In addition to what you have outlined (updated tables from the ISS long-term analysis set including AE tables and safety laboratory data), you should submit updated ISS datasets with your 90-day safety update.

Meeting Discussion: Refer to the Sponsor's response document dated May 7, 2021. No additional discussion occurred.

Question 5: *Does the Agency agree with the proposed plan to incorporate placebo data into the ISS integrated datasets and analyses?*

FDA Response to Question 5:
The proposed plan to incorporate placebo data into the ISS integrated datasets and analyses appears reasonable.

Meeting Discussion: ***Refer to the Sponsor's response document dated May 7, 2021. No additional discussion occurred.***

Question 6: *AbbVie intends to submit 2 concurrent applications, a separate BLA for the IV induction dosing regimen and an sBLA for the SC maintenance dosing regimen for the treatment of moderately to severely active Crohn's disease in patients aged 16 years and older. AbbVie understands that submitting a separate application for the IV presentation will not affect the filing of the application if it is otherwise suitable for filing, or its review, if it is otherwise ready for review, as described in the December 23, 2020 letter from Dr. Beitz. If the separate BLA for the IV presentation is approved, our understanding is that it will be maintained as a separate BLA; i.e., that the BLA for the IV presentation will not be converted to a sBLA or otherwise merged into BLA 761105. Is AbbVie's understanding in this regard correct?*

FDA Response to Question 6:
Refer to the Introductory Comments above regarding your proposed plan for submission of 2 concurrent applications.

Based on our current understanding, if a separate BLA is approved, it will be maintained as a separate BLA.

Meeting Discussion: ***Refer to the Sponsor's response document dated May 7, 2021. The Sponsor acknowledged the Agency strongly recommending a single submission rather than a separate original BLA for the IV formulation and an sBLA to the existing BLA for the SC formulation, but plans to submit two separate applications to avoid the unintended consequences of increased patient out-of-pocket costs and CMS drug spending. The Sponsor sought clarification that if two applications are submitted, the Agency will not seek to collapse or merge them into a single application during the review period. FDA agreed.***

> ***Question 6a:*** *Does the Agency agree that the planned content of the BLA and sBLA, as displayed in the tables of contents provided in the briefing package, is adequate to be considered as complete for each application?*
>
> ***FDA Response to Question 6a:***
> **Refer to the Introductory Comments above regarding your proposed plan for submission of 2 concurrent applications. We strongly recommend all the necessary data and information on both formulations intended for use in CD patients are included in a single submission.**

Although this is not the recommended approach, if you ultimately choose to submit your package as two separate applications as described in your meeting package, the planned content for the two applications as outlined in the draft table of contents in the meeting background package appears acceptable for filing the applications. The adequacy of the data will be a review issue. During the review cycle, we request that any response to information request is submitted to both applications, for ease of review.

***Meeting Discussion:* Refer to the Sponsor's response document dated May 7, 2021. AbbVie acknowledged and agrees to submit responses to information requests during the review cycle to both applications.**

Question 6b: *Does the agency have any advice about the proposed structure of the dossiers that would facilitate the review of the applications?*

FDA Response to Question 6b:
Refer to the Introductory Comments above regarding your proposed plan for submission of 2 concurrent applications.

The proposed structure of the BLA and sBLA dossiers appears acceptable.

***Meeting Discussion:* Refer to the Sponsor's response document dated May 7, 2021. AbbVie acknowledged FDA's response that the proposed structure of the separate original BLA and sBLA dossiers appears reasonable.**

Question 6c: *Does the Agency agree that the currently approved nonproprietary name of risankizumab-rzaa approved under BLA 761105 is appropriate for the IV presentation, and a new suffix is not necessary for the IV presentation?*

FDA Response to Question 6c:
Refer to the Introductory Comments above regarding your proposed plan for submission of 2 concurrent applications.

The FDA-designated suffix described in our guidance, Nonproprietary Naming of Biological Products, is applicable to originator biological products, related biological products, and biosimilar or interchangeable products newly licensed under section 351(a) or 351(k) of the PHS Act, as applicable. Thus, any new BLA submission is within the scope of the guidance and the need to designate a unique suffix for each new BLA would be a matter of review evaluated at the time of the BLA submission.

We continue to recommend that you submit the data as a single supplemental BLA to the existing BLA 761105. However, if you intend to submit a separate BLA, and you consider that the use of a unique suffix for each BLA is not applicable to your product, you may provide your

justification with your BLA submissions and we will evaluate your justification.

Meeting Discussion: ***Refer to the Sponsor's response document dated May 7, 2021.***

The Sponsor asked FDA why a 4-letter suffix would be required for the IV presentation. FDA clarified that the naming convention outlined in the guidance applies to all 351(a) and 351(k) biologic products submitted under the PHS act. If the Sponsor believes a new suffix is not required for their proposed BLA, they can provide a justification for FDA's consideration. FDA will review the justification and make the determination on the proper name during the BLA review. FDA cannot make this determination prior to filing. FDA will communicate the decision regarding the suffix determination as early in the review cycle as feasible, but could not provide a definitive timeline for making this determination.

The Sponsor asked about potential trade name implications and whether or not it would be possible to keep the same trade name, Skyrizi, even if a unique suffix is designated. FDA clarified that the appropriateness of the trade name is also made during the BLA review and that they could not opine on the trade name consideration at this time, but committed to communicating with the Sponsor regarding naming issues as early in the review cycle as possible, should the need arise.

The Sponsor asked if a late determination of a need for unique suffix could result in a review clock extension or delay in action and how likely this would be. FDA responded that a review clock extension may occur if review issues are complex, and/or if additional substantial data are required and submitted during the review cycle, and more time is needed to inform the final decision; accordingly, FDA was unable to quantify the potential risk of a review clock extension relating to naming / suffix considerations, but committed to providing feedback on the naming and suffix as early as possible in the review cycle, and working with the Sponsor to address any concerns in a timely fashion.

Question 6d: *Does the agency agree that a single United States Prescribing Information (USPI) is sufficient to adequately label all Skyrizi presentations and indications?*

FDA Response to Question 6d:
Refer to the Introductory Comments above regarding your proposed plan for submission of 2 concurrent applications.

Your proposal to utilize a single USPI appears generally reasonable; however, the final determination as to whether a single United States

Prescribing Information (USPI) is sufficient to adequately label all Skyrizi presentations and indications will be made during the review cycle(s).

