# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761105Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113306

**MEETING MINUTES**

AbbVie Inc.
Attention: Mary Konkowski
Director, Regulatory Affairs
1 N. Waukegan Road
Dept. PA77/Bldg. AP30-4
North Chicago, IL 60064

Dear Ms. Konkowski:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for risankizumab injection, 90 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on December 13, 2017. The purpose of the meeting was to discuss the development program for risankizumab injection, 90 mg/mL.

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 Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

David Kettl, MD
Clinical Team Leader
Division of Dermatology and Dental 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:** Type B
**Meeting Category:** Pre-BLA

**Meeting Date and Time:** December 13, 2017 at 8:30 am ET
**Meeting Format:** Teleconference

**Application Number:** IND 113306
**Product Name:** risankizumab injection, 90 mg/mL
**Proposed Indication:** for the treatment of moderate to severe plaque psoriasis in adults
**Sponsor Name:** AbbVie Inc.

**Meeting Chair:** David Kettl, MD
**Meeting Recorder:** Cristina Attinello, MPH

## FDA ATTENDEES

David Kettl, MD, Clinical Team Leader, DDDP
Amy Woitach, DO, MS, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jiaqin Yao, PhD, Pharmacology Reviewer, DDDP
Jie Wang, PhD, Acting Clinical Pharmacology Team Leader, DCP 3
Mohamed Alosh, PhD, Biostatistics Team Leader, Division of Biometrics III
Carin Kim, PhD, Biostatistics Reviewer, DB III
Joanna Zhou, PhD, Chemistry Review Chief, OPQ/OBP
Cishan Li, PhD, Chemistry Reviewer, OPQ/OBP
Charlotte Jones, MD, PhD, MSPH, Medical Officer, OSE/DRISK
Tri Bui-Nguyen, PhD, Safety Regulatory Project Manager, OSE
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP

## SPONSOR ATTENDEES

Guenter Blaich, PhD Scientific Director, Global Preclinical Safety
Simon Cooper, MBBS Group Project Leader, Immunology
Lu Cui, PhD, Head of Immunology Clinical Statistics, Data and Statistical Sciences
Ann Eldred, MD, Medical Director, Immunology Clinical Development
Mary Flack, MD, Senior Clinical Program Leader, Immunology (Boehringer Ingelheim)
Ziqian Geng, Manager, Statistics, Data and Statistical Sciences
Yihua Gu, Associate Director, Statistics, Data and Statistical Sciences
Shyamala Jayaraman, PhD, Director, Regulatory Affairs CMC

Ping Jiang, Director, Safety Statistics, Data and Statistical Sciences
Amit Khatri, PhD, Associate Director, Clinical Pharmacology and Pharmacometrics
Mary Konkowski, Director, Global Regulatory Strategy, US/Canada Lead
Richard Manski, Senior Director, Statistical Programming
Laura C. Navarre, Director, Global Regulatory Strategy, Global Regulatory Lead
Steven Padula, MD, Vice President, Therapeutic Area Head of Medicine Immunology, Boehringer Ingelheim Pharma GmbH & Co KG
Wei Qian, PhD, Associate Director, Statistical Programming
Teri Robinson, PhD, PharmD Pharmacist Development Program
Ranjeeta Sinvhal, MD, Senior Medical Director, Immunology, Medical Safety Evaluation, Pharmacovigilance and Patient Safety
Elizabeth HZ Thompson, PhD Group Scientific Director, Immunology Clinical Development
Brian Waterhouse, Principal Research Statistician, Safety Statistics, Data and Statistical Sciences
Katherine Wortley, PhD Director, Regulatory Affairs CMC

## 1.0 BACKGROUND

**Purpose of Meeting:**
The purpose of this meeting is to discuss the planned original BLA submission for risankizumab injection, 90 mg/mL

**Regulatory Correspondence History:**

We have had the following meetings/teleconferences with you:
- 06/14/2017 Written Responses Only (Type C)
- 04/05/2017 Guidance Meeting
- 03/29/2017 Guidance Meeting
- 11/16/2016 Guidance Meeting
- 11/04/2016 Written Responses – Meeting Cancelation
- 11/17/2015 CMC Only meeting
- 10/29/2015 Written Response Only Meeting
- 06/24/2015 End of Phase 2 Meeting
- 01/18/2012 Pre-IND Meeting

We have sent the following correspondences:
- 11/15/2017 Advice Letter
- 10/09/2017 Proprietary Name Granted Letter
- 03/09/2016 PSP Initial Agreement Letter
- 03/09/2016 Advice Letter
- 02/19/2016 Advice Letter
- 11/16/2015 PSP Written Response Letter
- 08/31/2015 Advice Letter
- 04/22/2015 Information Request

- 08/27/2014 Advice Letter
- 08/06/2014 Advice Letter
- 07/10/2014 Advice Letter
- 04/09/2014 Advice Letter
- 04/17/2013 Advice Request Letter
- 12/13/2012 Information Request
- 05/10/2012 Study May Proceed Letter

## 2. DISCUSSION

### 2.1. Regulatory

***Question 13:***
Does the Agency agree that the planned content of the BLA, as displayed in the proposed BLA table of contents (TOC) including the proposed placement of the combination product/device information in the BLA, is adequate to be considered a complete application?

***FDA Response to Question 13:***
The proposed content appears adequate for filing and placement of the combination product/device information in the BLA is acceptable. Applications are expected to be complete at the time of submission. See additional comments below, as well as "Discussion of the Content of a Complete Application," under Administrative Comments.

See additional comments below related to technical aspects of the application:

- If you are utilizing m1 v2.01 DTD, then FDA Form 3397 and Form 3674 can be placed in in m1.2 cover letter section, with a clear leaf titles. Otherwise, if you are utilizing v3.3 DTD, Forms 3397 and 3674, should reside in the respective m1.1 sections.

- Notes to Reviewers can be provided as a single pdf file, with clear bookmarks, table of contents and hyperlinks.

- When cross referencing using m1.4.4, a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (non- eCTD or paper) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document and if possible, hyperlinks to the referenced documents.
- In m1.6.3. (meeting correspondence), please make sure that the single pdf file does have clear bookmarks, table of contents and hyperlinks.

- If you are utilizing v3.3 DTD, please place the Proprietary name document in m1.18 (Proprietary Names) and use a leaf title that is indicative of the content. However, if you are utilizing v2.01 DTD, you may place your proposed proprietary names and rationale information as a separate document from the cover letter in the module 1 cover letter section or in 1.12.4 (Request for comments and advice). Please use a leaf title that is indicative of the content. It is very important that you include the eCTD location of the content in the cover letter and if possible, provide hyperlinks, so the information can be quickly and easily accessed by reviewers.

