CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211675Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

IND 114717

MEETING MINUTES

AbbVie Inc.
1 N. Waukegan Road
Dept. PA77/Bldg. AP30-4
North Chicago, IL 60064

Attention: Juliana Correa Leite
Director, Regulatory Affairs

Dear Ms. Leite:

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

We also refer to the meeting between representatives of your firm and the FDA on May 1, 2018. The purpose of the meeting was to discuss the planned submission of the New Drug Application (NDA) for upadacitinib for the indication of rheumatoid arthritis.

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 me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Phuong Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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: Pre-NDA

Meeting Date and Time: May 1, 2018, 9:30 - 10:30 AM
Meeting Location: White Oak Building 22, Conference Room 1309

Application Number: IND 114717
Product Name: Upadacitinib

Indication: Rheumatoid arthritis
Sponsor Name: AbbVie Inc.

Meeting Chair: Sally Seymour, MD
Meeting Recorder: Nina Ton, PharmD

FDA ATTENDEES

Mary Thanh Hai, MD, Acting Director, Office of Drug Evaluation II (ODEII)
Sally Seymour, MD, Acting Division Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Nikolay Nikolov, MD, Associate Director for Rheumatology, DPARP
Rachel Glaser, MD, Acting Clinical Team Leader, DPARP
Nadia Habal, MD, Clinical Reviewer, DPARP
Andrew Goodwin, PhD, Acting Pharmacology/Toxicology Supervisor, DPARP
Brett Jones, PhD, Pharmacology/Toxicology Reviewer, DPARP
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Robert Abugov, PhD, Acting Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
William Koh, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Rajesh Savkur, PhD, Reviewer, Biopharmaceutics Branch I, Division of Biopharmaceutics, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Teresa McMillan, PharmD, Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA), Office of Surveillance and Epidemiology (OSE)
Laura Zendel, PharmD, Risk Management Analyst, Division of Risk Management, OSE
Michael Sinks, PharmD, Safety Regulatory Project Manager, OSE
Brittani Tran, Student, Temple University School of Pharmacy
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES
Steve Pulaski, MS, MBA, Group Project Leader, Immunology Clinical Development
Aileen Pangan, MD, Executive Medical Director, Immunology Clinical Development
Jose Jeffrey Enejosa, MD, Senior Medical Director, Immunology Clinical Development
Heidi Camp, PhD, Senior Scientific Director, Immunology Clinical Development
Yijie Zhou, PhD, Associate Director, Statistics
Lu Cui, PhD, Senior Director, Statistics
Barbara Hendrickson, MD, Therapeutic Area Head, Medical Safety and Evaluation Pharmacovigilance and Patient Safety
Nasser Khan, MD, Senior Medical Director, Medical Safety and Evaluation Pharmacovigilance and Patient Safety
Mohamed-Eslam Mohamed, PhD, Assistant Director, Clinical Pharmacology and Pharmacometrics
James Echlin, RPh, Director, Regulatory Affairs, Global Product Strategy
Juliana Correa Leite, PharmD, Director, Regulatory Affairs, Area & Affiliate, US and Canada
Kelly Norton, PhD, Director, Regulatory Affairs, Chemistry, Manufacturing & Controls
Gerard Heneghan, PhD, Director, Chemistry, Manufacturing & Controls Development

1. BACKGROUND

AbbVie submitted a meeting request dated January 19, 2018, to the Division of Pulmonary, Allergy, and Rheumatology Products, and the Division granted the meeting on February 1, 2018. The purpose of the meeting was to discuss the planned submission of the NDA for upadacitinib for the indication of rheumatoid arthritis. The Division provided preliminary comments to AbbVie's questions in the briefing package via electronic correspondence dated April 27, 2018. Juliana Correa Leite, AbbVie's Director, Regulatory Affairs, communicated to the Division via email dated April 30, 2018, that AbbVie requested to discuss Question 4.1, 4.3b and Additional Comment, Question 6c, Question 7 and ISS SAP follow-up questions, Question 12, and Question 13. AbbVie also provided clarification questions and responses to the FDA's preliminary comments which are incorporated under the corresponding FDA response. The Sponsor's questions from the briefing package submitted on March 29, 2018, responses, and clarification questions are provided below in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

Question 1
Does the Agency agree that the nonclinical study program is adequate to support the NDA in the proposed indication?

FDA Response
The nonclinical program appears adequate to support the filing of the proposed NDA.

Rheumatoid arthritis is considered a chronic indication. Therefore, our safety assessment at the time of the NDA review will be based on an acceptable daily intake of (b) (4) ug per day for mutagenic or potentially mutagenic impurities. We may have additional comments or requests

for information following review of your submissions dated June 29, 2017, and February 6, 2018.

Meeting Discussion
This question was not discussed.

Question 2
Does the Agency agree that the clinical pharmacology package is adequate to support the NDA in the proposed indication?

FDA Response
The clinical pharmacology information is adequate to support the filing of the NDA. The adequacy of the information will be a review issue.

Meeting Discussion
This question was not discussed.

Question 3
Does the Agency agree with AbbVie's plan to use the (b) (4) *specification limit for the* (b) (4) *dissolution time points for upadacitinib extended-release tablets and the plan to support these specifications using exposure-response analyses?*

FDA Response
Your approach seems reasonable. Based on the exposure-response analysis from your phase 2 study, a formulation with (b) (4) dissolution profile (b) (4) is not predicted to result in a meaningful difference in efficacy or effects on changes compared to the phase 3 formulation. We agree with your plan to use the (b) (4) specification limit for the (b) (4) (b) (4) dissolution time points for your extended-release tablets, and the plan to support these specifications during exposure-response analysis.

Note that the final determination on the acceptability of the dissolution method is a review issue. However, the acceptability of the proposed dissolution acceptance criteria for your product is based upon the review of the data from the phase 3 study, and the totality of the dissolution data.

Meeting Discussion
This question was not discussed.

Question 4
Does the Agency agree that the planned safety and efficacy data package from the upadacitinib clinical program (Phase 2 Studies M13-537, M13-550 and M13-538, plus Phase 3 studies in csDMARD-IR subjects [Study M13-549], MTX-IR subjects [Studies M14-465 and M15-555], bDMARD-IR subjects [Study M13-542)], and MTX-naïve subjects [Study M13-545]) are sufficient to support the planned NDA for the proposed indication?

FDA Response
The planned safety/efficacy data package as described above appear sufficient to support filing of an NDA; whether the data will support the proposed indication will be a review issue. We remind you of the information requested in our review of your SAP as outlined below:

1. For each study M13-542, M13-549, M14-465, M15-555, and M13-545, include all programs and macros, in individual text files, used to generate efficacy, disposition and safety results reported in the CSR.

Meeting Discussion
AbbVie clarified that tipping point analyses will be provided in the NDA submission including key secondary analyses. FDA stated that AbbVie's proposal to submit all programs and macros, as individual text files, used to generate efficacy, disposition, safety, as well as tipping point analyses, was reasonable.

2. We note that you plan to include monotherapy study M13-545 as part of the data package to support the planned NDA. This study was not previously discussed in any of the earlier communications, including the Type C Written Response Only dated June 22, 2017, and was only included during the ISE and ISS submitted in December 15, 2017.

   The finalized SAP for this study was recently received on April 17, 2018. There was no earlier version of the SAP submitted for review. Whether the SAP provides appropriate statistical analyses will be a review issue.

Meeting Discussion
This topic was not discussed.

3. Your revised SAP for M13-542, M13-549, M14-465, and M15-555 continue to omit prospectively planned tipping point analyses to evaluate the impact of missing data on your study results. You stated however in Appendix G, pp 410-411, post-hoc exploratory analysis will be included.

   a. Include the procedure, with full documentation of the approach, for these post-hoc exploratory analysis in your submission.

   b. Include also the programs and macros, in individual text files, used to generate all the exploratory analysis with appropriate documentation. Include any datasets that were generated from the multiple imputation procedure.

