CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213082Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

IND 117400

MEETING PRELIMINARY COMMENTS

Pfizer Inc.
500 Arcola Road
Collegeville, PA 19426

Attention: Alicia Holsey, M.S., RAC
Senior Manager, Pfizer Global Regulatory Affairs

Dear Ms. Holsey:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tofacitinib.

We also refer to your July 31, 2019, correspondence, received July 31, 2019, requesting a meeting to discuss the overall content and format of the planned application of the planned new drug application for tofacitinib for the treatment of polyarticular juvenile idiopathic arthritis (pJIA).

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me at (301) 796-5073.

Sincerely,

{See appended electronic signature page}

Elaine Sit, PharmD
Regulatory Health Project Manager
Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

ENCLOSURE:

- Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: October 28, 2019 at 2:30PM – 3:30PM
Meeting Location: FDA White Oak, Room 1309

Application Number: 117400
Product Name: Tofacitinib

Indication: Polyarticular juvenile idiopathic arthritis
Sponsor Name: Pfizer Inc.

FDA ATTENDEES (tentative)
Nikolay Nikolov, MD, Associate Director of Rheumatology, DPARP
Rachel Glaser, MD, Clinical Team Leader, DPARP
Jin Chen, MD, PhD, Clinical Reviewer, DPARP
Carol Galvis, PhD, Pharmacology/Toxicology Team Leader, DPARP
Steve Leshin, PhD, Pharmacology/Toxicology Reviewer, DPARP
Craig Bertha, PhD, CMC Lead, Division of New Drug Products Branch IV, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Rebecca Rothwell, PhD, Acting Biostatistics Team Lead, Division of Biometrics II (DBII), Office of Biostatistics (OB)
Cesar Torres, PhD, Biostatistics Reviewer, DBII, OB
Jianmeng Chen, PhD, Acting Team Lead, Division of Clinical Pharmacology II (DCPII), Office of Clinical Pharmacology (OCP)
Lei He, PhD, Clinical Pharmacology Reviewer, DCPII, OCP
Elaine Sit, PharmD, Regulatory Health Project Manager, DPARP

SPONSOR ATTENDEES
Chinyu Su, MD, Xeljanz Global Medicine Team Lead
Keith Kanik, MD, Global Clinical Lead
Cheng Chang, PhD, Clinical Pharmacology Lead
Andrea Shapiro, Safety Risk Lead
Richard Zhang, PhD, Statistics Lead
Gary Perry, BSc, Global Regulatory Lead
John Larmann, PhD, Pharmaceutical Sciences Technical Lead
Alicia Holsey, MS, RAC, US Regulatory Lead

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for October 28, 2019, at 2:30-3:30PM, FDA White Oak between Pfizer Inc. and the Division of Pulmonary, Allergy, and Rheumatology Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

Pfizer requested a Type B pre-NDA meeting on July 31, 2019, to discuss a planned NDA for tofacitinib for the treatment of polyarticular juvenile idiopathic arthritis (pJIA). The Division granted a meeting at FDA White Oak for September 27, 2019 in a letter dated, August 6, 2019. It was later determined that not all FDA reviewers would be available on this date, so FDA and Pfizer rescheduled for October 28, 2019, via e-mail correspondence to Alicia Holsey, dated August 12, 2019. Pfizer submitted the briefing package containing their questions for this meeting on August 26, 2019. Pfizer's questions from the briefing package are listed below in **bold font** and FDA responses are provided in normal font.

2.0 DISCUSSION

2.1. Submission Strategy

Question 1: Does the FDA concur with the proposed format and placement of the information in the electronic submission for the planned NDA for tofacitinib oral solution and sNDA for Tofacitinib IR tablet?

FDA Response to Question 1:

Yes, we agree.

2.2. Clinical Pharmacology

Question 2: Does the Agency agree with the proposed content of the Clinical Pharmacology section to support the planned sNDA submission?

FDA Response to Question 2:

The proposed content of the Clinical Pharmacology section appears to be sufficient to support the planned sNDA submission. However, the final determination of the adequacy of the information will be a review issue.

2.3. Clinical Efficacy

Question 3: As per previous correspondence dated 07 March 2019 Pfizer proposes to provide a Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) and will not plan to include an Integrated Summary of Efficacy (ISE) or Integrated Summary of Safety (ISS) in the tofacitinib pJIA sNDA. Does the FDA agree that our approach meets the details outlined in the correspondence pertaining to the presentation of efficacy and safety data?