- Human Factors submissions for the combination product should be located in eCTD section 5.3.5.4 Other Study Reports, with links from appropriate Module 3 files, and should include the appropriate human factors file tag (e.g., HF-validation protocol, HF-validation report, HF-validation other) to describe the document's contents. Additionally, you may cross reference from Module 5 to Module 3 as applicable.

- The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.

- Providing Table of Contents in 4.1, is not necessary in the eCTD structure. Please provide a reviewer's aid, instead.

**Meeting Discussion:**
The sponsor provided a response document, which is appended. The Agency affirmed this approach is acceptable.

- Please note that Study Tagging Files (STF) files are required for submissions to the FDA when providing study information in modules 4 and 5 with the exception of module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References. Each study should have an STF and all components regarding that study should be properly file tagged and placed under the study's STF, including case report forms (crfs). Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. For more information on file tags, please refer to The eCTD Backbone File Specification for Study Tagging Files 2.6.1 (PDF - 149KB) (6/3/2008) - http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf.

**Meeting Discussion:**
The sponsor provided a response document, which is appended. Upon consultation with the edata team, the approach outlined by the sponsor is acceptable.

## 2.2. Chemistry, Manufacturing and Controls (CMC)

***Question 1:***

Does the Agency agree with the proposal to include a document in 3.2.R with hyperlinking to the relevant Module 3 sections to meet the requirements of the Method Validation Package?

***FDA Response to Question 1:***

Your proposed approach to meet the requirements of the Method Validation Package is acceptable. It is unclear what "samples" will be provided upon an information request by the Agency. Sufficient information (e.g., on experiments, test parameters and test materials) and data should be provided in the BLA to enable an evaluation of method validation.

**Meeting Discussion:**

The sponsor provided a response document, which is appended. The Agency affirmed this approach is acceptable.

***Question 2:***

Does the Agency agree with the proposal for providing batch records?

***FDA Response to Question 2:***

The proposed batch records as listed in the meeting package, and the English translated copies of the batch records to be included in the BLA are acceptable.

***Question 3:***

Does the Agency agree (b) (4)

***FDA Response to Question 3:***

(b) (4)

## 2.3. Nonclinical

***Question 4:***

Does the Agency agree that the completed nonclinical data package, including toxicology is sufficient to support the filing of the BLA?

***FDA Response to Question 4:***

It appears the completed nonclinical data package is sufficient to support the filing of the BLA. However, the adequacy of the nonclinical data will be determined after review of the study reports.

***Question 5:***

Does the Agency agree with AbbVie's plan to provide the Trial Summary files for all in-scope studies for risankizumab, as per FDA's 03 November 2016 Technical Rejection Criteria for Study Data?

***FDA Response to Question 5:***

It is acceptable for filing.

## 2.4. Clinical Pharmacology

***Question 6:***

Does the Agency agree that the clinical pharmacology package is adequate to support the proposed BLA?

***FDA Response to Question 6:***

Yes, we agree that your proposed clinical pharmacology package appears to be reasonable for our review of the BLA.

***Question 7:***

Does the Agency agree with the plan for submission of the PK and anti-drug antibody datasets from Phase 1, 2 and 3 studies in healthy subjects or subjects with psoriasis?

***FDA Response to Question 7:***

Yes, we agree that your proposed plan for submission of the PK and anti-drug antibody datasets is generally acceptable.

We have the following general recommendations regarding the immunogenicity assessments:

- For the evaluation of the anti-drug antibodies (ADA) impact on PK, we recommend that you include between-subject comparison (i.e., between ADA positive subjects and ADA negative subjects) as well as within-subject comparison (i.e., before ADA positive and after ADA positive) of PK data.
- For the ADA positive subjects observed in Phase 2 and 3 trials, provide a summary of study number, study subject ID, serum risankizumab concentrations at each PK time-point, sample ADA status at each immunogenicity assessment time-point, and the primary efficacy outcome.

## 2.5. Clinical/Biostatistics

***Question 8:***

Does the Agency agree with AbbVie's proposal for the subject narratives and subject case report forms to be included in the BLA?

***FDA Response to Question 8:***

Your proposal is reasonable. Also, include narratives on pregnancy outcomes for subjects who have been exposed to risankizumab, to conform with PLLR guidances.

**Meeting Discussion:**
The sponsor provided a response document, which is appended. The Agency affirmed this approach is acceptable.

***Question 9:***
Does Agency agree with the proposal to provide the CSR for Study 1311.38 to the IND as a routine information amendment when the CSR becomes available?

***FDA Response to Question 9:***
Your approach appears reasonable, assuming no labeling claims are based on this information.

***Question 10:***
Does the Agency agree with the proposed drug abuse and liability assessment (DALA) approach?

***FDA Response to Question 10:***
Your approach appears reasonable.

***Question 11:***
Does the Agency agree with the proposed approach for the analysis and presentation of the adjudicated cardiovascular (CV) endpoint data?

***FDA Response to Question 11:***
Your approach appears reasonable.

***Question 12:***
Does the Agency agree with the AbbVie's proposal to support self-administration in the proposed labeling that will be included in the initial BLA submission?

***FDA Response to Question 12:***
Your proposal appears reasonable.

***Question 14:***
Does the Agency agree with the proposed plan (b) (4)

***FDA Response to Question 14:***
(b) (4)

***Question 15:***
Does the Agency agree with the proposed plan and data cutoff date for the 4-month safety update report?

***FDA Response to Question 15:***

Your approach appears reasonable based on your anticipated patient exposure.

***Question 16:***

Does the Agency agree with the proposed list of covered clinical studies for submission of financial disclosure information?

***FDA Response to Question 16:***

Your approach sounds reasonable as it appears you intend to rely on your Phase 3 studies to establish safety and efficacy. If you should find that the safety of your product will rely on other studies in which a single investigator makes a significant contribution to the demonstration of safety, these studies should be included as per *Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators.*

***Question 17:***

Regarding FDA's requirement for biologic common names to include a 4-letter suffix:

a. Does the Agency agree with AbbVie's proposal to submit the 4-letter suffix proposals in the BLA?
b. Is the proposed Module 1 location for this information acceptable?
c. What is the approximate time during the BLA review that FDA would target to provide AbbVie with the four-letter suffix decision and final approval of the tradename?

***FDA Response to Question 17:***

a. We agree with your proposal to submit the 4-letter suffix proposals in the original BLA.

b. For Version 3.2 of the eCTD you can submit it in Module 1 under 1.12.4 Request for comments and advice and label the leaf as 'Request for Review of Suffixes for Proper Name'.