Meeting Discussion
AbbVie reasoned that computed datasets do not need to be submitted since they can be reproduced with planned provision of random number seeds and the submitted SAS scripts. FDA agreed that this proposal is acceptable if the datasets can be reproduced from this information.

4. Include all data monitoring committee charters, meeting minutes (both closed and open), and the cardiovascular adjudication committee charters for studies M13-542, M13-549, M14-465, M15-555, and M13-545 in your NDA submission.

Meeting Discussion
This topic was not discussed.

Additional Comment
To further support your NDA, submit a justification for the dose selection and thorough analyses of dose- and exposure-response for both efficacy and safety, including laboratory parameters.

AbbVie Response
In reference to the FDA's additional comment under question 4, further clarification of exposure-response analyses planned to be included in the submission in support of upadacitinib dose(s) is provided below.

1) Exposure-Response Analyses Conducted to Support the Selection of Phase 3 Doses in RA

Data from the Phase 2 studies in subjects with RA (M13-537 and M13-550) were used to conduct exposure-response analyses for upadacitinib efficacy and effects on laboratory parameters in subjects with RA to support the selection of doses to evaluate in Phase 3. The report describing these analyses will be included in the NDA submission.

Efficacy

- *Exposure-response analyses were conducted which characterized the relationship between upadacitinib plasma exposures and the percentage of subjects achieving ACR20, ACR50, or ACR70 responses. Exposure-response analyses were conducted utilizing data from the full time course of ACR20/50/70 responses in Markov chain analysis.*

Effects on Laboratory Parameters

Logistic regression analyses were conducted which evaluated the relationship between upadacitinib plasma exposures and changes from baseline in hemoglobin, LDL, HDL, NK cells, neutrophils, and CPK at Week 12.

2) Exposure-Response Analyses to Support Upadacitinib Proposed To Be Marketed Dose(s)

AbbVie is planning to conduct exposure-response analyses for efficacy, safety, and changes in laboratory parameters using a combined dataset for Phase 2 and 3 studies in subjects with RA to support justification of the proposed marketed dose(s). Summary of the planned exposure-response analyses is provided.

Efficacy:

Exposure-Response analyses will be conducted for the following efficacy endpoints:

- *The percentage of subjects who achieved ACR20, ACR50, or ACR70*
- *The percentage of subjects who achieved low disease activity or clinical remission (based on DAS28-CRP)*

Safety and Effects on Laboratory Parameters:

The relationship between upadacitinib plasma exposures and the percentage of subjects who experienced each of following endpoints for safety and changes in laboratory parameters at Week 12 will be evaluated:

- *> 2 g/dL decrease in hemoglobin from baseline*
- *> 2 g/dL decrease in hemoglobin from baseline and hemoglobin less than the lower limit for normal*
- *Hemoglobin < 8 g/dL*
- *Absolute lymphocyte count < 1000 /µL*
- *Absolute lymphocyte count < 500 /µL*
- *Absolute neutrophils count < 1000 /µL*
- *Platelets ≥ 600,000 /µL in subjects with ≤ 400,000/µL at baseline*
- *Platelets > 400,000 /µL in subjects with ≤ 400,000/µL at baseline*
- *Herpes Zoster infection (anytime during the 12-week period)*
- *Pneumonia (anytime during the 12-week period)*
- *Serious infections (anytime during the 12-week period)*

In addition, comparison of upadacitinib plasma exposure will be conducted between subjects who experienced and who did not experience VTE or MACE (including available data beyond week 12).

Does the agency agree that the analyses described are sufficient to justify upadacitinib dose(s) and to support of the NDA filing?

Meeting Discussion

AbbVie provided an overview of the 5 studies as presented in the attached slides. The sponsor noted that 4 out of 5 studies have been unblinded and similar efficacy was found between 15 and 30 mg doses, except for the monotherapy study, in which the 30 mg dose showed better efficacy than the 15 mg dose. AbbVie plans to determine the proposed treatment dose after the final study is unblinded. FDA commented that this approach is reasonable but advised AbbVie to provide justification of the efficacy and safety for the dose(s) selected. The justification should include an assessment of safety including adverse events, as well as changes in laboratory parameters.

Question 5
Does the Agency agree that the proposed number of subjects exposed to upadacitinib and the duration of exposure in Phase 2 and Phase 3 studies are adequate to support a NDA filing, regardless of whether only 15 mg or both 15 mg and 30 mg are proposed for approval? Does the Agency agree that the extent of long-term safety exposure to the active comparator adalimumab is sufficient to support a NDA filing?

FDA Response
The extent of exposure appears reasonable to support NDA filing.

Meeting Discussion
This question was not discussed.

Question 6
Does the Agency agree with the proposed cardiovascular event definitions and planned analyses, including thromboembolic events?

FDA Response
You plan to summarize the following cardiovascular and thromboembolic events as adverse events of special interest:

- Major adverse cardiac events (MACE) defined as cardiovascular death, non-fatal myocardial infarction, and nonfatal stroke
- Undetermined/unknown cause of deaths
- Other adjudicated cardiovascular events
- Venous thromboembolic events (VTE), specified as deep vein thrombosis (DVT) and pulmonary embolism (PE)
- Other venous thrombotic events
- Arterial thromboembolic events (non-cardiac, non-neurologic)

Your plan is acceptable. We remind you of the Agency comments provided on April 5, 2018:

a. We recommend that you include an independent adjudication committee to evaluate all thrombosis events, regardless of drug relatedness, in your RA program (including phase 2 and phase 3 studies). All these events, including events that may have occurred after discontinuation of study drug during the safety follow-up, should be reported in the safety summary. Include details and investigate any potential adverse events that are related to the thrombosis events. In addition, include clear documentation and a procedure as to how these potential adverse events were identified.

b. We note that you have a Cardiovascular Adjudication Committee in your studies to assess for potential cardiovascular events. Submit the Charter for review during NDA submission and include the cases identified as potential cardiovascular events during review.

c. To facilitate planning of your safety report, we strongly recommend that the following adverse events be presented in the summary report for each study as well as the proposed integrated safety analyses:

i. Deaths
ii. Serious Adverse Events
iii. AEs leading to discontinuation
iv. AESI (including infections, serious infections, opportunistic infections, TB, malignancy, thrombosis (venous and arterial), and any additional events your safety team has identified as a potential signal.

Meeting Discussion

AbbVie discussed the safety and efficacy data to be included in the NDA submission as summarized on slide 9 of the attached slides. The sponsor noted that each study has its own extension but varies in cutoff date; patients who reach the cutoff points will be included in the initial submission and ISS/ISE, as indicated on slide 9. The sponsor added that long-term safety data with narratives will be provided in ISS in Module 5. AbbVie estimated that the safety database on submission will include 1000 patients exposed to upadacitinib 15 mg and 700 patients exposed to upadacitinib 30 mg for one year. FDA commented that the total exposure is reasonable but asked whether safety data for Study M13-545 through Week 48 would be submitted. AbbVie responded that available data for this study is through Week 24 but not all the randomized patients from M13-545 would have complete Week 48 safety data. FDA raised concerns about the assessment of rare events without adequate long term data and controlled comparisons, particularly for events that are not dose dependent or that have long latency. AbbVie replied that the Week 48 data from Study 13-545 would be included in the safety update. The sponsor further clarified that the ISS will specify the number of AEs included in the CSRs in the initial submission, the number of additional AEs reported after the cutoff date for the CSRs, and will also indicate in which studies the AEs were reported.