Meeting Discussion: ***Refer to the Sponsor's response document dated May 7, 2021. The Sponsor acknowledged the Agency's response that proposing a single USPI for all Skyrizi presentations and indications is generally reasonable.***

FDA reminded the Sponsor that if this application is ultimately filed under two separate BLAs, as the Sponsor is proposing, it will be the Sponsor's responsibility to submit any proposed PAS labeling supplement to both BLAs to ensure they stay aligned post-approval, if the product is approved.

Question 7: *Does the FDA agree that the data included in the proposal are sufficient for the Agency's purposes of site inspection selection?*

FDA Response to Question 7:
We agree with the proposed list of BIMO data/documents. In addition to what you outlined, please include a listing of subject protocol deviations and listing for relevant laboratory assessments to support safety and efficacy of the application as part of the PDF files for each clinical site.

For the BIMO submission, include the proposed data and documents for all trials used to support safety and efficacy claims in the application.

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 and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/media/85056/download

https://www.fda.gov/media/85061/download

Meeting Discussion: ***Refer to the Sponsor's response document dated May 7, 2021.***

FDA agreed with the Sponsor's proposal to include BIMO data for the controlled phase 3 studies.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

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[1] and Pregnancy and Lactation Labeling Final Rule[2] 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.

[1] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[2] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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 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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: NDA, ANDA, BLA, Master File (except Type III) and Commercial INDs must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[3]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification Specification for Transmitting Electronic Submissions using eCTD Specifications. For additional information, see FDA.gov.[4]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used

[3] http://www.fda.gov/ectd
[4] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[5] and the guidance for industry, Identification of Manufacturing Establishments in

[5] https://www.fda.gov/media/84223/download

Applications Submitted to CBER and CDER Questions and Answers[6]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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, and the associated conformance guide, 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.[7]

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.

---

[6] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

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

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 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.

ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's slide presentation of responses to FDA Preliminary Comments is attached.

12 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

JAY R FAJICULAY
05/20/2021 12:15:14 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118701

MEETING MINUTES

AbbVie
Attention: Richard Perner
Associate Director, Regulatory Affairs
Department PA72, Building AP30-4
1 North Waukegan Road
North Chicago, IL 60064

Dear Richard Perner:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for risankizumab.

We also refer to the teleconference between representatives of your firm and the FDA on January 31, 2017. The purpose of the meeting was to discuss key elements of the risankizumab Phase 3 clinical development plan to support the proposed indication.

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

If you have any questions, call me at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Lawrence Allan
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	End of phase 2
Meeting Date and Time:	January 31, 2016 from 1:00 – 3:00
Meeting Location:	Teleconference
Application Number:	IND 118701
Product Name:	Risankizumab
Indication:	Crohn's disease
Sponsor/Applicant Name:	AbbVie
Meeting Chair:	Anil Rajpal
Meeting Recorder:	Lawrence Allan

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products (DGIEP)
Donna Griebel, MD. Division Director
Anil Rajpal, MD. Medical Team Leader
Aisha Peterson-Johnson, MD, MPH, MBA. Medical Officer
Sushanta Chakder. PhD, Supervisory Pharmacologist, Pharmacology Team Leader
Dinesh Gautam. PhD, Pharmacology Reviewer
Lawrence Allan. Regulatory Project Manager

Office of Clinical Pharmacology (OCP)
Yow-Ming Wang, PhD. Clinical Pharmacology Team Leader
Anand Balakrishnan, PhD. Clinical Pharmacology Reviewer

Office of Biostatistics (OB)
Yeh-Fong Chen, PhD. Statistical Team Leader
Feiran Jiao, PhD. Statistical Reviewer

Division of Pediatric and Maternal Health (DPMH)
Mona Khurana, MD. Medical Team Leader
Jacqueline Spaulding, MD. Medical Reviewer
Jacquline Yancy, PhD, Regulatory Project Manager

Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Banu Karimi-Shah, MD. Medical Team Leader
Kathleen Donohue, MD. Medical Reviewer

Office of Surveillance and Epidemiology
Mishale Mistry, PharmD, MPH. DEMPA Reviewer
Eileen Wu, PharmD. Pharmacovigilance Team Leader
Kimberly Swank, PharmD. Pharmacovigilance Reviewer
Sukhminder Sandhu, PhD, MPH, MS. Epidemiology Team Leader
Joel Weissfeld, MD, MPH. Epidemiology Reviewer

Clinical Outcome Assessments (COA) Staff
Elektra Papadopoulos, MD, MPH. COA Associate Director
Sarrit Kovacs, PhD. COA Reviewer

Office of Executive Programs
Cherryn Chang, PharmD. CDER Product Jurisdiction Officer
Kristina Lauritsen, PhD. CDER Product Jurisdiction Officer

Center for Devices and Radiological Health (CDRH)
CDR Alan Stevens. CDRH Team Leader
Sapana Patel, PharmD. CDRH Reviewer

SPONSOR ATTENDEES

AbbVie Attendees
Simon Cooper, MD. Group Project Leader, Immunology, Pharmaceutical Development
Sangeeta Gupte, PhD. Director, Global Regulatory Strategy, Regulatory Affairs
Bidan Huang, PhD. Director, Statistics, Pharmaceutical Development
Maureen Kelly, MD. Group Medical Director, Immunology, Pharmaceutical Development
Anette Koenigsdorfer, PhD. Scientific Director, Drug Product Development, Pharmaceutical Development
John Liu, MD. Senior Medical Director, Pharmacovigilance and Patient Safety
Ahmed Othman, PhD, FCP. Director, Clinical Pharmacology and Pharmacometrics, Pharmaceutical Development
Richard J. Perner, MS. Associate Director, Global Regulatory Strategy, Regulatory Affairs
Ann Marie Rahman, MS. Associate Director, Regulatory Affairs Chemistry, Manufacturing and Control (CMC)
Anne Robinson, PharmD. Group Scientific Director, Immunology, Pharmaceutical Development
Ranjeeta Sinvhal, MD. Senior Medical Director, Pharmacovigilance and Patient Safety
Kori Wallace, MD, PhD. Medical Director, Immunology, Pharmaceutical Development
Katherine Wortley, PhD, RAC. Director, Regulatory Affairs CMC, Combination Products and Medical Devices
Troy ZumBrunnen, PharmD. Senior Director, Global Regulatory Strategy, Regulatory Affairs

Boehringer Ingelheim
Wulf Boecher, MD. Associate Therapeutic Area Head, Immunology
Robert Kumi, PhD, RAC. Sr. Associate Director, Regulatory Affairs

BACKGROUND

On 12 Oct 2016, Boehringer Ingelheim (BI) submitted a type B (EoP2) meeting request under this IND. On 17 Oct 2016, BI transferred the IND to AbbVie, who is now the IND sponsor. Risankizumab is a humanized monoclonal immunoglobulin G1 (IgG1) antibody that is directed against IL-23 p19. It is currently developed in the indications psoriasis (IND 113306; intended indication for the initial BLA), psoriatic arthritis (IND 118702), (b) (4) and Crohn's disease (IND 118701).