   For Version 3.3 of the eCTD you can submit it in Module 1 under 1.18 Request for comments and advice and label the leaf as 'Request for Review of Suffixes for Proper Name'.

c. We will review any submitted proposed suffixes in accordance with the application milestones as part of the BLA review.

   With regards to your proposed proprietary name, we note that your proposed name Skyrizi was submitted to IND 113306 and was found conditionally acceptable on October 9, 2017. We recommend you submit a request for a proposed proprietary name review to the BLA. If you require information on submitting a request for proprietary name review or performance goals associated with proprietary name reviews, we refer you to the following:

   Guidance for industry *Contents of a Complete Submission for the Evaluation of Proprietary Names*
   http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2013 through 2017 http://www.fda.gov/downloads/ForIndustry/UserFees/PrescriptionDrugUserFee/UCM270412.pdf

***Question 18:***

Does the Agency agree that the Agreed Initial Pediatric Study Plan (iPSP) would fulfill the Pediatric Research Equity Act (PREA) requirements for this BLA?

***FDA Response to Question 18:***

Your agreed upon pediatric plan form March 2016 should be submitted with the BLA. Decisions on fulfillment of the PREA requirement will not be made until BLA submission and review is complete. Discussion regarding timing of pediatric assessments will be informed by review of the adult data and will be further discussed during the BLA review.

***Question 19:***

Based on the information provided in the briefing book, does the Agency foresee an advisory committee meeting will be necessary for risankizumab?

***FDA Response to Question 19:***

Decisions regarding the need for Advisory Committee discussion will not be made until BLA submission and filing reviews have been completed.

However, we currently are not aware of any novel or complex regulatory issues that would necessitate Advisory Committee discussion at this stage of development.

**Additional Comments from CDRH:**

Provide the following information to support the device constituent parts of the combination product. It is recommended that you refer to the eCTD Technical Conformance Guide published in September 2016 (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmis sions/UCM465411.pdf ) when determining the location of the following information within your submission.

For more information regarding cGMP requirements for combination products, refer to guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products* (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf ).

1. A complete and detailed description of your device constituent design and delivery system, including any features and functionalities unique to your device. This should also include engineering drawings and detailed descriptions of the individual device constituent components.

2. Detailed descriptions of the principles of operation of your device, from beginning to end of the activation process, in which you explain the mechanical drug delivery mechanisms of your device constituent in order for it to achieve its intended use.

3. A complete and detailed device constituent design requirements and specifications document, including design inputs and outputs in accordance with 21 CFR 820.30 design controls. Ensure that you clearly describe the acceptability of your design control inputs within the context of the intended use of your combination product. Be sure to identify the essential performance requirements of your device. The essential performance requirements of any device constituent parts are the design outputs necessary for your device constituent to safely and effectively achieve the product's intended use. The essential performance requirements of the should be developed in accordance with the risk profile of the entire combination product and may vary depending on the indications for use, patient and/or user population, and design of the constituent parts of the combination product. Your design requirements and essential performance requirements should consider the desired level of reliability of the product and level of risk associated with failure to meet the essential performance requirements.

   For pre-filled syringes, we expect the essential performance requirements to include, at a minimum, the following:

   - Dose Accuracy
   - Break loose / Glide Force

4. Design verification documentation. Verification testing documentation may include summary test results of established test methods for the product (e.g. recognized consensus standards, FDA Guidance, etc.) or complete verification test reports for unique or unrecognized test methods. All verification testing should be directly traced to the design requirements of the device. Ensure that you utilize test methods and preconditioning that simulate the intended use of your product. You should conduct testing to verify the essential performance requirements of the combination product with the to-be-marketed version of the device constituent and the intended biologic/drug product; however, if you plan to rely on verification testing conducted with a different test fluid be sure to provide a scientific rationale for the acceptability of the test fluid as a surrogate for the intended biologic/drug product (i.e. fluid characteristics, viscosity, etc.). Valid justifications for any test results not being able to pass its acceptance criteria should be provided, if applicable. Furthermore, you should utilize a sufficient number of device constituent test samples that will be statistically relevant for your performance testing.

5. Design validation documentation. Design validation documentation should be performed to ensure that the device constituent parts of the combination product meet the intended use of the combination product as a whole. Design validation documentation may be in the form of clinical studies with the to-be-marketed presentation of the device, bridging studies that successfully validate the to-be-marketed presentation of the device constituent through clinical and/or bench top studies of the essential performance requirements of the device constituent in the context of the intended use of the combination product, literature review regarding the use of the to-be- marketed device constituent presentation in the context of the intended use of the combination product, human factors studies, and/or simulated actual-use studies. It is highly recommended that you conduct clinical studies with the to-be-marketed presentation of the combination product and capture any device constituent

failures/malfunctions as part of the clinical study protocol in order to successfully validate the device constituent parts of the combination product.

6. Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. You should outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g. DFMEA, UFMEA, Fault Tree Analysis, etc.).

7. Biocompatibility evaluation. You should provide documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to guidance for industry *Use of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"* (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf ) for more details.

8. Stability and shelf-life testing. You should provide documentation that ensures the final finished combination product maintains its essential performance requirements up to the labeled date of expiry.

9. Shipping studies. You should provide documentation that ensures that the final finished combination product maintains its essential performance requirements after actual or simulated shipping.

10. Lot release specifications. Provide the lot release specifications associated with the device constituents of the combination product, including all essential performance requirements.

11. It is recommended that a traceability matrix is provided to ensure each design requirement has been adequately verified and validated. The following is an example traceability matrix for the essential performance requirements of the device constituent as a summary of the testing completed to support the device constituents of the combination product:

| **Essential Performance** | **Specification** | **Verification** | **Validation** | **Shelf Life / Stability (Y/N)** | **Shipping / Transportation (Y/N)** | **Lot Release Testing (Y/N** |
|---|---|---|---|---|---|---|

12. As the owner of the combination product it is expected that you maintain the requirements for your product within your marketing application. If you intend to refer to documentation (e.g. verification testing) held within another submission and/or master file be sure to provide a letter of authorization or right of reference alongside a detailed description of the location of the information within the file (i.e. volume, page number, section header, etc.). It

is recommended that you provide a brief overview of how the referenced information is intended to support the review of your submission.

**Meeting Discussion:**
The sponsor provided a response document, which is appended. The sponsor approach for ADaM IG v1.0 is acceptable.