Post-meeting Comment

The Division's recommendation is to include the 48 week data from Study M13-545 in the original NDA submission. Given the safety issues associated with JAK inhibitors, the complexity of the safety analyses, and the potential for an advisory committee (AC) meeting, it would be important to have the complete 48 week safety database at the time of NDA submission.

Question 7

Does the Agency recommend any further analyses of other AESIs?

FDA Response

We refer you to the Agency comments provided on April 5, 2018, for recommended analyses of AESI.

AbbVie Clarification Questions

ISS SAP Feedback April 5th 2018 - Clarification Questions

1. *We take the suggestion (comment e ii) and will rename the "* (b) (4) *Upadacitinib 15 mg QD" treatment group to be "Upadacitinib 15 mg QD (no ADA cross-over)". Please note the subjects included in this treatment group do not change. Please confirm this addresses the comment e ii.*

2. *There is no planned comparison of upadacitinib versus a control in the long-term integrated safety summary, and therefore we proposed "Any Phase 3 Upadacitinib 15 mg and 30 mg" and "Any Phase 3 Upadacitinib 15 mg" long-term analysis sets to integrate across all Phase 3 trials. Please help us understand the rationale of the additional separate long-term integrated safety analyses for the pbo-controlled studies (M13-542 & M13-549, Table 4) and MTX-controlled studies (M13-545 & M15-555, Table 6).*

   2.1 To account for within subject correlation between outcomes, Abbvie plans to utilize a mixed effect Poisson regression model with treatment as a fixed effect and subject as a random effect, with exposure as offset variable. Does the agency agree with proposed model?

3. *We plan to conduct the long-term integrated safety summary with all accumulated data. Please help us understand the rationale of additionally restricting it to 0-52 weeks.*

4. *Our interpretation of the suggested analysis of "unadjusted cumulative incidence rate" is the raw proportion of subjects with an event. For the "exposure adjusted incidence rates", the number of subjects with an event is used as the numerator and the total exposure is used as the denominator. Please confirm our interpretation is correct.*

5. *An integrated 3-month safety summary of M15-555 and M13-545 will be performed as FDA suggested in Table 5. However, we believe it is challenging to interpret a 6-month integrated safety due to differences in study design. M15-555 has a 3-month controlled period and M13-545 has a 6-month controlled period, which will be reported separately. Does the Agency agree?*

Safety Assessment – Clarification Questions

6. *Does FDA consider multidermatomal herpes zoster as more than one dermatome involvement OR involvement beyond 2 adjacent dermatomes?*

7. *The AbbVie Opportunistic Infection CMQ which is being proposed to identify opportunistic infections in the program does not contain localized forms of fungal infection commonly reported in immunocompetent individuals (such as acute pulmonary histoplasmosis and vaginal candidiasis) – is that acceptable to FDA?*

Meeting Discussion

FDA agreed that AbbVie's suggestion as noted in clarification question 1 was reasonable.

AbbVie planned to integrate across all phase 3 studies for long-term integrated safety analyses as indicated in clarification question 2. AbbVie asked FDA to clarify the rationale for the separate long-term integrated safety analyses for the placebo-controlled studies and methotrexate-controlled (active-controlled) studies. Given the multiple cross-overs between treatment groups, FDA expressed concerns regarding the specific objectives of the proposed "Any Phase 3 Upadacitinib 15 mg and 30 mg" and "Any Phase 3 Upadacitinib 15 mg" analyses. As an example, FDA referred to Table 4 in the comments provided to AbbVie on April 5, 2018. In that Table, FDA clarified that integrating studies M13-542 and M13-549 using only 12-14 week data would address the objective of comparing AE rates for doses of upadacitinib relative to placebo during the placebo controlled period. Using Table 4, the 52-week integrated safety analyses only included upadacitinib doses. In the absence of a concurrent placebo or MTX only arm in the 52 week analysis, FDA clarified that the 52-week or long term analysis can only be used to compare the AE rates between 15 mg upadacitinib and 30 mg upadacitinib if the integrated studies both include the 15 mg and 30 mg dose of upadacitinib.

AbbVie asked for clarification on the use of mixed effect Poisson regression model to account for within subject correlation between outcomes. FDA stated the choice of the analysis to account for correlation would depend on the objective of the comparison, the summary measure, and the comparators. FDA pointed out that the current ISS SAP has limited description of objectives of the different analyses sets, the summary measure to describe the event rates, and the metric used to compare upadacitinib with placebo or methotrexate during the controlled period. The revised ISS should address these concerns.

AbbVie asked FDA in clarification question 3 for the rationale of restricting the data to 52 weeks since the sponsor has data beyond this time period. FDA responded that it would be helpful to look at safety data from baseline through Week 48 or 52, depending on study designs, to understand if AE rates change over cumulative time periods and whether there are differences in AE rates between doses. FDA agreed that the proposed long-term safety analysis is a reasonable way to look at safety rates over a longer time period. AbbVie proposed a by time-interval analysis (e.g, 0-6 months, 6-12 months) to address the Agency's concerns on AE rates changing over time periods. FDA agreed with the sponsor's proposal but also requested a cumulative time period approach and that AbbVie include Kaplan Meier curves to describe incidence rates for key AESI.

FDA confirmed that AbbVie's interpretation for clarification question 4 was correct, but requested further detail regarding the definition of 'total exposure.' AbbVie replied that total exposure would be calculated as the sum of all patient time on study drug, regardless of occurrence of adverse events. FDA responded that this definition would not be appropriate for analyses of rate of first incidence or time to first incidence, since the data for this measure is effectively censored after first incident; in general, 'exposure' should reflect time at risk for an event, and time on study drug regardless of occurrence of events would only be appropriate for an analysis of recurrent rates where patients on study drug remain at risk after the first event. FDA advised AbbVie to carefully consider the foregoing when defining safety analyses, detailing the objectives, statistical tests, and exposure times in the ISS SAP, including, for example: scenarios in which a subject does or does not have an AE, how data will be handled when patients discontinue study or study drug, and whether recurrent events will be analyzed. Appropriate exposure times should be provided in the analysis datasets for each patient and each named adverse event, according to the analysis planned.

FDA advised AbbVie to provide a revised ISS SAP addressing comments issued on April 5, 2018. FDA will attempt to provide additional feedback as resources permit.

In response to clarification question 6, FDA clarified that while there is no regulatory definition for multidermatomal herpes zoster, the Agency would take a conservative approach to ensure all events are captured and define multidermatomal herpes zoster as involvement of two or more dermatomes.

In response to clarification question 7, FDA asked AbbVie to provide a list of preferred terms in the AbbVie Opportunistic Infection CMQ. Additionally, FDA asked whether tuberculosis (TB) is captured separately from opportunistic infections and AbbVie confirmed that it is. AbbVie also confirmed that there is a separate CMQ for herpes zoster. The sponsor agreed to include the preferred terms in the CMQs in the dossier.

FDA also noted that there have been cases of thrombotic events and asked how these events will be captured and reported. AbbVie commented that all cases in phase 3 studies will be adjudicated, and cases in phase 2 studies will be respectively adjudicated.

Post-meeting Comment
Regarding calculation of adverse event rates, we further refer you to https://www.phuse.eu/documents/working-groups/cs-whitepaper-adverseevents-v10-4442.pdf. We also recommend that, for each proposed analysis, you include diagrams for the time at risk to be used for different scenarios, e.g., patients who experience an event during the 12/14 week period vs after they cross-over. In addition, you should document how many events occurred after patients discontinued study treatment during follow-up.

Question 8
Does the Agency agree that the planned content of the NDA, as displayed in the table of contents, is adequate to be considered a complete application?