The sponsor is seeking to obtain feedback and agreement on key elements of their Phase 3 clinical development plan to support the proposed indication for the treatment of Crohn's disease in patients 16 years and older. Due to the number of questions submitted, the sponsor submitted an additional meeting request to allow sufficient time to address their issues. Subsequently, this meeting will be spread out over two one-hour consecutive teleconferences. The FDA granted the meeting requests on October 21, 2016, and Nov 4, 2016, respectively. FDA sent Preliminary Comments to AbbVie on January 31, 2017.

DISCUSSION

FDA INTRODUCTORY COMMENTS:

A. Please clarify whether or not patients with prior exposure to anti-integrin therapy will be allowed to enroll in your phase 3 studies.

The sponsor stated they will include vedolizumab exposed patients in Study M16-006. The patients with a prior history of vedolizumab exposure will not be included in Study M15-991, which will include a vedolizumab comparator arm.

B. Please clarify your intentions in product labeling for including the results of the vedolizumab treatment arm in Study M15-991. The study protocol lists "proportion of subjects with clinical remission at Week 6 (risankizumab vs vedolizumab)" as the 6th ranked secondary endpoint. Do you also plan to compare the risankizumab patients with the vedolizumab patients at 12 weeks as part of the primary endpoint assessment?

The sponsor is not proposing a superiority claim in the label; (b) (4) (b) (4).

POST MEETING COMMENT: We do not agree with including results of your proposed active control study (risankizumab vs. vedolizumab) that imply comparative effectiveness or safety claims not supported by substantial evidence; see 21 CFR 201.57(c) (2) (iii).

C. For your planned maintenance study (M16-000), while it is acceptable to re-randomize responders, the primary analysis set should be those patients in remission at the beginning of the study.

Discussion: The sponsor stated that there will be an analysis of remitters on entry as a ranked secondary endpoint. The sponsor clarified that the entire population will be a refractory population and 2/3 of Study M16-006 will be refractory. FDA finds this reasonable; however, the labeled indication will reflect the primary and other endpoints that were met.

D. While the SC route of administration generally is thought to be more sensitizing and immunogenic than an IV route of administration, we do not believe this is an inherent barrier to evaluating the SC formulation for self-administration. We have the following recommendations:

No further comments.

(i) It appears that only n=30 patients will receive the to-be-marketed formulation of risankizumab. This is a significant limitation of the proposed program. Since the concentration and route of administration may impact immunogenicity and the risk of hypersensitivity and injection site reactions, we recommend that the administration of SC risankizumab in the confirmatory studies reflect the mode of administration anticipated in the product label. For example, if you intend for all patients to receive the first few doses of risankizumab as an IV infusion in a monitored, health-care setting, followed by long-term SC self-administration at home, then this should be assessed in a robust fashion in the phase 3 trials.

Discussion: Sponsor agreed to provide further information in future submission.

(ii) Injection site reactions are likely to be more frequent in patients receiving the 150 mg/ml concentration. You should include an analysis of the rate of injection site reactions in that population, without diluting the estimate by including patients who received a lower concentration formulation.

(iii) The investigators brochure makes no mention of premedication. We recommend that the protocols specify permitted concomitant medications and collect information on any medications used specifically for premedication purposes. In general, we discourage the routine use of premedication in the program (unless the data indicate that this must be done to assure safety), as premedication may mask early signs or symptoms of a hypersensitivity reaction that would otherwise prompt a patient to seek medical treatment after self-administration.

(iv) We recommend that you provide formal education for patients on the signs and symptoms of hypersensitivity reactions and how to respond to them.

(v) Subjects and/or their caregiver should be trained by their healthcare provider on the self-injection technique. The protocol specifies that subjects will receive their first SC dose during a clinic visit. Subjects or their caregivers should self-inject the first dose of risankizumab SC under the supervision of the health care provider.

(vi) For the at-home injections, subjects and/or caregivers should be advised to observe and report any injection-related adverse events.

(vii) For self-administration outside of an office visit, subjects should be instructed to report adverse events to the investigator at the time of occurrence, and to seek immediate medical care if hypersensitivity develops.

(viii) Subjects who experience a hypersensitivity reaction or severe or serious injection-related reaction (e.g., shortness of breath, wheezing, stridor, angioedema, life-threatening change in vital signs) should be withdrawn from the study.

(ix) The protocol should prospectively define the namifestations of anaphylaxis and should specify that anaphylaxis to SC home administration is considered an adverse event of special interest, with appropriate monitoring and reporting, similar to what is planned for the IV doses. The protocol should specify a dedicated supplemental eCRF based on the NIAID/FAAN diagnostic criteria for anaphylaxis[1] and consider independent adjudication for hypersensitivity events observed in the program for home administration of SC doses.

E. You state that the to-be-marketed formulation will have a concentration (amount per unit volume) of 150 mg/mL. The final volume will be a result of the selected commercial dose. The drug will be delivered in a suitable delivery device. No additional information has been provided regarding the device constituent and there arehas no specific device questions in this briefing packet. Based upon the information provided, it appears you may be using a pre-filled syringe for the device constituent of your combination product. For your future marketing submission of your device, please be sure to address the following characteristics of the pre-filled syringe:

(i) Provide a description of the complete system

(ii) Product labeling and instructions for use of the prefilled syringe.

(iii) A complete description of design control inputs, in the form of device requirements and specifications, which fully describe the attributes of the system and their acceptability in the context of the intended use of the system and the medication being delivered.

(iv) Design output information in the form of test reports and other activities which verify the individual requirements and specifications for the system and validate the system is fit for its intended use within the context of the medication being delivered.