## 3.0 ADMINISTRATIVE COMMENTS

## DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

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

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

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

## PREA REQUIREMENTS

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

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

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

**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* and *Pregnancy and Lactation Labeling Final Rule* 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.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which 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* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

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. As of **May 5, 2017,** the following submission types: **NDA**, **ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018.** Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

## MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|---|---|---|---|---|
| 1. | | | | |
| 2. | | | | |

## Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the 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).**

Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
Site number
Principal investigator
Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
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.

Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
Number of subjects screened at each site
Number of subjects randomized at each site
Number of subjects treated who prematurely discontinued for each site by site

Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
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
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.

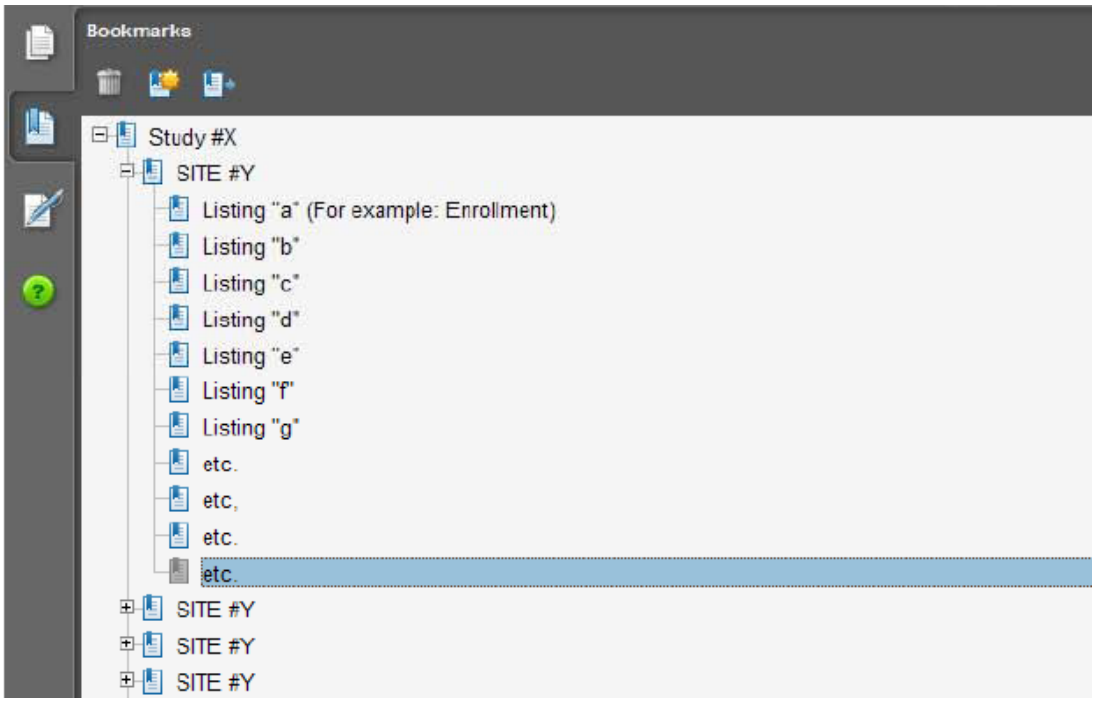
If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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).
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.

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

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[1]** | **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 |

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.

[1] 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

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

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/s/

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DAVID L KETTL
12/13/2017

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 113306

**MEETING MINUTES**

Boehringer Ingelheim Pharmaceuticals Inc.
Attention: Robert O. Kumi, Ph.D.
Associate Director, Regulatory Affairs
900 Ridgebury Road
P.O. Box 368
Ridgefield, CT 06877

Dear Dr. Kumi:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BI 655066.

We also refer to the meeting between representatives of your firm and the FDA on June 24, 2015. The purpose of the meeting was to discuss the development program for BI 655066, humanized monoclonal antibody directed against IL 23 p 19.

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

If you have any questions, call Cristina Attinello, Senior Regulatory Project Manager at (301) 796-3986.

Sincerely,

*{See appended electronic signature page}*

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

Enclosures:
Meeting Minutes
Appendix to Minutes
BI's Responses to FDA Draft Comments

**FOOD AND DRUG ADMINISTRATION**
CENTER FOR DRUG EVALUATION AND RESEARCH

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Type B |
| **Meeting Category:** | End of Phase 2 |
| **Meeting Date and Time:** | June 24, 2015, 11 AM |
| **Meeting Location:** | Bldg. 21, Rm. 1539 |
| **Application Number:** | IND 113306 |
| **Product Name:** | BI 655066 |
| **Proposed Indication:** | for the treatment of moderate to severe psoriasis in adult patients who are candidates for phototherapy or systemic therapy |
| **Sponsor Name:** | Boehringer Ingelheim Pharmaceuticals Inc. |
| **Meeting Chair:** | Kendall Marcus, MD |
| **Meeting Recorder:** | Cristina Attinello, MPH |

**FDA ATTENDEES**
Julie Beitz, MD, Director, ODE III
Kendall A. Marcus, MD, Director, DDDP
Jill Lindstrom, MD, FAAD, Acting Deputy Director, DDDP
Gordana Diglisic, MD, Clinical Team Leader, DDDP
Denise Cook, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Jiaqin Yao, PhD, Pharmacology Reviewer, DDDP
Lin Zhou, PhD, Clinical Pharmacology Reviewer, DCP 3
Jie Wang, PhD, Clinical Pharmacology Reviewer, DCP 3
Jeffry Florian, PhD, Pharmacometric Team Leader, OCP/DPM
Dhananjay D. Marathe, PhD, Senior Pharmacometric Reviewer, OCP/DPM
Sarah Kennett, PhD, Review Chief, OPQ/OBP
Jee Chung, PhD, Product Quality Team Leader, OPQ/OBP
Mark Paciga, PhD, Product Quality Reviewer, OPQ/OBP
Mohamed Alosh, PhD, Biostatistics Team Leader, DB III
Matthew Guerra, PhD, Biostatistics Reviewer, DB III
Ashley Slagle, Reviewer, COA Staff
Yasmin Choudhry, Reviewer, COA Staff
Carlos Mena-Grillasca, Reviewer, OSE/DMEPA
Roy Blay, PhD, Reviewer, DGCAB
Cristina Attinello, MPH, Senior Regulatory Health Project Manager, DDDP
CDR Lydia Springs, RN, BSN, MSHS, CPHM, Regulatory Project Manager, DDDP

