CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218347Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 114717

MEETING MINUTES

AbbVie Inc.
1 N. Waukegan Road
North Chicago, IL 60064

Attention: Leilane Oshiro
Senior Manager, Regulatory Affairs

Dear Ms. Oshiro:[1]

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 video conference between representatives of your firm and the FDA on March 22, 2023. The purpose of the meeting was to discuss the proposed supplemental NDA to support the expansion of the indication to pediatric patients with polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) and juvenile psoriatic arthritis (JPsA), and to discuss the proposed concurrent NDA for a new dosage form of upadacitinib (oral solution formulation 1 mg/mL).

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

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

If you have any questions, call me at 240-402-1604.

Sincerely,

{See appended electronic signature page}

Suprat Saely, PharmD, BCPS, FCCM
Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations –
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA/pre-supplemental NDA
Meeting Date and Time:	March 22, 2023, 11:30 AM to 12:30 PM ET
Meeting Location:	Virtual Face-to-Face via Zoom
Application Number:	IND 114717
Product Name:	Upadacitinib
Indication:	Polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) and juvenile psoriatic arthritis (JPsA)
Sponsor Name:	AbbVie Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Ozlem Belen, MD, MPH
Meeting Recorder:	Suprat Saely, PharmD, BCPS, FCCM

FDA ATTENDEES

Ozlem Belen, MD, MPH, Deputy Director, Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII)
Nikolay Nikolov, MD, Director, DRTM, OII
Rachel Glaser, MD, Associate Director for Therapeutic Review, DRTM, OII
Anil Rajpal, MD, MPH, Clinical Team Leader, DRTM, OII
Eric Gapud, MD, PhD, Clinical Reviewer, DRTM, OII
Jianmeng Cheng, MD, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP), Office of Pharmacology (OCP)
Lei He, PhD, Clinical Pharmacology Reviewer, DIIP, OCP
Karen Higgins, ScD, Supervisory Mathematical Statistician, Division of Biometrics III (DBIII), Office of Biostatistics (OB)
Yura Kim, PhD, Biostatistics Reviewer, DBIII, OB
Craig Bertha, PhD, CMC Lead, New Drug Product Branch 4 (NDPB 4), Division of New Drug Products (DNDPII), Office of New Drug Products (ONDP)
Henry Startzman, MD, Director Orphan Drug Designation Program, Office of Orphan Products Development
Christina Thompson, PharmD, MS, Division of User Fee Management, Office of Management
Suprat Saely, PharmD, BCPS, FCCM, Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation (DRO-II), Office of Regulatory Operations (ORO)

SPONSOR ATTENDEES
Steve Pulaski, MS, MBA, Asset Strategy Leader, Immunology Clinical Development
Alvina Chu, MD, Executive Medical Director, Immunology Clinical Development
Peter K. Wung, MD, MHS, Group Medical Director, Immunology Clinical Development
Anna Shmagel, MD, MSc, Medical Director, Immunology Clinical Development
Heidi S. Camp, PhD, Group Scientific Director, Immunology Clinical Development
Arathi Setty, MD, MPH, Senior Medical Director, Immunology Clinical Development
Mohamed-Eslam Mohamed, PhD, Director, Clinical Pharmacology
Yuli Qian, PhD, Senior Clinical Pharmacologist, Clinical Pharmacology
Juliana Leite-Schnell, Director, Global Regulatory Lead, Global Regulatory Strategy
Denise E. Schulz, BS, Senior Director, RA Global Therapeutic Area head, Global Regulatory Strategy
Leilane Oshiro, Senior Manager, US/Canada Regulatory, Global Regulatory Strategy
Kristina Unnebrink, PhD, Senior Principal Research Statistician
Derek Coombs, Director, Immunology Safety Statistics
Nasser Khan, MD, Senior Medical Director, Medical Safety and Evaluation Pharmacovigilance and Patient Safety
Jianzhong Liu, MD, MS, Group Medical Director, Medical Safety Evaluation

1.0 BACKGROUND

On January 20, 2023, AbbVie submitted a request for a Type B meeting to discuss the planned supplemental NDA to support expansion of the indication to pediatric patients with polyarticular (b) (4) juvenile idiopathic arthritis and juvenile psoriatic arthritis, and to discuss the proposed concurrent NDA for a new dosage form of upadacitinib.

AbbVie's specific questions from the briefing document received February 21, 2023, are listed below in *italics*, and FDA responses are listed in normal font.