FDA Response
The planned content of the NDA appears reasonable. A determination of whether the NDA is complete to allow for adequate review will be made after receipt of the application.

Meeting Discussion
This question was not discussed.

Question 9
Does the Agency agree with the proposed location of the patient profiles within the CSR structure?

FDA Response
The location of the patient profiles within the CSR structure is acceptable.

Meeting Discussion
This question was not discussed.

Question 10
Does the Agency agree with the proposed plan for the 4-Month Safety Update?

FDA Response
Your proposed plan appears reasonable.

Meeting Discussion
This question was not discussed.

Question 11
Does the Agency agree that the Agreed Initial Pediatric Study Plan (iPSP) would fulfill the Pediatric Research Equity Act (PREA) requirements for this NDA?

FDA Response
Your proposed pediatric study plan appears reasonable. Final determination on the requested waivers and deferrals will be made during the review of your NDA. See Section 3 regarding PREA REQUIREMENTS.

Meeting Discussion
This question was not discussed.

Question 12
Does the Agency have any additional advice given that Abbvie is considering the use of a Priority Review Voucher for this NDA?

FDA Response
Use of the priority review voucher is at your discretion. However, we note that upadacitinib is a new molecular entity with a complicated clinical program and based on prior experience with similar programs, we have found these applications to be quite complex. As such, reviews of such complex programs typically generate additional information requests during the review period, which raise the possibility of extending the review timeline. Also, refer to the FDA's response to Question 13 on the expectation for an advisory committee meeting which will also need to be accounted for in the review timeline. We remind you that in the case that you decide to use your priority review voucher, your safety update would also be required earlier (i.e. at 90 days).

To facilitate our review, we request that the final study reports for the remaining nonclinical studies (e.g., carcinogenicity, PPND) be submitted to the IND as they become available.

Meeting Discussion
AbbVie asked FDA to clarify the possibility of a review timeline extension. FDA noted that this drug is a new molecular entity with 5 phase 3 studies which will likely be a complex review because of the complexity of the program design. In addition, there are concerns with the safety analysis because of the limited controlled data and cross-over between 2 arms. Additional information may be needed during the review. Whether such additional

information would be considered a major amendment under 21CFR314.60 would be determined during the review cycle.

Question 13
Based on the information provided in the briefing book, does the Agency foresee an advisory committee meeting will be necessary for upadacitinib?

FDA Response
Upadacitinib is a new molecular entity; therefore, we anticipate it would be the subject of an advisory committee meeting.

Meeting Discussion
AbbVie noted that upadacitinib is not the first drug in its class and inquired whether a JAK inhibitor would require an AC meeting. FDA responded that there are safety concerns associated with JAK inhibitors. Upadacitinib is a new molecular entity and it is unknown at this time if there are any new safety signals associated with its use. If new safety issues are identified, an AC meeting may be warranted. The determination on the need for an AC will be made after submission of the NDA.

Question 14
Does the Agency agree with the proposed list of covered studies for submission of financial disclosure information?

FDA Response
The following 5 pivotal phase 3 studies are proposed as the "covered clinical studies" for submission of financial disclosure information for the NDA:

- Study M13-542
- Study M13-549
- Study M13-545
- Study M14-465
- Study M15-555

This proposed list is acceptable.

Meeting Discussion
This question was not discussed.

Question 15
Does the Agency have any comments on the draft mock-ups?

FDA Response
From the quality perspective, we have no comments at this time. A complete evaluation of all labels and labeling will be done during the review of the application.

Meeting Discussion
This question was not discussed.

Question 16
Does the Agency agree with the executed batch records proposed to be submitted with the NDA?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

Question 17
Does the Agency agree with only including the cross references to the Other Applications, including DMFs, in Section 1.4.4 Cross Reference to Other Applications with no DMF references presented in Module 3?

FDA Response
No, we do not agree. Place letters of authorization to applicable DMFs in module 1 and reference these DMFs in the pertinent sections of module 3 (e.g., reference applicable packaging DMFs in P.7; reference non-compendial excipient DMFs in P.4). Inclusion of appropriate cross-references will make evaluation of your application easier for the reviewers.

Meeting Discussion
This question was not discussed.

Question 18
Does the FDA agree that the Subject Level Data by Clinical Site for the 5 pivotal Phase 3 studies (Studies M13-549, M14-465, M15-555, M13-542 and M13-545) are sufficient for the Agency's purposes of site inspection selection?

FDA Response
Yes, we agree.

Meeting Discussion
This question was not discussed.

3. ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our February 1, 2018, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and

mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm.

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.

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* (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.

MANUFACTURING FACILITIES

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

where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

Please refer to the draft Guidance for Industry Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

4. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items that were identified during the meeting.

6. ATTACHMENTS AND HANDOUTS
A copy of presented slides is attached.

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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.

/s/

PHUONG N TON
05/31/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 114717

MEETING MINUTES

AbbVie Inc.
1 N. Waukegan Road
Dept. PA77/Bldg. A30-1
North Chicago, IL 60064

Attention: Meg Drew, MPH
Director, Regulatory Affairs

Dear Ms. Drew:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ABT-494.

We also refer to the meeting between representatives of your firm and the FDA on October 26, 2015. The purpose of the meeting was to discuss the proposed phase 3 development program for ABT-494, a small molecule selective JAK1 inhibitor, for the treatment of rheumatoid arthritis.

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 me at (301) 796-1648.

Sincerely,

{See appended electronic signature page}

Nina Ton, PharmD
Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
Office of Drug Evaluation II
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: October 26, 2015; 9:00 – 10:00 AM EST
Meeting Location: White Oak Building 22, Conference Room 1315

Application Number: IND 114717
Product Name: ABT-494
Indication: Rheumatoid Arthritis
Sponsor Name: AbbVie Inc.

Meeting Chair: Badrul A. Chowdhury
Meeting Recorder: Nina Ton

FDA ATTENDEES

Badrul A. Chowdhury, MD, PhD, Director, Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Sarah Yim, MD, Supervisory Associate Director, DPARP
Nikolay Nikolov, MD, Clinical Team Leader, DPARP
Keith Hull, MD, PhD, Clinical Reviewer, DPARP
Timothy Robison, PhD, Pharmacology/Toxicology Supervisor, DPARP
Brett Jones, PhD, Pharmacology/Toxicology Reviewer, DPARP
Ping Ji, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Jianmeng Chen, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Craig Bertha, PhD, CMC Lead, Division of New Drug Products II Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Gregory Levin, PhD, Biostatistics Team Leader, Division of Biometrics II, Office of Biostatistics (OB)
Yongman Kim, PhD, Biostatistics Reviewer, Division of Biometrics II, OB
Nina Ton, PharmD, Senior Regulatory Project Manager, DPARP

SPONSOR ATTENDEES

Heidi Camp, PhD, Scientific Director, Immunology Clinical Development, Research and Development
Meg Drew, MPH, Director, Regulatory Affairs, Area and Affiliate Strategy, US/Canada
James Echlin, RPH, Director, Regulatory Affairs, Global Product Strategy

Alan Friedman, MD, Medical Director, Immunology Clinical Development, Research and Development
Ahmed Othman, PhD, Director, Clinical Pharmacology and Pharmacometrics, Research and Development
Nasser Khan, MD, Senior Medical Director Medical Safety and Evaluation, Pharmacovigilance and Patient Safety
John Medich, MD, VP, Humira Development, Research and Development
Steve Pulaski, MS, MBA, Senior Project Leader, JAK Program, Research and Development
Aileen Pangan, MD, Group Medical Director, Immunology Clinical Development, Research and Development
Andrew Storey, BSc, Vice President, US and Canada Regulatory Affairs
Li Wang, PhD, Assistant Director, Statistics, Data and Statistical Sciences
Yijie Zhou, PhD, Assistant Director, Statistics, Data and Statistical Sciences
Troy ZumBrunnen, PharmD, Senior Director, Regulatory Affairs, US and Canada Regulatory Affairs

1. BACKGROUND

AbbVie submitted a Type B meeting request dated August 28, 2015, to the Division of Pulmonary, Allergy, and Rheumatology Products to discuss the proposed phase 3 development program for ABT-494, a small molecule selective JAK1 inhibitor, for the treatment of rheumatoid arthritis. Upon review of the meeting package, the Division provided preliminary comments to the Sponsor's questions via electronic correspondence on October 22, 2015. Troy ZumBrunnen, AbbVie's Senior Director, communicated to the Division via email dated October 23, 2015, that the Sponsor requested to focus the meeting discussion to Questions 6, 7a/b, 15, 19, 21, 23 and 25. In addition, AbbVie provided clarification for Question 10 and this question was also discussed. AbbVie's questions and clarification are in *italics*, FDA's responses are in normal font, and the meeting discussion is in **bold**.