**SPONSOR ATTENDEES**
Matthias Arndt, PhD, Project Manager Biopharmaceuticals
Axel Roth, PhD, Project Manager Devices
Diann Blanset, PhD, DABT, Toxicologist, Nonclinical Drug Safety
Mary Flack, MD Clinical Program Leader, Medicine
Wulf Boecher, MD Medical Affairs
Steven Padula, MD, Therapeutic Area Head, Medicine Immunology
Laurent Vernillet, PhD, PharmD, Clin. Pharm. Project Leader
Bojan Lalovic, PhD, Pharmacometrician, Translational Medicine
Joe Scherer, MS, Biostatistician, Biometrics/Data Management
David Hall, PhD, Statistical Expert, Biometrics/Data Management
Annette Galler, PhD, International Project Leader
Robert O. Kumi, PhD, RAC, Assoc. Director Regulatory Affairs
Karen Sitney, PhD, Director CMC Regulatory Affairs
Otmar Pfaff, PhD, Regulatory Affairs Lead, Immunology
Joanne Palmisano, MD, Vice President Regulatory Affairs

**Purpose of the Meeting:**
To discuss the development program for BI 655066, humanized monoclonal antibody directed against IL 23 p 19

**Regulatory Correspondence History**

We have had the following teleconference with you:
- January 18, 2012: Pre-IND Meeting

We have sent the following correspondences:
- April 22, 2015: Advice/Information Request Letter
- August 27, 2014: Advice/Information Request Letter
- August 6, 2014: Advice/Information Request Letter
- July 10, 2014: Advice/Information Request Letter
- April 9, 2014: Advice/Information Request Letter
- April 17, 2013: Advice/Information Request Letter
- December 13, 2012: Advice/Information Request Letter
- May 10, 2012: Study May Proceed Letter

**Chemistry, Manufacturing and Controls (CMC)**

**Question 19:**
Does the Agency concur with the analytical comparability approach to support the use of Phase III clinical trial supply?

**Response:**
Based on the information provided in the meeting package, your proposed analytical comparability approach to support the use of Phase 3 clinical trial supply seems reasonable. However, the final decision will be dependent on the review of all the relevant data submitted to

the IND (release data, stability data, characterization data, including the assessment of the removal of product and process related impurities and forced degradation studies).

**Question 20:**
Does the Agency concur that demonstration of the proposed analytical comparability between the Phase I/II prefilled syringe and the Phase III prefilled syringe support use of the new primary packaging in Phase III trials?

**Response:**
Yes, in general the FDA concurs with your proposed approach. However, the final decision will be dependent on the review of the data from the forced degradation studies, as well as data from accelerated and long term stability studies. The review of the adequacy of the data in the (b) (4) DMF for the (b) (4) PFS is deferred to CDRH.

**Question 21:**
(b) (4)

**Response:**
(b) (4)

**Non-Clinical**

**Question 1:**
Does the Agency concur that the current nonclinical safety package supports the initiation of Phase III trials?

**Response:**
Yes, we agree.

**Question 2:**
Does the Agency concur that the studies supporting initiation of Phase III, as well as the completion of the planned enhanced pre- and postnatal developmental study in cynomolgus monkey and carcinogenicity risk assessment (Submitted March 27, 2015; SEQ 041), will be adequate to support a BLA submission?

**Response:**
We agree that a traditional 2-year rodent carcinogenicity study is not needed to support a BLA submission. This decision received Exec CAC concurrence on May 28, 2015.

In addition to the full study reports from the completed nonclinical studies and the proposed enhanced pre- and post-natal developmental study in cynomolgus monkeys, adequate labeling based on nonclinical studies conducted with BI 655066 and from literature provided for the assessment of carcinogenic risk should be included in the BLA submission.

**Clinical Pharmacology/Biopharmaceutics**

**Question 15:**
Does the Agency concur with the overall proposed approach to assess the effect of immunogenicity on the pharmacokinetics, efficacy and safety of BI 655066?

**Response:**
Your proposed approach appears to be reasonable. See comments in response to Question 18.

**Question 16:**
Does the Agency agree that due to the size of BI 655066 monoclonal antibody, QT assessments are not required?

**Response:**
Yes, we agree that a TQT study is not required. However, periodic EKG monitoring during the Phase 3 trials should be performed (see response to Questions 4 and 11)

**Question 17:**
Does the Agency agree with the proposed approaches for assessing therapeutic protein drug interaction with BI 655066 as a perpetrator (effect of therapeutic protein on drugs) and a victim (effect of drugs on therapeutic protein)?

**Response:**
We acknowledge the meta-analysis and in vitro data you submitted as the basis for not conducting a therapeutic protein-drug interaction study to evaluate your product as a perpetrator. However, we continue to recommend that you conduct in vivo studies in the target patient populations to determine the DDI potential between your drug product and CYP450 substrates, because 1) meta-analysis on difference in serum concentration of inflammatory cytokines between healthy subjects and psoriasis patients cannot rule out the possibility of therapeutic protein –drug interaction in vivo, and 2) recent studies have indicated that in vitro or animal studies have limited value in the qualitative and quantitative projection of clinical interactions. The in vivo evaluation of your drug product in targeted populations can be conducted with individual substrates for specific CYP enzymes, or studies can be conducted using a "cocktail approach".

We agree with you regarding the use of population PK model-based approach to evaluate the effect of the most commonly used concomitant medications in psoriasis patients on BI 655066

disposition. As a part of this analysis, please note in the analysis data set the period/percentage of time over which subjects were on the concomitant medications and incorporate the timing for change in concomitant medication status for each subject in population PK analysis for situations where these medications may have changed while on treatment.

**Meeting Discussion:**
There was a general discussion regarding the clinical drug interaction study design. The Agency agreed to the sponsor's proposal to conduct a therapeutic protein-drug interaction study with BI 655066 using a cocktail that includes probe substrates for CYP isoenzymes 1A2, 2C9, 2C19, 2D6 and 3A4. The Agency also agreed that the proposed drug interaction study should be conducted in subjects with psoriasis (which could also include subjects with psoriatic arthritis). The Agency noted that there are limitations to study the disease DDI only after a single dose administration of BI 655066 and recommended that the DDI study should characterize the PK profile of the probe substrates, both following a single dose administration and at steady state of BI 655066.

**Question 18:**
Does the Agency concur that no specific, dedicated clinical pharmacology studies are needed to assess the effects of major intrinsic and extrinsic factors on the disposition of BI 655066?

**Response:**
Yes, we agree. However, we remind you that incorporating the anti-drug antibody (ADA) status as a covariate in the population PK model can only provide supporting evidence with respect to the impact of ADA on PK of BI 655066. As a part of this analysis, incorporate the timing for ADA status change for each subject and evaluate the impact of time-dependent change in ADA status for situations where the ADA status may have changed while on treatment.