FDA sent Preliminary Comments to AbbVie on March 20, 2023. In an email correspondence received March 21, 2023, AbbVie requested further discussion on questions 5, 7, 10, and 11.

2.0 DISCUSSION

2.1. Regulatory

Question 1: *Does the Agency agree that the new indications of* (b) (4) *and JPsA can be submitted simultaneously in one sNDA?*

FDA Response to Question 1:
We do not agree. One supplemental new drug application (sNDA) should be submitted for the polyarticular (b) (4) juvenile idiopathic arthritis (b) (4) indication and a second separate sNDA for the juvenile psoriatic arthritis (JPsA) indication. From the guidance

cited, *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees*,[2] note section B, NDA and BLA Supplements, Changes to Indications, where it states, "*A request for approval of a new indication, or a modification of a previously approved indication, should be submitted individually in a separate supplement to an approved original application*." However, shared information or data between the two supplements do not have to be submitted twice but can be provided as cross reference to the first supplement via hyperlink(s) in the second supplement. Also note that there are no user fees for supplements.

We remind you that the Final Report submission for PREA PMR 3680-1, i.e., "Conduct a multiple-dose pharmacokinetic study in children from 2 to less than 18 years of age with juvenile idiopathic arthritis (JIA)," is due March 2023.

Meeting Discussion for Question 1:
No discussion occurred.

Question 2: *The Applicant plans to submit a Type 3 NDA for the oral solution formulation concurrently with the sNDA, and to cross-reference relevant sections from the sNDA. Does the Agency agree with this approach?*

FDA Response to Question 2:
Yes, we agree.

Meeting Discussion for Question 2:
No discussion occurred.

Question 3: *Does the Agency agree that the planned content of the sNDA and the Type 3 NDA, as displayed in the table of contents, is adequate to be considered a complete application?*

FDA Response to Question 3:
We do not agree with the planned content of the sNDA as displayed in the table of contents. See FDA Response to Question 1. Additionally, for your clinical trials, include all components supporting the study reports, including protocols and amendments (with dates), statistical analysis plans (SAPs), generated treatment assignment lists, the actual treatment allocations (along with the date of enrollment/randomization), and annotated case report forms (CRFs) for all subjects with major safety events in studies for which you plan to submit clinical study reports (CSRs). These events include, but are not limited to, deaths, serious adverse events (SAEs), discontinuations of investigational product and/or the study for adverse events adverse events (AEs), and pre-specified adverse events of special interest (AESIs).

[2] https://www.fda.gov/media/72397/download

Meeting Discussion for Question 3:
No discussion occurred.

Question 4: *Does the Agency agree with the proposed list of covered studies for submission of financial disclosure information?*

FDA Response to Question 4:
Your proposal appears reasonable. However, the final decision on the adequacy of this list will be made after you have submitted complete applications.

Meeting Discussion for Question 4:
No discussion occurred.

Question 5: *Does the Agency agree that all supportive safety information from the adolescent and pediatric AD studies can be summarized in the Clinical Overview and that respective source data can be provided in Module 5?*

FDA Response to Question 5:
Yes, we agree in principle. We note, however, on page 45 of the briefing document, you stated that electronic components from the supportive pediatric and adolescent safety data from atopic dermatitis (AD) studies will not be submitted. Clarify what will be submitted in Module 5 as the source data. See also FDA Responses to Questions 1, 3, and 11.

Meeting Discussion for Question 5:
AbbVie clarified that summary tables (without subject level data) of the pediatric and adolescent safety data from AD studies will be provided. AbbVie asked the Agency if this proposal is acceptable?

FDA stated that an internal discussion is needed and will provide AbbVie with a post meeting comment to address this question. See below.

Post Meeting Comment:
Your proposed safety database includes all safety data available from Parts 1/2/3 of Study M15-340 and safety data from the pediatric and adolescent subjects in the AD program. You should also submit subject-level data in an appropriate format (i.e., SDTM and ADaM) for Study M16-049 (pediatric AD patients 2 to <12 years of age). For Studies M16-045, M16-047, M18-891 (pooled long-term safety data for adolescent AD patients 12 to <18 years of age), we agree that it is reasonable to submit summary level data; however, subject-level data may be requested during review of your submissions if needed. The adequacy of the safety database will be a review issue in the context of overall benefit-risk assessment.

Question 6: *Does the Agency agree that the data provided in support of the application for the treatment of* (b) (4) *and JPsA patients, concurrently with the oral solution*

formulation, are sufficient to support designation of a priority review for the sNDA and respective NDA?