2. DISCUSSION

NONCLINICAL

Question 1
Does the Agency agree that the nonclinical development program is adequate to support Initiation of the Phase 3 studies and planned NDA submission?

FDA Response
We agree that the nonclinical development program is adequate to support the proposed phase 3 clinical trials. At this time, it is premature to comment on the adequacy of the nonclinical development program for a planned NDA submission.

Meeting Discussion
This question was not discussed.

Question 2
Does the Agency agree with AbbVie that no further studies are required at this time to assess the abuse potential or potential for driving impairment for ABT-494?

FDA Response
At this time, there is insufficient information to answer this question. Provide your rationale for proposing this question. If there are concerns with abuse potential or potential for driving impairment for ABT-494, we recommend that you assess them in the proposed phase 3 clinical development.

Meeting Discussion
This question was not discussed.

CLINICAL PHARMACOLOGY

Question 3
Does the Agency agree that the clinical pharmacology program as described below is adequate to support the initiation of the Phase 3 studies and planned NDA submission?

FDA Response
Yes, we agree that the completed and planned clinical pharmacology studies described in the meeting package appear to be adequate to support the initiation of the phase 3 studies. We acknowledge that you plan to enroll patients with hepatic or/and renal impairment in phase 3 studies. Before you recruit those patients, we recommend that you finish the dedicated PK studies in renal impairment and hepatic impairment patients. Based on the results of these studies, you may consider dose adjustment as necessary in these patients in phase 3 studies.

Additional Comments
In the proposed single dose relative bioavailability study (first study in Table 3), bridging the proposed phase 3 extended-release (ER) tablet formulation to the phase 2 capsule formulation, the least common interval should be used in formulation bridging, i.e., a single dose of 15 mg ABT-494 ER tablet versus two doses of 6 mg capsules (morning and evening), and a single dose of 30 mg ABT-494 ER tablet versus two doses of 12 mg capsules (morning and evening). Refer to the guidance for industry "*Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs "*,
(http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm389370.pdf).

Meeting Discussion
This question was not discussed.

Question 4
Given that the dose-response and concentration-response analyses of the QTc data from the Phase 1 single and multiple ascending dose studies of ABT-494 did not demonstrate a potential effect of ABT-494 on the QT interval, AbbVie does not plan to conduct a thorough QT study for ABT-494. Does the Agency agree that a thorough QT study is not warranted for ABT-494?

FDA Response

We consider a well-designed and conducted early QTc assessment based on concentration-QTc analysis may be an alternative approach to a TQT study. The adequacy of the early QTc assessment will depend on the trial design (e.g., number of subjects tested, the tested supratherapeutic exposure compared to the potential maximum therapeutic exposure, the PK/ECG collection, etc.), the ECG quality, the concentration-QTc relationship, etc. It seems that you might already have adequate information from the early phase assessment. Submit the following items for review:

a. Copies of the study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed

b. Electronic copy of the study report

c. Electronic or hard copy of the clinical protocol

d. Electronic or hard copy of the Investigator's Brochure

e. Annotated CRF

f. A data definition file which describes the contents of the electronic data sets

g. Electronic data sets as SAS.xpt transport files (in CDISC SDTM format ,if available) and all the SAS codes used for the primary statistical and exposure-response analyses

h. In the ECG raw data set, include the following information: subject ID, treatment, period, ECG date, ECG time (up to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (any corrected QT as points in your report, e.g. QTcB, QTcF, QTcI, etc., if there is a specifically calculated adjusting/slope factor, include the adjusting/slope factor for QTcI, QTcN, etc.), Lead, and ECG ID (link to waveform files if applicable)

i. Data set whose QT/QTc values are the average of the above replicates at each nominal time point

j. Narrative summaries and case report forms for any
   i. Deaths
   ii. Serious adverse events
   iii. Episodes of ventricular tachycardia or fibrillation
   iv. Episodes of syncope
   v. Episodes of seizure
   vi. Adverse events resulting in the subject discontinuing from the study

k. ECG waveforms to the ECG warehouse (www.ecgwarehouse.com). If you use Holter recording and select 10-second segments to measure, submit either the entire Holter recording or at least the entire analysis windows.

l. A completed Highlights of Clinical Pharmacology Table

Advancing in this field –and possibly reducing the burden of conducting QT studies depends critically upon obtaining the most comprehensive understanding of existing data. Consider making your data, at least placebo and positive control data, available for further research purposes; we refer you for examples in the Data Request Letter at www.cardiacsafety.org/library.

Meeting Discussion
This question was not discussed.

DOSE SELECTION

Question 5
Considering the Phase 2 results and the dose selection rationale, does the Agency agree with the proposed doses of ABT-494 to be studied in Phase 3?

FDA Response
We cannot agree with your proposed ABT-494 dose selection at this time due to insufficient data. Addressing this question will depend on the results of your proposed phase 1 study investigating the comparability between the capsule formulation used for BID dosing in your phase 2 clinical studies and the proposed tablet formulation to be used as daily dosing in your phase 3 studies. However, based on the results from your phase 2 studies, the 6 mg capsule BID and 12 mg capsule BID doses appear to be a reasonable goal to base future development.

Meeting Discussion
This question was not discussed.

LABELING

Question 6
Does the Agency agree that the proposed Study M15-555 is adequate to support a label claim for use of ABT-494 as monotherapy?

FDA Response
Note that a dedicated monotherapy study may not be necessary to support the efficacy of ABT-494 as a monotherapy, as long as this population is included elsewhere in the clinical development.

As currently proposed, Study M15-555, may demonstrate the efficacy of ABT-494 in rheumatoid arthritis subjects who are MTX-inadequate responders. (b) (4)

(b) (4)

Meeting Discussion

AbbVie discussed (b) (4) **Thus, the Sponsor proposed to extend Study M15-555 from 12 weeks to 14 weeks. FDA asked AbbVie for the objective of this study and the Sponsor responded the objective is to obtain monotherapy claim for ABT-494. FDA noted that a monotherapy claim is largely historical in nature and was initially used for the first few TNF-inhibitor biologics to distinguish the need for co-administrating MTX to limit immunogenicity. Currently, the Division's view is that drugs that are deemed safe and effective in patients with RA typically receive a claim stating that the drug is approved for use to treat rheumatoid arthritis in the studied patient population. Given the Sponsor's overall development program, Study M15-555 would not be necessary to support an application for demonstrating the efficacy of ABT-494 in patients with RA. As currently designed, Study M15-555 would not adequately demonstrate ABT-494 monotherapy compared to MTX** (b) (4) **FDA further noted that the Sponsor's planned study to compare ABT-494 versus MTX in MTX/DMARD-naïve patients represents a reasonable study design to assess ABT-494 monotherapy.**

Question 7a

AbbVie acknowledges that labeling is a review issue; however, in principle does the Agency agree that positive results from Study M14-465 as currently designed will support inclusion of data in the Clinical Trials Section of the Full Prescribing Information relating to inhibition of the progression of structural damage?