We recommend that you also use the conventional methods (i.e., within-subject and between-subject comparison of drug concentration data) to evaluate the impact of ADA on PK of BI 655066.

**Clinical/Clinical Pharmacology/Biostatistics**

**Question 3:**
Does the Agency concur that the dosing regimen selected for Phase III is supported by the Phase I and II data?

**Response:**
The 150 mg dose with dosing at Week 0, Week 4 and every 12 weeks thereafter for Phase 3 appears reasonable based on the provided information.

While your modeling and simulation analysis predicts a marginally lower efficacy in subjects with higher body-weight (~3% lower PASI 90 for higher body-weight at Week 12), the data from study 1311.2 show 11% lower PASI 90 at Week 12 for body-weight subgroups >100 kg vs. ≤100 kg. This could be due to a limited range of body-weights used in the higher body-weight category for simulation purposes while the actual population could have a broader range leading

to less efficacy in the higher body-weight subgroup. Thus, for appropriate dosing for subjects in the higher body-weight category, you may consider investigating the dose for this subgroup further. One possible approach could be to prospectively study an additional higher dose or a more frequent dosing regimen with 150 mg dose in the higher body-weight subgroup. In addition, we recommend that you continue to evaluate the impact of body-weight on the efficacy and safety measures in the Phase 3 trials and submit these evaluations in the BLA submission to assist in reviewing the appropriateness of dosing for different body-weight ranges.

**Question 4:**
Does the Agency concur that the Phase III trials (1311.3 and 1311.4) as designed are adequate to support the proposed indication?

**Response:**
In Trial 1311.3 you propose a multicenter, randomized, double-blind, double dummy, placebo and active controlled trial in subjects with moderate to severe plaque psoriasis for a 40-week treatment period with 500 subjects randomized 2:1:1 to BI 655066, ustekinumab, and placebo, respectively. Subjects will be dosed with 150 mg of BI 655066 and ustekinumab subjects will be dosed according to the approved labeling at 0, 4, and q 12 weeks. You have determined that the efficacy time point will be at Week 16 with PASI 90 and sPGA of clear/almost clear (0 or 1) being the coprimary endpoints. You have proposed multiple secondary endpoints with varying PASI scores and the Psoriasis Symptom Inventory (PSI).

In Trial 1311.4 you propose a multinational, multicenter, randomized, double-blind, double-dummy placebo controlled, 52-week trial with a 40-week treatment period and a 12-week follow-up period evaluating the efficacy and safety of BI 655066 in 500 subjects with moderate to severe plaque psoriasis. Subjects will be randomized 4:1 with BI 655066 and placebo, respectively. Subjects will be dosed with 150 mg BI655066 or placebo at Weeks 0 and 4. The efficacy timepoint will be at Week 16. Both placebo and active arms will receive BI 655066 at Week 16 but subjects in the original active arm will be re-randomized at Week 28 to receive either placebo or BI 655066 at Weeks 28 and 40.
You have determined that the efficacy time point will be at Week 16 with PASI 90 and sPGA of clear/almost clear (0 or 1) being the coprimary endpoints. You have proposed multiple secondary endpoints with varying PASI scores and the Psoriasis Symptom Inventory (PSI). You have added a sPGA of clear at Week 16 as a secondary endpoint in this trial.

The proposed coprimary endpoint of PASI 90 and sPGA of clear/almost clear with 2- grade improvement with an adequate sPGA scale is acceptable. However, we cannot comment on acceptability of the proposed coprimary endpoint sPGA of clear/almost clear, as the briefing document did not contain a description of the sPGA severity assessment scale that will be used in your Phase 3 trials. We recommend that the sPGA severity scale be a 5-point scale with morphologic descriptors of the global disease for each level of severity (clear, almost clear, mild, moderate, severe). The category descriptors should be clearly defined, mutually exclusive, and non-comparative. The assessment should be static and objective. The “clear” category should represent true absence of disease. Regarding your secondary endpoint, the PSI, see response to Question 13.

In addition, in Trial 1311.4, which will evaluate loss of response of BI 655066 after randomized withdrawal to placebo, you should further design the trial to evaluate retreatment of subjects with BI 655066 who experience a loss of response. This prospectively designed retreatment should include an assessment of treatment response after 16 additional weeks of treatment for subjects who relapsed during randomized withdrawal to placebo. You could consider the criteria of sPGA ≥3 or propose an alternative suitable threshold for relapse as a retreatment criteria for this evaluation.

The design of the trials to evaluate safety is not adequate. You propose only to perform EKG and physical exam/vital signs at screening only, and laboratory evaluation at screening and Weeks 28 and 52. Safety monitoring of subjects should include more frequent laboratory evaluations, periodic EKG, and physical exams with vital signs.

In addition, if you intend that BI 655066 will be a self-administered product, if approved for marketing, then one of your pivotal Phase 3 trials should include provisions for subjects to self-administer the drug product.

**Meeting Discussion:**
The sponsor clarified that Phase 3 trials will be carried out with the product administered by the investigator (b) (4) In general, the Agency recommends that Phase 3 trials be conducted with self-administration of the final, to-be-marketed formulation.

**Question 5:**
Does the Agency concur that the PASI 90 and sPGA (0 or 1) at week 16 are suitable coprimary endpoints in the Phase III trials?

**Response:**
See response to Question 4.

**Question 6:**
Does the Agency concur with the overall statistical testing strategy?

**Response:**
For this meeting, you have submitted protocol summaries for your proposed Phase 3 trials. Additional comments may be conveyed once full protocols are submitted to the Agency.

Your proposal to use a hierarchal testing strategy to control the Type I error rate appears to be reasonable; however, there are discrepancies between Section 10.2.4 of the meeting package and the appendices (i.e., the protocol summaries) in terms of the secondary endpoints listed and the ordering of the secondary endpoints. In addition, the lists of secondary endpoints differ between the proposed trials. Secondary endpoints intended for labeling claims should be replicated in at least two trials.

Descriptive statistics describing the loss of response over time after withdrawing BI 655066 may be reasonable; (b) (4)

**Question 7:**
Does the Agency concur that Study 1311.3 and 1311.28, in addition to the supportive data from 1311.2, are adequate (b) (4)

**Response:**
You propose in Trial 1311.28 a multi-national, randomized, double-blind, double dummy, active controlled trial of BI 655066 with ustekinumab. You propose to randomize 400 subjects with moderate to severe psoriasis in a 4:1 ratio of BI 655066 and ustekinumab, respectively for a 52-week treatment period. You are proposing coprimary endpoints and efficacy timepoint that are the same as in Trial 1311.3.