FDA Response to Question 6:
It is premature to comment. Review designation (as priority or standard) of a future marketing application will be determined after the application has been submitted. Refer also to FDA Response to Question 1.

Meeting Discussion for Question 6:
No discussion occurred.

Question 7: *Does the Agency agree that AbbVie can claim an application fee exemption for the new dosage form Type 3 NDA given the Orphan Drug Designation #15-4854 for upadacitinib to treat pediatric patients ages 2 and older with* (b) (4) *and JpsA?*

FDA Response to Question 7:
Yes, we agree. According to Section V.A.1 of the User Fee Waivers, Reductions, and Refunds for Drug and Biological Products guidance,[3] a human drug application for a product that has been designated as a drug for a rare disease or condition (referred to as an orphan drug) under section 526 of the Act is not subject to an application fee unless the human drug application includes an indication for other than a rare disease or condition. If the proposed indication is outside the scope of the designated orphan indication or if the designated indication is under a different applicant, a PDUFA application fee may be assessed.

If the application is not orphan excepted, the amount of PDUFA application fee due depends on rather or not the application requires clinical data for approval. A half PDUFA application fee is due if the application does not require clinical data, and a full PDUFA application fee is due if the application does require clinical data. The term clinical data, for purposes of assessing user fees, encompasses a broad range of studies that are purported to be adequate and well-controlled investigations submitted in support of approval. For additional information, please visit the *Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees* Guidance.[4]

Note that the final user fee determination will be made when the application is submitted in its entirety to the FDA for review.

Meeting Discussion for Question 7:
AbbVie stated that upadacitinib received the orphan designation for pediatric patients, ages 0 through 16 with JIA categories, excluding systemic JIA. AbbVie would like to

[3] https://www.fda.gov/media/72340/download
[4] https://www.fda.gov/media/72397/download

confirm that the type 3 NDA in support of the new dosage form (oral solution) to support dosing in pediatric patients <30 kg who cannot swallow the tablets with the proposed indication for pediatric patients with (b) (4) and JPsA (both considered under JIA according to ILAR categories) for the age range of 2 years and older is exempt from a user fee.

FDA stated that the proposed indications fall within the scope of the orphan designation.

Question 8: *Does the Agency have any additional comments regarding the information presented herein in support of the submission of upadacitinib for the proposed indications?*

FDA Response to Question 8:
We have no additional comments at this time on the proposed structure and organization of your planned submissions. However, we may have additional comments after you have submitted complete applications.

Meeting Discussion for Question 8:
No discussion occurred.

2.2. Clinical Development and Safety

Question 9: *Does the Agency agree with the proposed plan and cutoff date for the 4-month safety update?*

FDA Response to Question 9:
You plan to submit the single sNDA for (b) (4) and JpsA by June 30, 2023, and 4-month safety update no later than October 30, 2023. Your proposed data cutoff date for the 4-month safety update for Study M15-340 is June 20, 2023, which is approximately 8 months after the September 22, 2022, initial data cutoff date. This proposed plan and data cut-off date for the 4-month safety update for Study M15-340 is reasonable.

Also refer to FDA response to Question 1.

Meeting Discussion for Question 9:
No discussion occurred.

Question 10: *Does the Agency agree with the adequacy of the clinical pharmacology studies and analyses to support the sNDA submission for upadacitinib in (b) (4) and JpsA?*

FDA Response to Question 10:
The proposed clinical pharmacology studies appear reasonable to support the planned application submissions for upadacitinib in (b) (4) and JpsA. We recommend that you provide adequate justification to address the Agency's previous comments upon the

sNDA submission. Refer to FDA Final Written Response dated July 22, 2022. You will also need to address the labeling issue for the potential interchangeable use of 15 mg extended-release tablets and the proposed immediate-release oral solution (1 mg/mL) to prevent any medical error. The final determination of the adequacy will be a review issue.

In addition, the proposed formulation bridging approach appears reasonable. The final decision of adequacy will be determined during review of the submissions.

Meeting Discussion for Question 10:
AbbVie provided their plans to include a labeling statement that the two formulations (current approved 15 mg extended-release tablets and the proposed immediate-release 1mg/mL oral solution) are not interchangeable with clear instructions on the dose and frequency in patients who have a body weight of 30 kg or higher. AbbVie asked the Agency if this would address the Agency's medication error concerns.

FDA restated the major medication error concerns are that prescribers will use the proposed immediate-release 1mg/mL oral solution as a once daily dosing regimen, rather than the BID dosing as intended. FDA indicated that AbbVie's plans to address this with clear labeling instructions appear reasonable at this time, but a final adequacy will be determined during review of the submissions.