FDA Response

Whether the radiographic data from a single study (Study M14-465) would be sufficient to support a claim of inhibition of radiographic progression of structural damage will depend on the data, which will be a review issue.

With respect to the time points chosen for analysis of radiographic data, it is reasonable to assess radiographic response at Week 24.

With respect to the analyses of the radiographic data, we are aware of the increasing difficulty of demonstrating the benefit of an investigational product for structural (i.e., radiographic) outcomes. This has been due to a number of factors:

- Improvements in present background standard of care which have resulted in low amounts of progression in placebo add-on control groups in the typical timeframe of a clinical trial.

- The ethical questionability of allowing patients to have uncontrolled disease activity for an extended period of time, which makes it necessary to limit the placebo-controlled period and include provisions for patients to receive rescue therapy by 12 to 16 weeks of

assigned study treatment. As a corollary, there will be difficulty in drawing conclusions about treatment effect based on comparator results that may be completely extrapolated.

- Concern that treatment effect on radiographic outcomes may be driven by few extreme observations that disproportionately impact the mean change from baseline in the radiographic score (e.g., modified Total Sharp Score).

Because of the issues stated above, it is clear that the approach to demonstrate effect on structural outcomes in RA clinical development programs needs to be changed. At this time we cannot provide you with definitive guidance. If you have alternative ideas that may address these concerns, you may provide a follow-up proposal.

See also our response to your Question 7b below. For further considerations on the assessment of radiographic data, we refer you to the Advice letter under PIND 125327, issued on April 02, 2015.

Question 7b

Does the Agency agree with the proposal to utilize linear extrapolation of data from Week 14 to Week 24 for "non-responders" (i.e., regardless of treatment group assignment) who converted early to active drug treatment at Week 14?

FDA Response

No, we do not agree with your proposed approach to use linear extrapolation to impute Week 24 radiographic scores in patients who escape or withdraw from the study early. In order to provide a reliable assessment of the intention-to-treat estimand (i.e., the difference in progression at Week 24 in all randomized patients regardless of adherence), the proposed linear extrapolation approach requires the strong and unverifiable assumption that patients' scores would have continued to change at exactly the same linear rate that was observed through the time of withdrawal. In addition, linear extrapolation is a single-imputation approach that does not appropriately take into account the uncertainty in the imputation process. Alternatively, one can interpret the linear extrapolation approach as providing an estimate of the difference between treatment groups in the on-treatment slope. However, this estimand may not be a meaningful surrogate for long-term benefit in all patients. For example, patients on ABT-494 who show no early progression but cannot tolerate or adhere to the therapy will show benefit (no decline) according to the on-treatment slope despite the fact that they may have progressed after treatment discontinuation.

You should clearly state the estimand that is being evaluated and justify that the estimand is clinically meaningful and can be estimated with minimal and plausible assumptions. We regard as critical the evaluation of the de facto estimand, i.e., the mean difference between treatment groups in mTSS in all randomized patients regardless of adherence or use of ancillary therapies. To help ensure reliable evaluation of this estimand, it is important that patients who discontinue study treatment early or initiate medication changes return for the regularly scheduled radiographic assessments.

See also our response to Question 25.

Meeting Discussion

AbbVie commented that radiographic response at Week 24 will be assessed in all patients in Study M13-542 as agreed; however, the Sponsor reasoned that some historical data suggest that linear extrapolation may be reasonable and proposed to conduct linear extrapolation in the analysis to evaluate radiographic progression. FDA acknowledged that linear extrapolation has been used in the past but reiterated that it now has serious concerns with this approach due to its reliance on a strong and unverifiable assumption and its failure to account for the uncertainty in the imputation process. FDA no longer recommends using it to provide the primary evidence of efficacy for radiographic endpoints. FDA recommended that the analysis evaluating the intention-to-treat or de facto estimand includes all Week 24 data in all randomized patients regardless of adherence or use of ancillary therapies, and indicated that this analysis would be critical from a regulatory perspective. FDA commented that conducting both linear extrapolation and ITT analyses may be reasonable. FDA also inquired as to whether the Sponsor was still considering alternative populations and designs to reliably evaluate effects on radiographic progression with minimal impact of escape and missing data. The Sponsor responded that it will also conduct a methotrexate naïve study to provide supportive radiographic data.

Question 8

Does the Agency agree that the proposed Phase 3 program is adequate to support a label claim for use of ABT-494 in the treatment of adult patients with moderately to severely active RA (b) (4) *?*

FDA Response

The overall proposed clinical program appears reasonable to provide evidence of efficacy of ABT-494 for the treatment of patients with moderately to severely active RA. The specific indication and labeling claims will be a review issue.

Meeting Discussion

This question was not discussed.

STUDY POPULATION

Question 9

Based on the key entry criteria listed below, does the Agency agree that the subject populations proposed for the 4 pivotal studies in the Phase 3 Program are representative of the target population moderately to severely active RA patients?

FDA Response

Your proposed key entry criteria appear reasonable.

Meeting Discussion

This question was not discussed.

ENDPOINTS

Question 10

Does the Agency agree that the use of two primary endpoints, ACR 20 and low disease activity (LDA) as defined by DAS28(CRP) ≤ 3.2, is acceptable to support a label claim for the treatment of moderately to severely active RA in patients who had an inadequate response to MTX (Studies M14-465 and M13-555) (b) (4) *?*

FDA Response

These endpoints are reasonable; however, clarify whether the two endpoints will be co-primary (i.e., statistical significance required in evaluations of *both* endpoints for the trial to be considered positive) or ACR20 will be the primary endpoint, with low disease activity as the first-ranked key secondary endpoint.

As outlined in the 2013 draft guidance for industry, *Rheumatoid Arthritis: Developing Drug Products for Treatment*, the use of ACR20 as the primary evidence of efficacy in the clinical response domain is acceptable. The DAS28 may be used as a supportive evidence of efficacy in in the clinical response domain. Note that while you have proposed a DAS-CRP ≤3.2 cut-off, the Agency has historically used a DAS28-CRP ≤2.6 to define a low disease activity status in rheumatoid arthritis.

Further, in addition to demonstrating efficacy for clinical response (signs and symptoms) of RA, marketing approval of ABT-494 for treatment of RA will also require demonstration of substantial evidence of benefit in the physical function domain. Thus, it is our expectation that your phase 3 program will also demonstrate substantial evidence of efficacy in the physical function domain via the proposed HAQ-DI.

AbbVie's Comment

The endpoints ACR 20 and LDA are not considered co-primary. They are two sequential primary endpoints.

Meeting Discussion

FDA commented that even though AbbVie has proposed to include DAS28 as a co-primary endpoint, the Agency will consider ACR20 as the primary endpoint and DAS28 a key secondary endpoint. AbbVie explained that both analyses are being used to satisfy the requirements from different regulatory agencies as part of their global development strategy. FDA noted the Sponsor's approach and commented that the use of ACR20 should be specified as the primary endpoint for studies used to support any future application submitted to FDA. Further, FDA commented that separate statistical analysis plans to address the different requirements from different regulatory agencies may be acceptable to FDA.

Question 11

Does the Agency agree that in the Biologic-IR study (Study M13-542), ACR20 at 12 weeks is an acceptable primary endpoint for assessing superiority of ABT-494 versus placebo in patients on background csDMARDs?

FDA Response
This is reasonable. See also our response to Question 10 above.

Meeting Discussion
This question was not discussed.