Your trials are designed to make comparative efficacy claims against Stelara at Week 16. Taking into account that Stelara was approved using the primary efficacy timepoint of Week 12, you should make comparative assessments at Week 12. You may assess the efficacy of your product at multiple timepoints (i.e., Weeks 12 and 16) using a predefined sequential testing procedure.

For Trial 1311.28, the absence of a placebo arm may be reasonable given that the placebo response rate is very small and Trial 1311.3 includes a placebo arm. However, if the efficacy results differ across the two trials, then the trial without the placebo arm may raise concerns about the interpretability of study findings.

We have the same safety evaluation comments regarding Trial 1311.28 as we do for Trial 1311.3 (see response to Question 4).

(b) (4)

**Meeting Discussion:**
The sponsor proposed to include a key secondary endpoint comparing BI 655066 to Stelara on PASI 75 at Week 12 in Trials 1311.3 and 1311.28. The Agency responded that in addition to PASI 75, the sponsor should include “clear/almost clear” on sPGA at Week 12 as a secondary endpoint. The sponsor agreed to include “clear/almost clear” on sPGA at Week 12.

**Question 8:**
Does the Agency concur that if the Phase III program demonstrates clinically meaningful superiority for BI 655066 versus the Stelara® comparator based on PASI 90, (b) (4)

**Response:**
See response to Question 7.

Specific to your development program, it may be reasonable to use EU-approved ustekinumab as an active control in a superiority clinical trial (b) (4)

If you seek to use data from clinical studies comparing BI 655066 to EU-approved ustekinumab, to support a claim of superiority of BI 655066 to US-licensed Stelara, you should provide adequate data or information to scientifically justify the relevance of these comparative data and establish an acceptable scientific bridge to US-licensed Stelara. We do not agree that the information you have provided to date establishes an acceptable scientific bridge as described. With respect to your development program, the type of bridging data needed to provide adequate scientific justification for this approach would include direct, comparative physico-chemical characterization of US-licensed Stelara and EU-approved ustekinumab, and may include a bridging clinical PK study. The comparisons should meet pre-specified acceptance criteria for analytical and PK similarity, respectively.

You may submit information, including the information provided to you by Janssen, regarding EU-approved ustekinumab to justify the extent of comparative data needed to establish an adequate scientific bridge to US-licensed Stelara. The adequacy of this scientific justification and bridge would be a review issue based on the data and information provided.

(b) (4)

**Meeting Discussion:**
The sponsor asked for clarification on what additional information would be required to establish an adequate scientific bridge (b) (4) The Agency stated that it appeared that this would be adequate; however the final decision would be dependent on exactly what Janssen provides to Boehringer

Ingelheim. The sponsor asked about requesting that Janssen re-evaluate the comparability aspect of the questionnaire based on only the EU-approved ustekinumab, and the Agency stated that any comparability-related information provided by Janssen would be useful. (b) (4)

**Question 9:**
Does the Agency concur that the proposed safety database will support a BLA submission for the proposed indication?

**Response:**
The safety database that you propose of 1800 subjects exposed to BI 655066 at 150 mg dosing and of at least 1000 subjects being exposed at this dose for a year seems reasonable.

**Question 10:**
Does the Agency concur that if the data from Trials 1311.3, 1311.4, 1311.28 and 1311.30 are consistent with respect to the effectiveness of BI 655066 in patients who are anti-TNF-α experienced, (b) (6)

**Response:**
You propose Trial 1311.30 to be a multicenter, randomized, double-blind, double-dummy, placebo and active comparator (adalimumab) controlled trial evaluating the efficacy and safety of BI 655066 for 40 weeks in subjects with moderate to severe plaque psoriasis. Subjects will be randomized 1:2 with BI 655066 and adalimumab, respectively. At Week 13, subjects treated with Humira who have not reached PASI 50 will be switched to BI 655066, subjects with "incomplete response" (between PASI 50 and PASI 90) will be re-randomized to continue on Humira or switched to BI 655066. Those who achieved a PASI 90 will remain on Humira.

The regulatory utility of the proposed trial is limited. Humira was approved after 16 weeks of therapy (i.e., an initial dose of 80 mg at Week 0 followed by a dose of 40 mg every other week starting at Week 1 through Week 15) using the endpoints of PASI 75 and "clear" or "almost clear" on PGA. In your proposed trial, subjects should receive the approved dose regimen of Humira, and the comparison between your product and Humira should be done at Week 16 using the endpoints of PASI 75 and "clear" or "almost clear" on PGA. In addition, "incomplete response" should be defined as those who did not achieve "clear" or "almost clear" on PGA and PASI 75 at Week 16.

**Meeting Discussion:**
The Agency believes that safety information from this trial may be useful (b) (4) you should provide a scientific rationale as to why you would expect this subpopulation of psoriasis patients to have a different response to BI 655066 and/or why you are proposing this treatment strategy. You should also address how you will analyze the data with

regard to the potential synergistic effect of the two products. If you are able to provide a sound rationale for the conduct of this trial and the data is reviewed (b) (4)

**Question 11:**
Does the Agency agree with the overall adverse event (AE) reporting plan, specifically the plan for adjudication of Major Adverse Cardiac Events?

**Response:**
We note that you plan to adjudicate any suspected MACE events observed in the trials by an independent MACE Adjudication Committee. We would also advise the following in the monitoring and assessment of any suspected cardiovascular events:

Your cardiovascular assessment should include documentation and adjudication of thrombotic events, cerebrovascular events and Major Adverse Cardiovascular Events (MACE). Major adverse cardiovascular events include non-fatal myocardial infarction (MI), non-fatal stroke, and cardiovascular death. Extended MACE include the following events: non-fatal MI, non-fatal stroke, cardiovascular death, unstable angina documented by a hospitalization or emergency department visit, and coronary revascularization (percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery (CABG)).

Other cardiovascular events include unstable angina documented by a hospitalization, coronary revascularization, transient ischemic attack, venous and peripheral arterial vascular thrombotic events, congestive heart failure, cardiac arrhythmia – no evidence of ischemia, and other serious non-MACE cardiovascular events such as syncope of a cardiovascular origin and severe/accelerated hypertension leading to hospitalization.