(v) Risk analysis information which characterizes and evaluates the risks to the user or patient both during normal use, reasonable foreseeable mis-use, and potential system failure states. Such an analysis should clearly describe system hazards, mitigations implemented to reduce the risk of those hazards, effectiveness of the mitigation, as well as conclusions of the acceptability of system risks within the final finished system.

(vi) Biocompatibility of the syringe materials per ISO 10993-1.

F. Your product is considered a drug-device combination product meeting the definitions found in 21 CFR 3.2(e)(1). Therefore, note that Part 4 obligations on current good manufacturing practice (CGMP) and postmarketing safety reporting for combination products apply. Refer to the Final Rules, available at https://www.federalregister.gov/documents/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products and https://www.federalregister.gov/documents/2016/12/20/2016-30485/postmarketing-safety-reporting-for-combination-products, respectively.

No additional discussion required per sponsor.

Clinical Pharmacology Questions

1. *Does the Agency agree with the overall proposed approach to assess the potential effect of immunogenicity on the pharmacokinetics (PK), efficacy, and safety of risankizumab?*

FDA Response to Question 1:

While your overall proposed approach appears to be reasonable, we are concerned about the sensitivity of the neutralizing antibody (nAb) screening assay due to the low drug tolerance (70 ng/mL). You must ensure that the neutralizing antibody assay has adequate sensitivity at drug levels that are expected in the phase 3 trials.

No additional discussion required per sponsor.

2. *Does the Agency agree:*

   a. *With the proposed approach for assessing therapeutic protein-drug interaction with risankizumab as a perpetrator (effect of therapeutic protein on drugs)?*

b. That no specific, dedicated clinical pharmacology studies are needed to assess the effects of intrinsic and extrinsic factors on the disposition of risankizumab?

FDA Response to Question 2 (a):

We do not agree with your plan to use the results from the disease-drug interaction study in psoriasis patients to inform the therapeutic protein-drug interactions in Crohn's disease. It is unclear whether or not the underlying disease related mechanism in psoriasis affecting the CYP enzymes will be representative of that in Crohn's disease. Furthermore, it appears that the doses for the CD indication will be higher than those for the psoriasis indication. Therefore, you should conduct a separate study to inform the potential for therapeutic protein - drug interaction in subjects with CD.

Refer to the following guidance for more information:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292362.pdf

The Sponsor stated that the risk for disease-drug interaction in Crohn's patients is very low given the lack of reported interactions in the literature. The Agency agreed that there is a lack of literature data on the topic; however, the Agency clarified that absence of literature data cannot be interpreted to reflect low risk for disease-drug interaction. In response, the Sponsor proposed to use the results from the ongoing disease-drug interaction study in psoriasis patients as a preliminary assessment of risk for disease-drug interaction in patients with Crohn's disease. The Agency reiterated the response provided in the preliminary comments.

POST-MEETING COMMENT: Scientifically speaking, whether or not patients with Crohn's disease have low risk for disease-drug interaction may be evaluated in a clinical study that compares PK of CYP substrates in healthy subjects versus in patients with Crohn's disease.

FDA Response to Question 2 (b):

While we agree that no specific, dedicated clinical pharmacology studies are needed to assess the effects of intrinsic and extrinsic factors on the disposition of risankizumab, we have the following comments.

(i) Based on your population PK analysis, body weight is shown to have a significant effect on risankizumab disposition; we recommend that you continue to evaluate the impact of body-weight on the efficacy and safety measures in the phase 3 trials. This will help assess if there is a need for dose adjustment for different body-weight ranges.

(ii) You plan to use model-based approach for the assessment of impact of immunogenicity on PK, i.e., incorporating the anti-drug antibody (ADA) status as a covariate in the population PK model. We recommend using both model-based

(e.g., covariate analysis in population PK modeling) and non-model-based approaches. Examples of non-model based analysis include between-subject comparison of PK data (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison of PK data (i.e., before ADA positive and after ADA positive).

No additional discussion required per sponsor.

3. *Does the Agency concur that the proposed bridging strategy will be sufficient to demonstrate comparability between the risankizumab 90 mg/mL pre-filled syringe (PFS) formulation to be utilized in the Phase 3 CD program and the 150 mg/mL formulation using a delivery device intended for commercialization?*

FDA Response to Question 3:

We do not agree with your proposed bridging strategy to support the to-be-marketed formulation (150 mg/mL) and the to-be-marketed product (with a yet to-be-determined delivery device) and have the following comments.

(i) The proposed two-step approach is reasonable for establishing PK comparability between two formulation strengths, as well as between the PFS and the to-be-marketed presentation, which is yet to be determined. However, you must adequately power Study 1311.12 to evaluate the PK comparability using the statistical criteria for bioequivalence, since the change in solution strength from 90 mg/mL to 150 mg/mL represents a significant formulation change.

No additional discussion required per sponsor.

(ii) If your to-be-marketed delivery device is an auto-injector, you must power Study 1311.37 adequately to evaluate the PK comparability using the statistical criteria for bioequivalence because autoinjectors have been found to deliver substantially different exposures than prefilled syringes.

No additional discussion required per sponsor.

(iii) Also, refer to the technical considerations guidance on pen, jet, and other related injectors, available at http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM147095.pdf.

No additional discussion required per sponsor.

(iv) For Study 1311.12 which is designed to compare the 90 mg/mL formulation in PFS to 150 mg/mL formulation in PFS, you proposed an SC dose of (b) (4) mg, but the SC doses you are planning to evaluate in the phase 3 maintenance trial are 180 mg and

360 mg. You must conduct this PK comparability study using a dose of 360 mg dose.