Question 12
Does the Agency agree that data on fatigue (FACIT-Fatigue) (b) (4) may be included in the Clinical Trials Section of the Full Prescribing Information if Phase 3 results are positive and are supported by appropriate qualitative and quantitative validation evidence?

FDA Response
Inclusion of any information in the product labeling will be a review issue. In your NDA submission, provide supportive evidence on the development of the selected measure and a justification for use of a given measure, which should include importance, clinical relevance, and nonredundancy of the proposed outcome with other measures. To support the utility and the interpretability of any of your proposed endpoints, provide the value of the clinically important difference between treatments and the value of the minimum important change within subjects. Explain how each value was developed, and how these values should be used to interpret the results.

Meeting Discussion
This question was not discussed.

Question 13
Does the Agency agree with the proposed use of the ACR50 response using a (b) (4)% non-inferiority margin at Week 24 in Study M14-465 (MTX-IR population) to assess non-inferiority of ABT-494 versus adalimumab (ADA) for improvement of signs and symptoms?

FDA Response
We agree that there is utility in the inclusion of an active comparator arm to provide longer-term randomized efficacy and safety comparisons than is possible with the placebo arm. However, the utility of the proposed assessment of non-inferiority (i.e., the proposed non-inferiority margin and hypothesis test) of ABT-494 versus adalimumab (ADA) is unclear from a regulatory perspective as it will not be required for the approval or labeling of ABT-494 for the treatment of patients with active RA, given the presence of a placebo arm in the study.

Further, explicit comparative effectiveness claims will generally require positive results from at least two adequate and well-controlled studies designed to compare two products. Such a development program would be subject to additional considerations which are outside of the scope of your proposed program.

Meeting Discussion
This question was not discussed.

Question 14

Does the Agency agree that two primary endpoints of ACR50 and LDA as defined by DAS28(CRP) ≤ (b) (4) are acceptable in the planned post-approval MTX-naïve study (Study M13-545)?

FDA Response

The design of the proposed Study M13-545 is at your discretion as it will not be necessary for the approval or labeling of ABT-494 for the treatment of patients with moderately to severely active RA.

Meeting Discussion

This question was not discussed.

Question 15

Does the Agency agree with the use of a 20% improvement in TJC and SJC in Study M14-465 to define criteria for early conversion to active treatment at the appropriate time points?

FDA Response

Your proposal to define criteria for early conversion/escape is reasonable.

However, we have concerns with the provisions for rescue therapy in Study M14-465. You propose (b) (4)

See also our response to Question 25.

Meeting Discussion

AbbVie stated that (b) (4)

AbbVie further proposed to assess signs and symptoms at Week (b) (4) and radiographic changes at Week (b) (4) The Sponsor acknowledged FDA's concerns with the cross-over design but proposed (b) (4)

AbbVie commented for Study M13-542, full response may take longer and switching may occur at Week 24 but the placebo group will be switched at Week 12. FDA stated that this proposal was reasonable.

SAFETY

Question 16

Does the Agency agree with AbbVie's proposed approach for monitoring cardiovascular safety in the Phase 3 program?

FDA Response

Your proposed approach for monitoring cardiovascular safety appears reasonable. We recommend that you use the following Standardized Definitions for Cardiovascular and Stroke End Point Events in Clinical Trials. (http://www.cdisc.org/system/files/all/standard/Draft%20Definitions%20for%20CDISC%20August%2020,%202014.pdf)

Meeting Discussion

This question was not discussed.

Question 17

Does the Agency agree that the proposed lymphocyte subset characterization in the Phase 3 program is adequate to understand the effect of ABT-494 on lymphocytes?

FDA Response

Your proposed approach for characterizing lymphocyte subsets appears reasonable but would be considered exploratory.

Meeting Discussion
This question was not discussed.

Question 18
Does the Agency agree with the planned procedures for clinical safety monitoring in the Phase 3 clinical trials?

FDA Response
Your proposed approach for monitoring clinical safety appears reasonable.

Meeting Discussion
This question was not discussed.

Question 19
Does the Agency agree with the proposed designs for extension studies to provide long-term safety data on ABT-494?

FDA Response
It is important to maintain subjects on the same dose of study drug to which they were originally randomized during the controlled period of the index study such that safety data is interpretable during the long-term extension studies to best interpret dose-response relationships between study drug and adverse events. This means that, if a patient continues to have active disease, they should be escaped to standard of care therapy (b) (4) We also recommend that you consider having patients originally randomized to adalimumab continue to receive adalimumab through the long-term extension study(ies) to provide long-term randomized, controlled comparisons of safety and efficacy. See also our response to Question 25.

Meeting Discussion
See meeting discussion for Question 15.

Question 20
Does the Agency agree that the proposed number of subjects exposed to ABT-494 and duration of exposure in Phase 2 and 3 studies with ABT-494 are adequate to support a NDA filing?

FDA Response
The estimated size of the safety database from phase 2 and phase 3 studies appears reasonable to support filing of your application. For immunosuppressive products intended for chronic use, such as ABT-494, the Agency has historically required a premarketing safety database that includes 1000-1500 subjects exposed for at least one year, in order to better characterize rare adverse events and adverse events of longer latency, such as malignancy.

We remind you that your application should be complete on submission, meaning that all efficacy and safety data that you consider necessary for approval should be included with the initial submission.

Meeting Discussion
This question was not discussed.

STATISTICS

Question 21
Does the Agency agree with the proposed multiplicity control on primary and key secondary endpoints?

FDA Response
No, we do not agree. Multiplicity adjustment methods for (b) (4) M145-555 appear to be reasonable. (b) (4)

In addition, we recommend that comparative evaluations against adalimumab are included in the multiple testing approach. See our response to Question 13 for additional discussion on the proposed active-control comparisons.

Meeting Discussion
AbbVie commented that the proposed (b) (4)

DA stated that this was not appropriate (b) (4)

Question 22
Does the Agency agree with the proposed primary analysis of Analysis of Covariance (ANCOVA) on mean change from baseline of mTSS score for evaluating the benefit on structure progression?

FDA Response
Yes, the proposed ANCOVA is reasonable, but see FDA responses to Question 7a for additional considerations on the assessment of radiographic data and Question 7b regarding the proposed linear extrapolation approach. In addition, because the distribution of mTSS change is often highly skewed and an evaluation of the difference in means (via ANCOVA) will be very sensitive to extreme observations, we recommend a supportive analysis (e.g., rank-based) that is less sensitive to extreme observations.

Meeting Discussion
This question was not discussed.

Question 23

Does the Agency agree with the following proposed handling of missing data for the primary analysis:

- *Non-responder Imputation (NRI) for binary endpoints (except for mTSS-based endpoints);*
- (b) (4)
- *Linear extrapolation analysis for mTSS-based endpoints.*

FDA Response

We have the following comments on your proposed handling of missing data:

- An approach to consider patients who discontinue investigational treatment early to be non-responders is reasonable, but with such an approach, the primary endpoint is in fact a composite measure of treatment success. For example, the primary ACR20 endpoint would be a composite measure that includes the following components: (1) remaining in the study, on treatment, and without protocol-prohibited medication changes through 12 weeks; and (2) achieving an ACR20 response at Week 12. The use of such a composite outcome combines the effects of treatment on adherence and signs and symptoms, so it will also be important to evaluate the treatment effect on each of the components of the composite outcome in supportive analyses (e.g., an evaluation of the difference in ACR20 response at Week 12 in all randomized patients regardless of treatment adherence or use of protocol-prohibited medications).