1. To capture all possible MACE and thrombotic events, examine all preferred terms (PT) and Standardized MedDRA Queries (SMQs) under:
   ● Ischemic Heart Disease SMQ /Myocardial Infarction SMQ/ Other Ischemic Heart Disease SMQ)
   ● Cardiac Arrhythmias SMQ
   ● Cardiac Failure SMQ
   ● Embolic and Thrombotic Events SMQ (including Embolic and Thrombotic Events, Vessel Type Unspecified and Mixed Arterial and Venous SMQ)
   ● Shock SMQ
   ● Torsade de pointes/QT prolongation SMQ
   ● Cerebrovascular Disorders SMQ
   ● Central Nervous System Haemorrhages and Cerebrovascular Accidents SMQ
   ● Vasculitis SMQ
   ● Cardiomyopathy SMQ
   ● Hemodynamic Edema, effusions, and fluid overload SMQ
   ● Hypertension SMQ
   ● Pulmonary Hypertension SMQ
   ● Renovascular Disorders SMQ

2. Review all of the following SOCs for possible cardiac events, thrombotic and MACE, since cardiac events may be found in several SOCs:
   - Vascular Disorders
   - Cardiac Disorders
   - Nervous System Disorders
   - Respiratory, Thoracic, and Mediastinal Disorders
   - General Disorders and Administration Site Conditions
   - Injury, Poisoning, and Procedural Complications
   - Investigations
   - Musculoskeletal and Connective Tissue Disorders
   - Surgical and Medical Procedures

3. Have all possible cardiovascular events (rather than only MACE) reviewed by a DMC with expertise in cardiovascular adverse events.

4. Have all TIAs reviewed by the DMC (rather than only those resulting in hospitalization).

5. Evaluate possible thrombotic events alone and MACE alone during the uncontrolled period of the global psoriasis studies. Refer to Appendix 1 for definitions of MACE events and other cardiovascular events.

**Question 12:**
Does the Agency concur that the clinical program is adequately designed to evaluate, identify and monitor the risk for serious infections, tuberculosis (TB) and malignancies?

**Response:**
See response to Question 4 concerning safety monitoring. You should clarify how you are going to monitor for malignancy.

**Question 13:**
Does the Agency concur that the (b) (4)

**Response:**
You propose to measure both symptoms and signs of psoriasis: itch, redness, scaling, burning, cracking, stinging, flaking and pain) (b) (4)

A claim might be granted for the symptoms of itching, burning, stinging and pain as we know that these symptoms are found in a subset of psoriasis patients, are important to patients and are supported by published qualitative research[1,2]. Ultimately, granting efficacy claims will be a

[1] (b) (4)

review issue and will be based on the whether the treatment effect is clinically meaningful and statistically robust.

You did not submit a copy of the proposed instrument. Submit a copy of the proposed instrument for our review and any other relevant information from the 2009 PRO Guidance and inform us of gaps if any.

We also suggest that you propose success criteria based on the severity of symptoms which takes into account assessment of symptom severity at the baseline and during the course of the trial. The responder definition should be specified a priori using data from previously conducted clinical trials or observational studies.

If you will be conducting multinational trials, we recommend that you consider translation and cultural adaptation of the proposed instrument early on.

**Question 14:**
Does the Agency concur that (b) (4)

**Response:**
See response to Question 13.

**Question 22:**
(b) (4)

**Response:**
(b) (4)

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[2] (b) (4)


**Question 23:**
Does the Agency concur that beyond the Human Factors Studies (HFS) and analytical comparability as discussed in Question 19, no clinical studies, such as pharmacokinetic (PK) bridging are required to support registration and use of the PFS equipped with a needle safety device (NSD)?

**Response:**
Yes, we agree.

**Question 24:**
Does the Agency concur that there is no need to conduct Human Factor Studies (HFS) for the pre-filled syringe (PFS) without needle safety device (NSD)?

**Response:**
Yes, we agree.

**Administrative Comments**

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.

2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT** (SPA). Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.

3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).

4. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.

5. You are encouraged to request a Pre-BLA Meeting at the appropriate time.

**PREA REQUIREMENTS**

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

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

For additional guidance on the timing, content, and submission of the PSP, including a PSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

**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* and *PLLR Requirements for Prescribing Information* websites including:

- 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 in the PI for human drug and biological products
- 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 42 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.

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

## DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation 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. CDER has produced a 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. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.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 CDER/CBER Position on Use of SI Units for Lab Tests (http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm).

Appendix

**Major Adverse Cardiovascular Events (MACE) Events – Definitions**

Non-Fatal Myocardial Infarction:
● The presence of 2 of the 3 following criteria: a) chest pain, b) any abnormal value of cardiac biomarkers (MB fraction of creatinine phosphokinase and/or troponin), c) myocardial injury current or the development of Q waves in 2 contiguous leads of the electrocardiogram.

Non-Fatal Stroke:
● Ischemic or hemorrhagic stroke defined as an acute, focal neurologic event that persisted for > 24 hours. Confirmation by imaging studies (magnetic resonance imaging or computerized tomography of the brain) will be sought in all cases, but will not be required for adjudication of the event.

Cardiovascular death:
● Including sudden/unexplained death, or other cardiac death (arrhythmia or congestive heart failure)

**Other Cardiovascular Events (includes serious ischemic, heart failure, and arrhythmia categories that do not meet the MACE criteria) – Definitions**

Unstable Angina:
● Documented by a hospitalization or emergency department visit, not meeting the acute MI definition above, and characterized by ischemic discomfort at rest for at least 10 minutes. Corroboration with cardiac testing and/or imaging typically is required.

Coronary Revascularization:
● Defined as percutaneous coronary intervention (PCI) or coronary artery bypass graft surgery

Transient Ischemic Attack:
● Documented by a hospitalization or emergency department visit, not meeting the stroke definition above, and characterized by focal, transient (< 24 hours) neurological signs and symptoms

Venous and Peripheral Arterial Vascular Thrombotic Events:
● Defined as evidence of deep venous thrombosis of the lower extremities or pelvis, pulmonary embolism, peripheral arterial embolism and/or occlusion, peripheral artery revascularization, including carotid endarterectomy.

Congestive Heart Failure:
● Defined as hospitalization due to dyspnea, shortness of breath, and/or edema accompanied by auscultator findings of pulmonary vascular congestion.

Treatment of the heart failure with conventional parenteral therapy is required. Radiographic and/or echocardiographic documentation is typically required

Cardiac Arrhythmia, no evidence of ischemia:
● Defined as atrial arrhythmias (atrial fibrillation, supraventricular tachycardias), ventricular arrhythmias (ventricular tachycardia (inclusive of torsades de pointe) or ventricular fibrillation), and high grade atrioventricular block (2nd degree Mobitz II or 3rd degree)

Other Serious Non-MACE Cardiovascular Events:
● Include syncope of a cardiovascular origin and severe/accelerated hypertension leading to hospitalization

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/s/

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KENDALL A MARCUS
07/08/2015