Sponsor indicated that they will conduct the PK comparability study to support the to-be-marketed device at a dose of 360 mg. For the formulation bridging study, the sponsor stated their preference to use a lower dose of (b) (4) ***The sponsor further clarified that a 360 mg dose would involve multiple injections and possibly at different sites, whereas testing a dose at*** (b) (4) ***mg will avoid these confounding factors. The Agency reiterated that since the highest dose in the phase 3 studies in Crohn's disease is 360 mg, to bridge the two formulations the PK comparability assessment would need to be conducted at a dose of 360 mg.***

POST-MEETING COMMENT: ***For the purpose of bridging the efficacy and safety data from the phase 3 trials conducted with the 90 mg/mL maintenance formulation to support the to-be-marketed 150 mg/mL formulation, evaluation of the performance of two formulations at the clinical dose of 360 mg is critical because variables such as different injection sites and number of injections can affect the exposure delivered and thereby impact efficacy.***

(v) We do not agree with your plan to expose 30 subjects in your phase 3 trial to get clinical experience with your to-be-marketed product, i.e., the 150 mg/mL formulation in the to-be-marketed presentation (or delivery device). Furthermore, you did not plan a blinded control evaluation of the safety of the to-be-marketed presentation. If you intend to market the 150 mL auto-injector, you will need to adequately assess the safety (e.g., local injection site reactions) within the context of a blinded, controlled trial in which a significantly increased number of subjects are exposed and there is systematic evaluation and capture of adverse reactions. In addition, you will need to assess the ability of subjects to self-administer (actual use study) the to-be marketed product.

No additional discussion required per sponsor.

Clinical Pharmacology/Clinical Questions

4. *Does the Agency concur that the proposed induction and maintenance dosing regimens to be evaluated in the Phase 3 program are adequate based on the preclinical toxicology data as well as the Phase 2 efficacy, safety, and exposure-response relationships data in subjects with CD?*

FDA Response to Question 4:

We do not agree with your proposed dosing regimen for the phase 3 program.

You propose two dose levels (600 and 1200 mg) to further explore dose-response for the induction phase in the phase 3 trials. Results from your phase 2 studies indicate that a significantly greater proportion of subjects in the risankizumab 600 mg IV q4w dose group achieved the primary endpoint of clinical remission at week 12. Given that the preferred primary endpoint (see our response to question #6) differs from the endpoint used in the ongoing phase 2 trial, we recommend that you reassess the selected dose regimen for the phase 3 program; for instance, exploratory analyses of the phase 2 data may be conducted utilizing FDA's preferred efficacy endpoint to assess whether the dose-response holds using the preferred endpoint.

Also, considering the significant influence of body weight on the disposition of risankizumab as described by your population PK model, we recommend that you evaluate if an alternative dosing strategy considering body weight (e.g., tiered-dosing) would be more appropriate than the proposed fixed dose. A thorough evaluation is particularly important given your plan to enroll adolescent subjects in the study.

Discussion: The sponsor explained that for their phase 3 program, having two dose levels will allow further assessment of body weight effect at the end of the phase 3 trials. The Agency stated that the proposed dosing regimen is reasonable for the phase 3 studies in adult population and clarified that the recommendation for exploring the potential for dose adjustment based on body weight was with the intent to address the dose regimen for younger adolescents who may have lower body weight.

Sponsor agreed to consider investigating their product in 12 – 15 years old adolescents, and they will evaluate approaches to support dose selection, including analysis of PK data available at the time of the interim analysis outlined in the response to question #7 below.

Clinical Questions

5. *Does the Agency agree that the proposed Phase 3 program study design, including the definition of the population of patients with moderately to severely active CD (patients with and without inadequate response to prior biologic treatment) and study duration, for the induction and maintenance studies (Studies M16-006, M15-991, and M16-000) is adequate to support the proposed indication of the treatment of moderately to severely active CD in patients 16 years and older?*

FDA Response to Question 5:

The adequacy of the clinical efficacy information to support a BLA will be determined at the time of BLA review. The specific labeling claim that is supported by your phase 3 trials will be determined in the course of reviewing the BLA. Regarding the definition of the population that will be enrolled, please address our questions above in the Introductory Comments. In order to have labeling for both populations (inadequate response/refractory and treatment naïve), you will need to have adequate power to

assess efficacy in each of the populations. We recommend that you conduct a separate trial for each population, and we recommend that you power each of the trials individually to yield a highly persuasive p-value, such that if one of the trials fails you can still be labeled for the population for which efficacy was established. If only one trial is positive and the p-value is not highly persuasive, efficacy will not have been established to support approval. See also our responses to other questions regarding the proposed trials' designs.

No additional discussion required per sponsor.

6. Does the Agency agree with the proposed clinical and endoscopic endpoint definitions?

FDA Response to Question 6:

No, we do not agree with your proposed clinical and endoscopic endpoint definitions. For phase 3 trials, we recommend a co-primary endpoint definition of remission that includes each of the following:

- **endoscopy (using SES-CD)**
- **symptoms - abdominal pain (using an 11-point scale (0 –10 NRS)), and loose/watery stool frequency (based on the Bristol Stool Form Scale (BSFS)).**

For phase 3 trials, we specifically recommend the following co-primary endpoint definition of remission:

- **Endoscopy: SES-CD ≤ 4 and at least 2 points point reduction versus baseline and no sub-score > 1 in any individual variable.**
- **Symptoms:**
  - **Abdominal pain: daily abdominal pain score below a specific cutoff for the 7 days prior to the visit (and not worse than baseline). Your proposed average daily AP score ≤ 1 appears reasonable.**
  - **Stool frequency: total number of liquid/very soft stools below a specific cutoff for the 7 days prior to the visit (and not worse than baseline). Your proposed average daily SF ≤2.8 appears reasonable. We recommend that you define liquid/very soft stools as consistency of Type 6 or Type 7 based on the BSFS (see additional comments below).**

Discussion: The sponsor stated that their phase 2 data in a refractory patient population indicate that a SES-CD ≤ 4 and at least 2 point reduction versus baseline and no sub-score > 1 in any individual variable would not be achievable; they believe a less stringent endoscopic endpoint definition would still reflect clinical benefit in a refractory population.

The Agency proposed that it would consider the proposal for a revised co-primary endpoint that relies on SES-CD 50% reduction as the endoscopic component if the population is

refractory and if the sponsor can provide adequate justification that a 50% reduction in SES-CD is clinically meaningful in this population. However, the indication would reflect that an endoscopic remission had not been achieved. Furthermore the Agency suggested the Sponsor could use the FDA's original recommended co-primary endpoint (as described in the responses above), but conduct the assessment of the endoscopic component at a different and later time point.

POST MEETING COMMENT: Please clarify whether the phase 2 data analysis you cited of SES-CD ≤ 4 and at least 2 points point reduction versus baseline and no sub-score > 1 in any individual variable was conducted as a co-primary or a composite endpoint analysis.