Question 11: *Does the Agency have any comments on the data package to support the proposed indications to treat pediatric patients ages 2 and older with* (b) (4) *and JPsA?*

FDA Response to Question 11:
See FDA Response to Question 10. In addition, regarding the proposed safety database at the time of the submissions, you plan to include safety information for 40 (b) (4) patients (2 to <18 years of age), and 22 pediatric AD patients (2 to <12 years of age), as well as 466 adolescent AD patients (12 to <18 years of age) exposed to upadacitinib for at least 52 weeks. The adequacy of the proposed database will be a review issue in the context of an overall benefit-risk assessment for patients with (b) (4) and JPsA. However, we reiterate the following advice previously communicated in FDA's Type C meeting Written Responses dated August 7, 2020, April 14, 2021, and July 21, 2022:

a. The final submission should include justifications of the relevance of safety in subjects with (b) (4) for patients with JPsA, and also with safety in subjects with AD for (b) (4) and JPsA patients.

b. Even with an adequate justification, the proposed safety database may still be small for reliable assessment of rare or latent events in patients 2 to < 12 years of age. Additional post-marketing safety information may be required.

c. There should be a sufficient distribution of subjects across all age and weight ranges for the proposed pediatric dosing. The adequacy of the safety assessment, particularly in the lower age groups, will be a review issue.

Meeting Discussion for Question 11:
AbbVie asked for Agency feedback and guidance regarding the data or information that would be needed to adequately address the comment about justification of the relevance of safety data in AD patients to (b) (4) and JPsA patients. AbbVie explained that their planned safety database will include safety information from a pediatric study in (b) (4) patients 2 to <18 years of age (Study M15-340) as well as safety data from Study M16-049 (AD patients 2 to <12 years of age) and pooled adolescent AD data from Studies M16-045, M16-047, and M18-901 (AD patients 12 to <18 years of age). AbbVie considers the safety data in AD patients 2 to <18 years of age to be supplemental in the proposed submissions for (b) (4) and JPsA. AbbVie's planned justification of the relevance of these supplemental safety data to (b) (4) and JPsA patients will be based on the following:

a. The systemic exposures of upadacitinib in (b) (4) patients 2 to <18 years of age are similar to those in AD patients 2 to <18 years of age; AbbVie expects the systemic exposures of upadacitinib to also be similar for JPsA patients 2 to <18 years of age and will provide these data in their planned submissions.
b. The safety data in (b) (4) patients 2 to <12 years of age are similar to the safety data in AD patients 2 to <12 years of age; AbbVie will provide the results of Study M15-340 and Study M16-049 in their planned submissions.
c. The safety data in AD patients 2 to <18 years of age and (b) (4) patients 2 to <18 years of age are generally consistent with the safety data in adult AD, rheumatoid arthritis, and psoriatic arthritis patients.

FDA stated that AbbVie's proposed justification of the relevance of safety data in AD patients to the (b) (4) and JPsA patient populations appears reasonable; however, FDA noted that the final determination will be made during review of the submissions. FDA added that the Division of Rheumatology and Transplant Medicine will coordinate the review of the data from AD patients 2 to <18 years of age with the Division of Dermatology and Dentistry.

2.3. Statistics

Question 12: *Does the Agency agree that the proposed electronic components (i.e., datasets and analysis read programs) from Study M15-340 are adequate to support review?*

FDA Response to Question 12:
Your proposed data standardization plan appears reasonable.

The analysis dataset documentation (Define.xml) should include adequate detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. Submit corresponding Define.pdf files in addition to the Define.xml files.

We refer you to the FDA guidance, *Study Data Technical Conformance Guide.*[5] For additional questions related to study data standards, contact the eData Team at cder-edata@fda.hhs.gov.

Meeting Discussion for Question 12:
No discussion occurred.

2.4. Clinical Site Inspections

Question 13: *Does the Agency agree that the proposed Subject Level Data by Clinical Site for the Phase 1 Study M15-340 are sufficient for the Agency's purposes of site inspection selection?*

FDA Response to Question 13:
The proposed Subject Level Data by Clinical Site for the Phase 1 Study M15-340 seems adequate at this time.

Meeting Discussion for Question 13:
No discussion occurred.

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

4.0 ACTION ITEMS
There are no action items.

5.0 ATTACHMENTS AND HANDOUTS
None.

[5] https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

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/s/

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