- The use of (b) (4) is not appropriate. (b) (4) We recommend the evaluation of the intention-to-treat or de facto estimand, e.g., the difference in mean HAQ-DI at Week 12 in all randomized patients regardless of adherence or use of ancillary therapies. If you propose an alternative estimand, you should justify that it is clinically meaningful and can be estimated with minimal and plausible assumptions. Regardless of the estimand chosen, the evaluation of de facto estimands will be critical to support claims of effectiveness.

- See our response to Question 7b regarding the proposed linear extrapolation approach.

- In order to minimize missing data in the evaluation of intention-to-treat or de facto estimands (e.g., the difference between treatment groups in ACR20 response at Week 12 in all randomized patients regardless of treatment adherence or use of ancillary therapies), patients who discontinue study treatment early or initiate medication changes (including those prohibited by the protocol) should continue to be followed for all regularly scheduled visits for safety and efficacy assessments. To help prevent missing data, we also recommend that: (1) the protocols and informed consent forms clearly differentiate treatment discontinuation from study withdrawal; (2) the only reasons for

study withdrawal are patient withdrawal of consent to contribute additional outcome information and loss to follow-up; (3) site investigators are trained about the importance of retention and steps to prevent missing data; (4) the consent forms include a statement educating patients about the continued scientific importance of their data even if they discontinue study treatment early; and (5) several approaches are implemented to retain patients who fail to actively maintain contact with the investigator (e.g., telephone calls to friends or family members, emails, offers for transportation to the clinic, etc.).

See also our response to Question 25.

Meeting Discussion

AbbVie proposed that non-responder imputation (NRI) be performed at Week 12 for binary endpoints and Week 24 for Study M14-465, with patients on rescue considered as non-responders. FDA agreed, but indicated that, with such an approach, the primary endpoint is in fact a composite. Therefore, reliable supportive evaluations of the components of the composite endpoint (e.g., ACR20 at Week 24 regardless of adherence or escape) will be important, and will rely on collection and inclusion of data through Week 24 for patients who discontinue study therapy and/or receive rescue therapy. AbbVie expressed understanding of FDA's concerns regarding the use of (b) (4) (b) (4) (b) (4) **AbbVie asked for an appropriate alternative and FDA responded that there is no perfect answer but advised the Sponsor to clearly state the estimand that is being evaluated and justify that it is meaningful and can be estimated with minimal assumptions. FDA also noted that it may be appropriate to handle patients who escape differently from actual missing data (e.g., due to dropout from the study).**

REGULATORY

Question 24

Does the Agency agree that a Proposed Pediatric Study Plan is not required and that the timing of submission of a Proposed Pediatric Study Request by 2Q 2016 is acceptable for issuance of a Written Request?

FDA Response

Approval of ABT-494 for the treatment of RA would trigger Pediatric Research Equity Act (PREA) (21 U.S.C. 355c). Thus, a pediatric assessment and an initial Pediatric Study Plan (iPSP) would be required. Refer to item #3, ADDITIONAL INFORMATION, PREA REQUIREMENTS below. Note that Proposed Pediatric Study Plan (PPSR) is under Best Pharmaceuticals for Children Act (BPCA) and is different from the required iPSP. Submitting a PPSR for a written request would be at your discretion.

Meeting Discussion
This question was not discussed.

Question 25
Does the Agency have any other additional comments regarding the information presented herein in support of the Phase 3 development program for ABT-494?

FDA Response
The possibility of cross-over between treatment arms (e.g., escape from placebo to ABT-494, (b) (4) or adalimumab to ABT-494) confounds long-term safety and efficacy comparisons between the randomized groups. In the presence of cross-over, there are two approaches to carry out intention-to-treat analyses, neither of which is satisfactory. If you ascertain patient outcomes after escape and include these outcomes in analyses, intention-to-treat comparisons would be difficult to interpret due to the fact that some placebo and low dose patients received the higher dose for some of the treatment period. If you instead consider patient outcomes after escape to be missing, analyses of 24-week endpoints (e.g., using only the complete data, or applying last observation carried forward or linear extrapolation) would rely on unverifiable assumptions about the missing data mechanisms.

To address this concern, we recommend the following protocol changes:

- Provide a rescue therapy option for all patients who continue to have active disease at the pre-specified timepoint, with provisions for preserving the blind. This includes patients in the ABT-494 and adalimumab arms.

- The rescue therapy provision should be a therapy that has established efficacy, i.e. standard of care. Patients should not cross over between study treatments.

- For patients who continue in trials for greater than 24 weeks, establish multiple, predetermined time points when patients will be evaluated for ongoing disease activity, as measured by signs and symptoms. Offer rescue therapies with established efficacy to patients with ongoing disease activity or structural damage progression.

- Assess the primary and key secondary endpoints at the time of initial rescue therapy to avoid confounding the primary and key secondary efficacy assessments. Note that this comment does not apply to the assessment of radiographic data (see our response to Question 7).

Meeting Discussion
See meeting discussion for Question 15.

3. ADDITIONAL INFORMATION

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 (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.

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.

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.

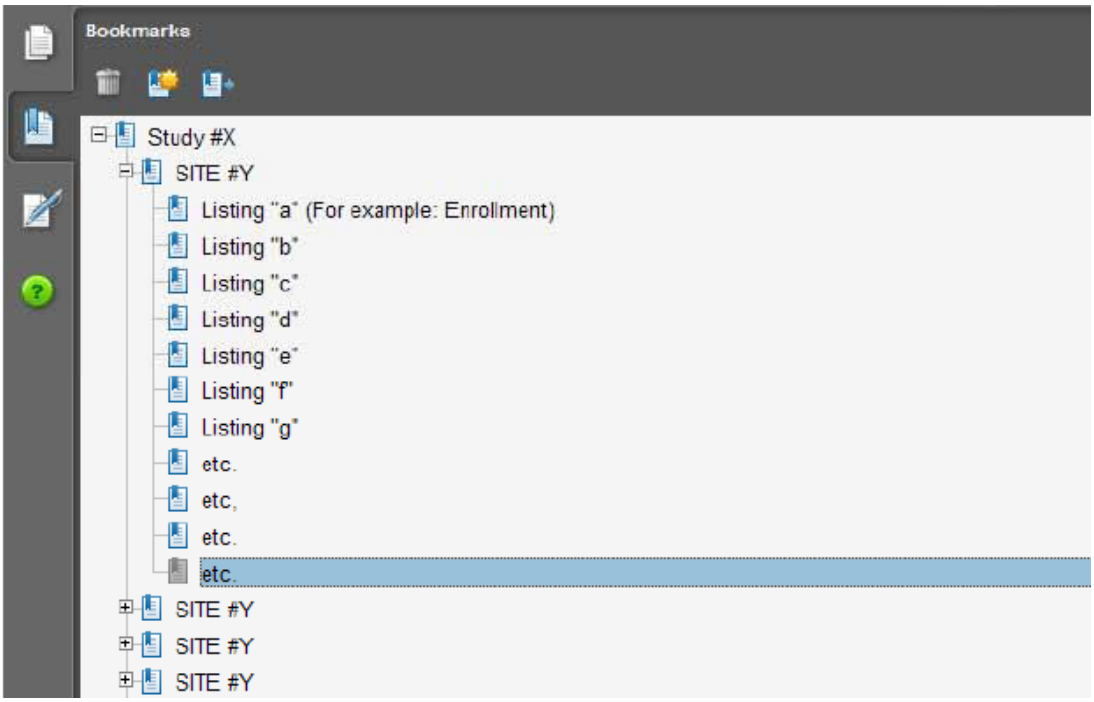
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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.

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[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

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.

[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

4. ISSUES REQUIRING FURTHER DISCUSSION
There were no issues requiring further discussion.

5. ACTION ITEMS
There were no action items.

6. ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes.

Reference ID: 4478900

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

/s/

PHUONG N TON
11/16/2015