We recommend that you use un-weighted scores for your co-primary endpoint. With regard to the stool frequency (SF) item, it is unclear whether or not you plan to include the Bristol Stool Form Scale (BSFS) as part of this item to illustrate to patients what is meant by "liquid or very soft stools" and whether patients are being instructed regarding how to count their stools. We have the following recommendations:

1. **We recommend performing usability testing as part of your ongoing psychometric evaluation study where you ask patients how they interpret the AP and SF items (i.e., how they define the concepts and response options) and ensure that patients can make meaningful distinctions between each of the response options.**

2. **We recommend either including the BSFS or the BSFS definitions with clear patient instructions regarding how to evaluate their liquid or very soft stools for this item. In addition, you should clarify how patients should rate stool frequency for the SF item when they pass more than one stool during the same toilet visit (i.e., all of the stools in the same toilet visit count only as one stool).**

Discussion: Sponsor agreed to provide the Agency with a visual example and definition of very soft stools that would be included in the patient assessment form and protocols. The sponsor agreed to provide guidance to patients on how to count stools.

7. *Does the Agency agree with the inclusion of subjects aged 16 and 17 years in the Phase 3 studies (Studies M16-006, M15-991, and M16-000)?*

FDA Response to Question 7:

We agree on the importance of trying to include adolescent patients in your planned phase 3 trials. While you have established proof of concept for risankizumab in the treatment of Crohn's disease, understanding the risks of both the highest proposed induction dose (1,200 mg IV) and the long-term safety of the proposed maintenance SC doses in adults would be important before opening enrollment of the phase 3 trials to

adolescent patients (21 CFR 50.52). We suggest you address these data gaps by developing a pre-specified plan for an interim safety analysis of adults enrolled in your phase 3 program. If your interim safety analysis supports opening enrollment of your phase 3 trials to adolescent patients, we recommend lowering the age limit for trial inclusion from 16 years to 12 years.

No additional discussion required per sponsor.

Labeling

8. *Does the Agency agree that the proposed primary and secondary endpoints and hierarchical testing procedures for the ranked secondary endpoints in the proposed pivotal Phase 3 studies (Studies M16-006, M15-991, and M16-000) will support the proposed label claims and inclusion of these data in the product label, including for subgroups of bio-IR and non-bio-IR subjects?*

FDA Response to Question 8:

No we do not agree. See our response to Question #6 regarding the primary endpoint for phase 3 trials in patients with Crohn's disease and our recommendation to have different patient populations in each phase 3 trial (bio-IR and non-bio IR). Whether your product can be labeled for each population will depend upon whether a statistically persuasive p-value is observed in each population.

9. *If supported by appropriate evidence of qualitative and quantitative validation in the target CD population, does the Agency agree that the proposed development plan for Crohn's symptom severity questionnaire (CSS) is sufficient to support a potential label claim?*

FDA Response to Question 9:

If your qualitative and quantitative research adequately supports the content validity and psychometric properties and performance of the CSS instrument, the Agency would be open to considering a labeling claim for the endpoint. You would need to demonstrate both statistical significance (in the pre-specified endpoint with adequate Type I error control) as well as clinically meaningful change in scores from baseline.

We have the following comments and recommendations:

1. **If feasible, we recommend that you consider electronic data capture (i.e., e-diary) of all patient-reported outcome (PRO) instruments. We recommend using electronic devices with reminder or alarm functions as these tend to facilitate operation and minimize the extent of missing data. For phase 3 trials, we recommend a paper or**

web-based back-up plan implemented in case there are any malfunctions with the electronic devices.

a. You should include general patient instructions in the beginning of your patient e-diary stating that the e-diary should be completed at the same time each day or week (e.g., evening, before bedtime, etc.) to ensure consistency within the patient as well as across patients in your study. To ensure a proper recall period (e.g., past 24 hours, past 7 days), we recommend that you implement a patient e-diary lock out time before/after which no entries can be made by patients.
b. Provide a rationale for your proposed 7-day recall period (versus "past 24 hours") based on qualitative research within your target patient population.

2. Provide an exact copy of the current version of the CSS instrument (e.g., screen shots) being included in your psychometric evaluation study, as well as a conceptual framework for the instrument, your proposed scoring algorithm, and training materials for patients, sites, and investigators. Provide also evidence of content validity in your target patient population including a qualitative study report including interviewer scripts, patient transcripts (if available), and item tracking matrices.

3. Your plan to consider further refining the CSS instrument based on your psychometric evaluation study results is reasonable. We recommend that you:

a. Determine your CSS responder definition prior to the initiation of your phase 3 trials, i.e., in your ongoing psychometric evaluation study. Submit your plans for establishing a CSS responder definition using anchor-based methods and cumulative distribution function (CDF) curves.
b. We recommend conducting usability testing within your psychometric evaluation study to assess with one-on-one cognitive interviews the device functionality, questionnaire comprehension, and ease of use in your patient population. This would minimize the risk of having poor quality data due to patients' misunderstanding or incomplete understanding of how to use the device and to ensure that the patients are able to choose their responses as intended.
c. If you intend to seek a CSS label claim for pediatric patients, you should ensure that you have evidence of content validity and adequate psychometric properties and performance in the pediatric patient population.
d. Submit a psychometric evaluation study report when it is available.

4. We acknowledge that you plan to include a patient global impression of change (PGIC) anchor scale. We recommend that you include in your phase 3 trial multiple anchor scales to provide an accumulation of evidence to help interpret a meaningful score change in all pre-specified PRO endpoints from a patient perspective. The anchor scales should be assessed at the same time points as the PRO endpoint scales, but completed after them. Provide the Agency with exact copies of the anchor scales you plan to include in your phase 3 trials, as they would

be administered to patients.

We recommend you include at least the following two types of anchor scales to generate responder definitions that represent a meaningful amount of change in patients' PRO scores:

(i) A static, current state patient global impression of severity (PGIS) scale asking patients about their current symptom severity experience in a non-comparative way (at different time points). For example, consider asking patients to rate how they would characterize the severity of their overall Crohn's disease symptoms (e.g., abdominal pain, diarrhea, etc.) at this point in time (ideally corresponding with the recall period of your pre-specified PRO endpoint).

(ii) A retrospective PGIC scale asking patients to compare their current symptom severity status to their status at baseline. (Note: In contrast to the PGIC, the PGIS is not subject to recall error and can also be used to assess change from baseline data.)