FDA Response to Question 3:

Given the small number of studies included in this application, this approach is acceptable. However, depending on the role you intend for your proposed integrated analyses to play in your submission, you may need to provide further details on how you intend to perform pooling of RA studies and pooling of the pJIA studies. See our comments under Question 6.

Question 4: For the tofacitinib Oral Solution NDA (213082) Pfizer proposes to cross-reference to the SCE and SCS documents along with the mapped ISE/ISE documents from the tablet sNDA (203214) dossier. Does the FDA agree our proposal for managing and presenting efficacy and safety data for tofacitinib Oral Solution is appropriate to support review of the tofacitinib Oral Solution NDA dossier?

FDA Response to Question 4:

Yes, we agree.

Question 5: The individual efficacy analysis plans for the pivotal Study A3921104 and the long-term extension Study A3921145 have been previously discussed with FDA, with the expectation that the results from Study A3921104 are the primary source to demonstrate tofacitinib is efficacious in patients with pJIA. Does FDA agree with the planned presentation of the efficacy data proposed below, which will be included in the SCE?
FDA Response to Question 5:

Given the focus of the efficacy analyses will be on Study A3921104, your planned presentation of the efficacy data appears to be reasonable.

We note that in Table 6 of the meeting briefing package, two subjects were excluded from the ACR30/50/70 analyses at Week 44 because these subjects were considered "outside window." Clarify what is meant by a subject being outside window. Regardless, this approach is effectively a completers analysis and does not follow what was prespecified in the Statistical Analysis Plan (SAP) for the pivotal study, submitted to the Agency for review on May 1, 2019. We expect that the SCE will reflect analyses that include these two subjects, using the missing data handling procedures described by the SAP.

Additional Statistical Note

In the description of the analyses for continuous endpoints, the mixed-effect models with repeated measures (MMRMs) will include "double-blind phase value" as a fixed effect. We assume that the meeting briefing package meant to state that "double-blind baseline value" will be included as a fixed effect. Clarify whether our interpretation is correct.

2.4. Clinical Safety

Introductory Comment

We acknowledge you are planning to submit three clinical studies with tofacitinib oral solution and IR tablet 5 mg to support the proposed pJIA indication and to satisfy the PREA requirements for Xeljanz (NDA 203214). The submission will include one multiple-dose PK study (A3921103), one phase 3 efficacy and safety trial (A3921104) and one long-term open-label extension study (A3921145) in pJIA patients 2 years to 18 years of age. You have not provided a summary of the preliminary safety data to be included in your submission. We are particularly interested in the potential long-term risks of tofacitinib on pediatric development due to known adverse effects on cartilage in animal studies with some JAK inhibitors. In the rat juvenile animal study (Report 10GR307) submitted with the NDA, bone and joint histopathology were not conducted, although there were no adverse findings in the juvenile monkey study (Report 09GR248).

We note that body weight, height and Tanner stages, without bone assessments, were included in the safety evaluations in A3921104 and A3921145. In your NDA submission, include available safety data on pediatric growth and development. You will need to address the potential risks of chronic therapy with tofacitinib on potential bone effects in the pediatric population in addition to overall long-term safety. While the proposed safety database may be adequate to support submission and filing of your application, additional long-term safety data may be needed.

Question 6a: Does the FDA agree with the JIA safety analysis plan, presentation, pooling and contextualization of the data?

i) Does FDA Agree with the Proposed Pooling of Data from the Three JIA Studies?

ii) Does FDA Agree with the Proposed Integrated Safety Analysis?

iii) Does FDA Agree with the Proposed Contextualization?