5. **We strongly suggest both translation and cultural adaptation of the CSS instrument (including instructions, items/domains, and response options) for multinational studies. Translation and cultural validation of outcome assessments can affect efficacy findings and it is important to ensure that efficacy assessments are standardized across sites. You may refer to the ISPOR principles for the translation and cultural validation process.[1]**

   No additional discussion required per sponsor.

10. Does the Agency agree that the proposed methodology to assess (b) (4) *is sufficient to support a potential label claim?*

FDA Response to Question 10:

No, we do not agree that your proposed methodology to determine (b) (4) **would be adequate to support a label claim.**

No additional discussion required per sponsor.

Statistics

11. Does the Agency concur with the overall statistical testing and inference strategy, as well as the proposed handling of missing data in the Phase 3 studies (Studies M16-006, M15-991, and M16-000)?

[1] Wild D, Grove A, Martin M, Eremenco S, McElroy S, Verjee-Lorenz A, Erikson P; ISPOR Task Force for Translation and Cultural Adaptation. Principles of Good Practice for the Translation and Cultural Adaptation Process for Patient-Reported Outcomes (PRO) Measures: report of the ISPOR Task Force for Translation and Cultural Adaptation. Value Health. 2005 Mar-Apr;8(2):94-104.

FDA Response to Question 11:

We recommend prospectively putting into place (in your protocols) procedures for minimizing missing PRO data (e.g., CSS instrument), including obtaining PRO data from patients at time of early withdrawal. Plans for handling missing PRO data at the total score level and item score level should be documented in your statistical analysis plan prior to phase 3 database lock and unblinding of those data.

We have the following additional comments:

a. Submit the Statistical Analysis Plan (SAP) to the Agency for review, including the key features of the trial, prior to conducting the trial. The key features should include, but not be limited to, the primary and key secondary endpoints, primary analysis methods (as well as the multiple comparison procedure, when feasible, for controlling the overall type I error rate), missing imputation method, and rationale for sample size calculation. We remind you that major changes to the statistical analysis plan after the start of a trial may compromise the interpretability of the results and/or present significant review concerns.

Discussion: Sponsor agreed to submit their SAP prior to initiation of the clinical trial.

b. An acceptable key secondary endpoint that may support labeling claims should measure different manifestations of the disease and should not provide redundant information with the primary endpoint or any other key secondary endpoint.

No additional discussion required per sponsor.

c. Regarding sample size planning, you need to provide the suitable justification for the assumed response rates, as well as the anticipated dropout rates. Any change of the planned sample size needs to be agreed by the Division and carefully documented in the SAP prior to the data lock and trial completion.

No additional discussion required per sponsor.

d. For dealing with dropouts, you have proposed to use LOCF as part of your primary analysis for continuous endpoint. To assess the impact of the dropouts on the final analysis, the statistical analysis plan should include several other missing data strategies for the primary endpoint (e.g., sensitivity analyses that impute dropouts as worst or best cases). In addition, you should consider other approaches that can handle data missing at random such as multiple imputations; when the missing data is informative (i.e., missing not at random), you should consider approaches such as pattern mixture models or selection models.

No additional discussion required per sponsor.

e. You have planned to recruit either 940 or 772 subjects from approximately 400 or 350 sites globally. On average, there will only be less than 3 patients per site. In order to ensure the blindness of the study, we recommend you consider centralized randomization.

No additional discussion required per sponsor.

f. You have planned to recruit subjects from Europe, Japan and United States. In order to assess regional effect, you should plan to conduct subgroup analyses for region.

No additional discussion required per sponsor.

g. You have planned to study two doses (i.e., 1200 mg and 600 mg dose groups) in both induction trials. For dealing with multiplicity, the Bonferroni procedure is proposed, i.e., alpha of 0.025 (two-sided) in comparing each dose and placebo. Since the Bonferroni procedure is too conservative, we recommend you use other more powerful procedures such as Hommel or Hochberg procedure.

Discussion: Due to many key endpoints proposed, the sponsor would like to use graphical approaches for dealing with multiplicity. They will include the detailed procedure in the SAP.

Safety

12. Does the Agency agree to the proposed safety monitoring plan for Studies M16-006, M15-991, and M16-000?

FDA Response to Question 12:

Your proposed safety monitoring plan for Studies M16-006, M15-991, and M16-000 appears to be reasonable. However, we remind you that un-blinding the safety data should not impact the blind of the efficacy data. Please submit the DMC charter, including the details of your standard operational procedure, for review.

No additional discussion required per sponsor.

13. Does the Agency agree that the proposed number of subjects exposed to risankizumab and the duration of exposure in the Phase 3 studies (Studies M16-006, M15-991, and M16-000) are adequate to support the safety of risankizumab for the proposed indication in the treatment of moderately to severely active CD in patients 16 years and older?

FDA Response to Question 13:

It is premature for us to provide agreement on what would be an adequate safety database for submitting an application. However, we are providing general comments below.

Your proposal generally meets or exceeds the typical premarketing safety database recommendations (i.e., for long-term treatment of non-life-threatening conditions) (as described in the ICH E1A guidance). However, exceptions to the typical database are also described in the guidance. For example, a larger and/or longer-term safety database will be needed if there is a concern that the drug will cause late developing adverse events that increase in severity or frequency over time; and a greater long-term safety database will be needed if there is a need to quantitate the occurrence rate of an expected specific low frequency adverse event.

Thus, from a risk assessment perspective, the required safety database for your product may be larger and/or longer duration than that proposed depending on the safety issues that are identified from sources including studies of your product, studies of other products in the same class, and postmarketing data for other products in the same class that are currently approved.

No additional discussion required per sponsor.

Regulatory

14. Under the Pediatric Research Equity Act (PREA), the requirements of PREA do not apply to any drug for an indication for which orphan designation has been granted under section 526 of the Federal Food, Drug, and Cosmetic Act. As risankizumab received orphan drug designation for the treatment of pediatric CD, risankizumab for CD is exempt from PREA, and an initial pediatric study plan (iPSP) is not required to be submitted. Does the Agency agree?

FDA Response to Question 14:
Since you received orphan drug designation on November 29, 2016 for risankizumab for the treatment of pediatric CD, PREA does not apply for this program and, therefore, an iPSP is not required to be submitted.

No additional discussion required per sponsor.

FDA ADDITIONAL COMMENTS:

We understand that you are planning to use risankizumab to treat Crohn's disease. Please provide the Agency with details regarding your proposed final-to-be-marketed product and a comprehensive use-related risk analysis.

Please note that a comprehensive use-related risk analysis should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis), the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors and task failures. Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

<u>If your proposed to-be-marketed product is a single-dose prefilled syringe, please note the following:</u>
Based on this risk analysis, you will need to determine whether you need to perform a human factors (HF) validation study under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product. The risk analysis can be used to inform the design of a human factors validation study protocol for your product. If you determine that an HF validation study is not needed for your product, submit your risk analysis and justification for not conducting the HF validation study to the Agency for review under the IND. The Agency will notify you if we concur with your determination.

<u>If your proposed to-be-marketed product is a prefilled pen/autoinjector or multiple pre-filled syringes are needed to administer the dose, please note the following:</u>
The risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 90 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. The following items will facilitate an efficient review of your HF study protocol:

- **(i) A summary of preliminary analyses and evaluations, including formative studies;**
  - **(a) Include in your summary a discussion of key findings and any changes made to your product or labeling, including how the findings were used to update the user interface and risk analysis**
- **(i) An updated risk analysis for your product;**
- **(ii) Detailed HF validation study protocol to include the following elements:**
  - **(a) Description of intended product users, uses, use environments, and training (if applicable) for commercial product**
  - **(b) Graphical depiction and written description of product user interface**
  - **(c) Summary of known use problems with previous models or similar products**
  - **(d) User task selection, categorization (e.g., critical) and prioritization**
  - **(e) Validation testing details**
    - **(1) Objective(s)**
    - **(2) Type of testing (simulated or actual use)**
    - **(3) Test environment and conditions of use**

(4) Training provided to participants and rationale for how it corresponds to real-world training (if applicable)
(5) Distinct user groups broken out by number and type of test participants and rationale for how they represent the intended user populations
(6) User tasks and use scenarios that will be studied
(7) Description of data to be collected and methods for documenting observations and interview responses
(8) Methods for root cause analysis of all use errors, difficulties, close calls
(9) Definition of performance success and performance failure
(10) Moderator transcript

(f) Intend-to-market labels and labeling (including an editable word version of the IFU if an IFU is proposed) that will be tested in the HF validation study
(g) Five intend-to-market samples of product that will be tested in the HF validation study

The requested information should be placed in eCTD section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:

a. Applying Human Factors and Usability Engineering to Medical Devices, available online at: http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

b. Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published four draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

a. Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development and can be found online at: http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

b. Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

c. Comparative Analyses and Related Comparative Use Human Factors Studies for Drug-Device Combination Products Submitted in an ANDA and can be found online at:

http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM536959.pdf

d. **Considerations in Demonstrating Interchangeability With a Reference Product and can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM537135.pdf**

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. Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a

Study Data Standards Resources web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm.

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or

cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the following items 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 field investigators who conduct those inspections (Item I and II). 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.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
   d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site

b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

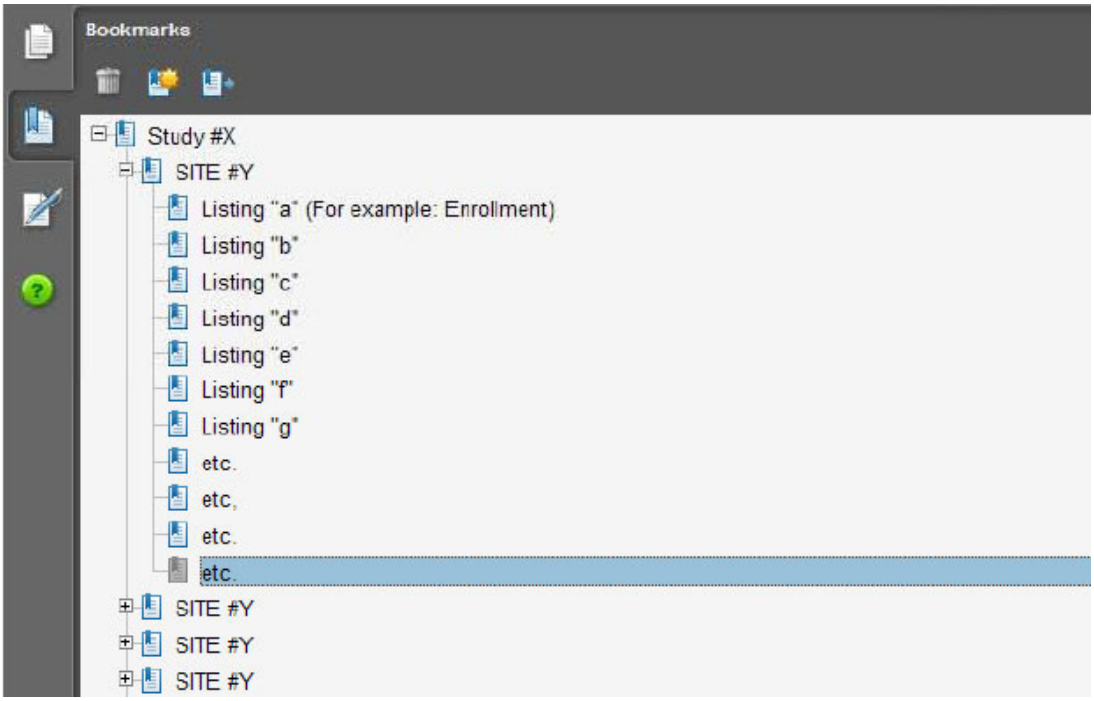
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
   e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
   f. By subject listing, of AEs, SAEs, deaths and dates
   g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
   h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
   i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)

j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new phase 2 or phase 3 protocol submissions to your IND or changes to these protocols include the following information:

1. Study phase
2. Statement of whether the study is intended to support marketing and/or labeling changes
3. Study objectives (e.g., dose finding)
4. Population

5. A brief description of the study design (e.g., placebo or active controlled)
6. Specific concerns for which you anticipate the Division will have comments
7. For changes to protocols only, also include the following information:
    - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
    - Other significant changes
    - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION

There were no additional issues warranting further discussion on the teleconference.

ACTION ITEMS

With the exception of the items indicated in the comments above, no other action items have been identified.

ATTACHMENTS AND HANDOUTS

The sponsor did not provide any attachments or handouts.

Attachment 1
Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[2]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

[2] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LAWRENCE W ALLAN
03/02/2017