FDA Response to Question 6a:

Proposed JIA Safety Analysis Plan and Presentation

We anticipate that the primary assessment of clinical safety will come from the controlled period of your phase 3 pJIA study. Under the assumption that the briefing package for this meeting and the SAP submitted to the Agency for review on May 1, 2019, together capture all of the details regarding the planned safety analyses of this controlled data, we have the following comments for your consideration:

Section 6.6 of the SAP describes the procedures to calculate incidence rates and 95% confidence intervals for adverse events in each treatment arm. This section also describes procedures to calculate a point estimate of the risk difference and 95% confidence interval according to the approach proposed by Chang & Zhang[1]. This approach is to be used for binary endpoints, suggesting that the metric for your risk difference calculations will be the incidence proportion, which is not the same as the incidence rate. For ease of clinical interpretation, we recommend that the by-arm estimates and confidence intervals use the same metric as between-arm estimates and confidence intervals. Specifically, we recommend that in addition to (or in place of) the incidence proportion risk difference estimates and confidence intervals the SAP prespecifies, you also provide incidence rate risk difference estimates and confidence intervals. These analyses should be prespecified in the SAP.

Furthermore, if you intend to present incidence proportion results, the period under consideration for the incidence proportion (e.g., double-blind Week 0 to double-blind Week 26) should be stated in the SAP, along with a description of how missing data will be handled.

Proposed Pooling of Data, Integrated Safety Analysis, and Contextualization

As indicated above, we anticipate that controlled comparisons will serve as the primary basis for the evaluation of safety of tofacitinib in pJIA. In this context, your proposed integrated safety analyses appear to be reasonable. Depending on the extent to which you intend for the uncontrolled, cross-study comparisons incorporating data from the RA program to serve as supplementary analyses providing more information regarding the safety profile in the pJIA population, it may

[1] Chan, Ivan SF, and Zhongxin Zhang. "Test-based exact confidence intervals for the difference of two binomial proportions." Biometrics 55.4 (1999): 1202-1209.

be necessary for you to provide additional details (e.g., the studies to be included, how pooling will be performed, how exposure time is calculated, and if any treatment comparisons will be performed).

Finally, the description in the meeting briefing package suggests that the integrated analyses will reflect a crude pooling approach. To avoid issues such as Simpson's Paradox, we recommend that you avoid crude pooling of the data. One candidate approach to achieve this is to adjust by study.[2]

Question 6b: Pfizer proposes to include the narratives within Study A3921104 Clinical Study Report (CSR) and in Study A3921145 Interim Report. Does the FDA agree with the Narrative Plan proposal?

FDA Response to Question 6b:

Your plan to provide the narratives within Study A3921104 CSR and Study A3921145 Interim Report appears reasonable. We acknowledge that the narratives will include serious adverse events, exposure in utero, adverse events of special interest as defined in Table 8 of the meeting package, and discontinuations due to adverse events, including pre-specified laboratory parameters.

Question 6c: Pfizer proposes to submit the updated RA safety data set that will be used for contextualization of JIA safety in the legacy PDS format; all data from the JIA studies will be in CDISC format. Does the FDA agree with the proposed presentation of these data?

FDA Response to Question 6c:

Your proposed presentation of the data appears to be reasonable.

Question 6d: Does the Agency agree with the proposed safety data cut-off date and content for the 4-month safety update?

FDA Response to Question 6d:

Your proposed safety data cut-off date of Q12020 to include data from LTE Study A3921145 is reasonable. Case Report Forms and patient narratives for deaths, SAEs, AESI, and AEs leading to discontinuation should be submitted with your Safety Update. Your application should be complete at the time of submission, meaning that all efficacy, safety, and AESI data necessary to support approval should be included with the initial submission for our review. Note that should your submission be granted a priority review, a 90-day safety update would be expected.

[2] Crowe, Brenda, et al. "Reporting adverse drug reactions in product labels." Therapeutic innovation & regulatory science 50.4 (2016): 455-463.

Question 7: Does the Agency agree with the proposed approach to communication of tofacitinib risks to JIA patients and their Healthcare Providers (HCPs)?

FDA Response to Question 7:

The approach to communication of risks of tofacitinib to JIA patients and their HCPs will be a review issue.

2.5. Labeling Strategy

Question 8: Does the FDA agree with our proposal to incorporate the Oral Solution formulation into the current labelling for Xeljanz/Xeljanz XR dossier?

FDA Response to Question 8:

It may be reasonable to incorporate the OS formulation into the Xeljanz/Xeljanz XR labeling. A final determination regarding the appropriate labeling for the OS formulation will be a review issue.

3.0 OTHER IMPORTANT MEETING COMMENTS

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.[3] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

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[5] and Pregnancy and Lactation Labeling Final Rule[6] 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

[3] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ELAINE SIT
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